Review

Inhibitory Synaptic Influences on Developmental Motor Disorders

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Abstract: During development, GABA and glycine play major trophic and synaptic roles in the establishment of the neuromotor system. In this review, we summarise the formation, function and maturation of GABAergic and glycinergic synapses within neuromotor circuits during development. We take special care to discuss the differences in limb and respiratory neuromotor control. We then investigate the influences that GABAergic and glycinergic neurotransmission has on two major developmental neuromotor disorders: Rett syndrome and spastic cerebral palsy. We present these two syndromes in order to contrast the approaches to disease mechanism and therapy. While both conditions have motor dysfunctions at their core, one condition Rett syndrome, despite having myriad symptoms, has scientists focused on the breathing abnormalities and their alleviation—to great clinical advances. By contrast, cerebral palsy remains a scientific quagmire or poor definitions, no widely adopted model and a lack of therapeutic focus. We conclude that the sheer abundance of diversity of inhibitory neurotransmitter targets should provide hope for intractable conditions, particularly those that exhibit broad spectra of dysfunction—such as spastic cerebral palsy and Rett syndrome.

Keywords: motor neuron; GABA; glycine; spasticity; cerebral palsy; Rett syndrome

1. Introduction

The motor system is a complex assembly of the nervous system, skeleton and skeletal muscle in order to effect movement. Movement in the neuromotor sense includes life-sustaining behavioural activities such as ventilation [1] and mastication/deglutition [2] and more goal-oriented activities such as locomotion and execution of fine and gross motor skills [3–6]. In humans and many other animals, the neuromotor system is essential for communication [7].

The prime effector of the motor system is the motor unit, comprising an individual motor neuron (MN) and all the muscle fibres it innervates [8]. Motor units are generally classified as either slow or fast fatigue-resistant (type S and FR), or fast fatigueable (type FF), with the former comprising smaller MN innervating type I or IIa skeletal muscle fibres and the latter units comprising larger MNs innervating type IIx/b skeletal muscle fibres [9,10]. Recruitment of motor units is related to MN surface area, such that smaller MNs (with higher input resistance and lower capacitance) are recruited before larger MNs (low input resistance and higher capacitance) [11]. This phenomenon is known as Henneman's Size Principle and underpins the gradations of force/torque production and fatigueability of muscular contractions to the desired behaviour [10].

Despite the cortical and pattern-generator (brainstem or spinal segment) influence on motor unit activation and the interactions of cerebellar and striatal regions on motor output, the MN is eminently capable of neural computation [12,13]. Indeed, the MN is the final common pathway, and receive excitatory (predominantly glutamatergic) inputs and both GABAergic and/or glycinergic inhibitory inputs, amongst a host of other extrinsic and intrinsic excitability modulators [14–30]. A simplified summary of neuromotor

control shows key differences between respiratory and locomotor circuits (Figure 1), with respiratory circuits governed by a centralized pattern/rhythm generator (the pre-Bötzinger complex) [10,31] and locomotor circuits with distributed pattern generation at various segments of the brainstem and spinal cord [32–35].
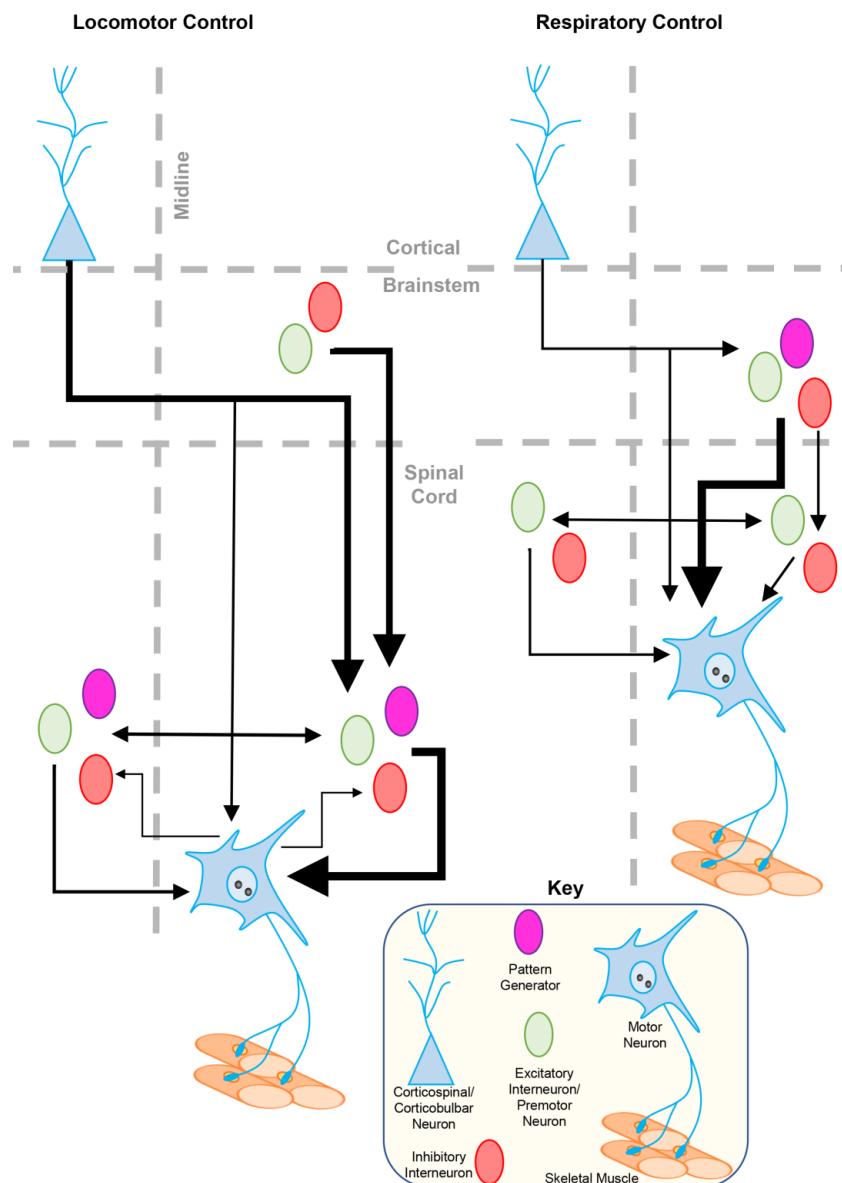

Figure 1. Locomotor and respiratory neuromotor control. In the case of locomotor control, there are corticospinal influences (blue pyramidal neurons) and bulbospinal influences on spinal cord central pattern generators (purple), and inhibitory (red) and excitatory (green) premotor neurons. These segment-level neurons coordinate motor outputs of the ipsilateral and contralateral side via projections. Ipsilateral and contralateral inhibition via circuits formed from recurrent motor axons also provides for coordination within these segments. In the locomotor system, the major inputs to motor neurons (blue neurons innervating skeletal muscle fibres) come from ipsilateral pattern and premotor neurons within the spinal cord segment. For respiratory neuromotor control, pattern generation and premotor excitatory and inhibitory circuits reside primarily in the brainstem, projecting to ipsilateral phrenic motor neurons. There are some segment-level premotor inputs to motor neurons; however, all pattern generation necessary for breathing resides in the brainstem, with a modicum of cortical modulation for a variety of post-inhibitory behaviours (e.g., speech/vocalisation).

It is well-established that a derangement of the balance between excitatory and inhibitory influences, specifically the impairment of synaptic inhibition can lead to a variety of conditions including epilepsy, autism spectrum disorders and schizophrenia [36]. In this review, we focus on the influence of GABAergic and/or glycinergic neurotransmission on motor disorders during development, including Rett syndrome [37] and spastic cerebral palsy, sCP [38]. We compare how Rett syndrome, with attention paid to both locomotor and respiratory motor symptoms and a widely adopted rodent model has an abundance of translatable information and therapeutic horizons, while sCP, with little focus on symptoms and no validated animal model remains plagued by limited understanding. We also outline how strategies aimed at restoring inhibitory activity or reducing excitatory/inhibitory imbalance may be useful in ameliorating symptoms or reducing disease morbidity.

2. Inhibitory Neurotransmission

2.1. GABA- and Glycinergic Neurotransmission

GABA (γ amino butyric acid) has a wide variety of synaptic (i.e., hyperpolarization) and extrasynaptic metabotropic effects on neurons [39–45], in addition to having influences on the immune system, the gastroenteric tract and in particular, pancreatic cells [46–53]. Ionotropic synaptic inhibition is predominantly mediated by transmembrane GABA-A receptors, with some GABA-C receptors present in certain brain regions. By contrast, metabotropic influences of GABA are mediated by GABA-B receptors [39,54]. In the present review, we will mainly focus on the postsynaptic effects mediated by ionotropic GABA-A receptors and drug interactions at GABA-B receptors (Figure 2).
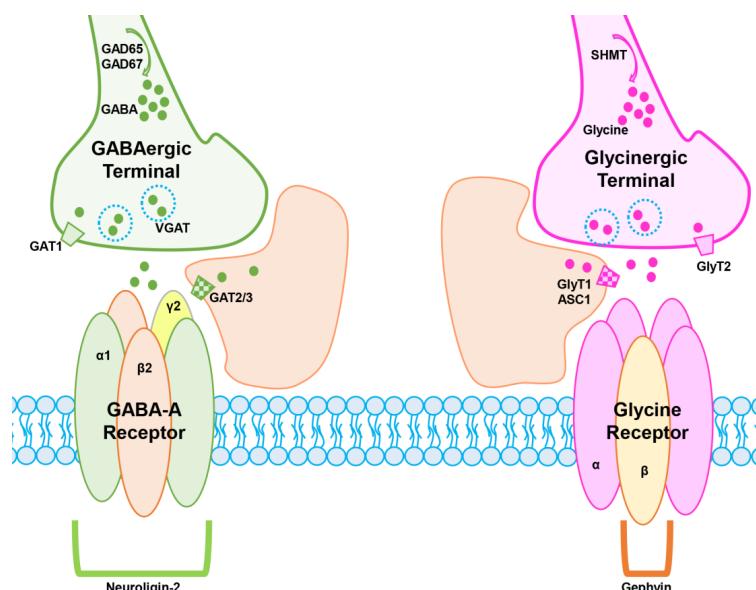

Figure 2. GABAergic and glycinergic synapses. GABA (green circles) is synthesized by GAD65 and GAD67 (green arrow) and packaged into synaptic vesicles by VGAT (blue dashed circles). Upon release into the synaptic cleft, GABA is bound by αβ subunit binding sites (green and orange subunits) at GABA-A receptors. γ subunits (yellow) provide the binding sites for modulators such as benzodiazepines. Following release into the synaptic cleft, GABA reuptake occurs presynaptically via GAT1 (green rhomboid) and in astrocytes (orange) via GAT2/3 (checked green rhomboid). GABA-A receptors are structurally maintained by Neuroligin-2 (green bracket). Glycine (pink circles) is synthesized by serine hydroxymethyltransferase (SHMT—pink arrow) and packaged into synaptic vesicles by VGAT. Upon release into the synaptic cleft glycine is bound by α subunit binding sites (pink subunits) at glycine receptors. Following release into the synaptic cleft, Glycine reuptake occurs presynaptically via GlyT2 (pink rhomboid) and in astrocytes via GlyT1/ASC1 (checked pink rhomboid). β glycine receptor subunits (peach) provide the binding sites for gephyrin (orange bracket) in order to structurally maintain the synapse.

GABA is synthesized from glutamate via the activity of the glutamate decarboxylase (GAD) whose two main isoforms are GAD65 and GAD67 in GABAergic interneurons [55–57]. In mature neocortex, hippocampul, cerebellar and spinal cord dorsal horn GABAergic neurons, GAD67 synthesizes the majority (~90%) of GABA within the cell, whilst GAD65 is found exclusively at presynaptic regions [58–60] (Figure 2). In terminal boutons within the cerebrum, striatum, cerebellum, and spinal cord, GABA is transported into presynaptic vesicles, by the vesicular inhibitory amino acid transporter (VGAT) prior to synaptic release [36,61–63]. In both the cortex and spinal cord, GABA reuptake from the synaptic cleft occurs at presynaptic terminals and astrocytes, with GABA transporter 1 (GAT1) predominating in the former, with astrocytic GAT2/3 providing ~20% of the total cycling [64–67] (Figure 2). GABA release influences the motor system, directly via synaptic inputs on MNs [16,68,69] and indirectly via synaptic inhibition of rhythm and motor pattern generators and supraspinal neuromotor circuits [70–72]. Direct GABAergic inhibition (neuronal hyperpolarisation) is particularly important in the more cranial regions of the central nervous system, such as the cortex, hippocampus, thalamus and brainstem [55,57,71], whereas presynaptic inhibition (i.e., the effect of GABA on the axon terminal, as opposed to the neuron) may play more of a role in the motor and sensory systems, particularly in the lumbar spinal cord [73–77]. Importantly, for the rest of this manuscript we will focus on direct GABAergic hyperpolarisation via GABA receptors, as opposed to presynaptic inhibition which diminishes the likelihood of excitatory presynaptic vesicle release.

Actions of GABA-A receptors are not uniform, with certain subtypes responsible for the synaptic fast acting phasic inhibition, with other subtypes mostly found in extrasynaptic tonically acting receptors [78,79]. The major subunit types of GABA-A receptors are the α, β, γ and δ, with each synaptic GABA-A receptor isoform a pentameric combination of subunits, with the majority containing two pairs of α/β dimers and one other subunit, usually γ [80] (Figure 2). Different GABA-A subtypes comprising different receptor subunit and splice variants exhibit marked pharmacological and pharmacokinetic variances. The major dimer α/β combination binds GABA [79,80], while the α/γ site binds GABA allosteric modulators such as benzodiazepines [81,82] (discussed later). Each subunit exhibits splice variants [80]; however, in homogenized mouse brain the majority of synaptic GABA-A receptors are $\alpha_1\beta_2\gamma_1$ [80,83], although α_2 combinations more prevalent in the spinal cord [84] and MNs [85], with further complexity of isoforms likely to be evident during development. Extrasynaptic GABA-A receptors include a δ subunit, often with an α_4 or α_6, which have higher affinities to GABA compared to other α/β dimers [79] (Figure 2). In the hippocampus, extrasynaptic α_5 subunits are involved in tonic inhibition and may also redistribute to synaptic areas in an activity-dependent manner [86]. Stabilisation of GABA-A receptors to the postsynaptic membrane is accomplished by Neuroligin-2 which form a trans-synaptic scaffold with presynaptic elements [87,88] (Figure 2).

2.2. Glycinergic Neurotransmission

Glycinergic inhibitory synaptic transmission is prevalent in the brainstem and spinal cord [17,21,22,89–98], although some other brain areas also demonstrate functional glycinergic transmission [90]. The ionotropic actions of glycinergic neurotransmission are mediated by the glycine receptor (Figure 2) and plays an important role in modulating motor patterns and motor circuit interneurons and MNs [90,99–101]. Despite presynaptic actions of glycine being an important modulator of neural activity, in this review, we will concern ourselves with synaptic inhibition of neurons via action at the glycine receptor, resulting in chloride mediated hyperpolarization [102] (Figure 2).

Glycine is synthesized by serine hydroxymethyltransferase within mitochondria, and like GABA, is bound in presynaptic vesicles by VGAT [36,61–63]. Subsequent to release, glycine reuptake from the synaptic cleft occurs at astrocytes and presynaptic terminals, with glycine transporter 1 (GlyT1) predominating in the former, with GlyT2 predominating at presynaptic release sites [103,104] and being the only reliable marker of glycinergic neurons [105] (Figure 2). In addition, the alanine–serine–cysteine-1 transporter (ASC1)

also plays a role in astrocytic and neuronal reuptake [106,107], potentially distinct from those of GlyT1 and GlyT2 [105]. Corelease and or mixed release of GABA and glycine and inhibitory synapses is not uncommon within the brainstem and spinal cord [96,108, 109]. As mentioned, the vesicular co-transporter of GABA and glycine, VGAT transports GABA and/or glycine to axon terminals prior to exocytosis—providing the mechanism for inhibitory co-release [36,61–63]. In cases where mixed release occurs, GABA predominates over glycine with regards to affinity to VGAT [61,62,110].

Glycine receptors are transmembrane proteins arranged as a pentamer of subunits (α [four], containing the ligand binding site and β) surrounding a pore, with the majority of fast inhibition occurring with the combinations of α_1 and a β heteromer [102,111,112]. Alternative α subunits exhibiting altered pharmacokinetics [102,111], while the β subunit is responsible for interacting with gephyrin, which anchors the glycine receptor the synapse [113,114]. Beyond, glycine, glycine receptors do exhibit affinities for other amino acids and for GABA [115,116].

Clearly, from the complex interactions between GABA and glycine release, the nature of their receptors and their locations within the neuraxis there are many roles for inhibitory neurotransmission in the pathogenesis and/or treatment of various motor disorders. However, the elucidation of specific developmental disease or drug effects is hindered by the marked effects on neural and other organ development that GABA and glycine exert and the interplay between developmental chloride homeostasis and the depolarizing or hyperpolarizing actions of GABA and glycine at synapses.

2.3. Developmental Aspects of GABA and Glycine as Signalling Molecules and Neurotransmitters

GABA and glycine seem to have potent cell signalling effects during pre- and postnatal development independent of their role in synaptic neurotransmission. However, the precise nature of these cell-signalling pathways is obscured by the germline mutation loss of function approaches used in many developmental models of altered GABA and/or glycine. In some cases, elimination of foetal movement may be the trigger for morphological deformations [117,118]. Nonetheless, a variety of mutants examining the role of GABA and/or glycine synthesis, transport or receptor alterations have been used to parse out the distinct roles of altered signalling or altered synaptic activity on the development of the nervous system and other organs.

For GABA, GAD67 is the major GAD isoform in utero and GAD67 knockout mice exhibit marked ~90% loss of GABA [119], displaying cleft palate (~75%) and defects in the abdominal wall (omphalocele, ~45%) [119], while GAD65 knockout mice exhibit only modest ~20% GABA loss with no birth or growth abnormalities [120,121]. In agreement, rats with a deletion of the gene encoding GAD65 (*Gad2*) or the gene encoding GAD67 (*Gad1*), leads to GABA reduction and palate deformation [122], while double GAD65/GAD67 knockout mice exhibit an increased chance of cleft palate, omphalocele and abnormal spine curvature (kyphosis) [123]. In GAD67 knockout mice, GABAergic synaptic transmission is markedly impaired from birth [124,125], influencing MN numbers, morphology and NMJ innervations [124,126], with synaptic defects occurring later in GAD65 knockouts [127,128]. By contrast to GABA synthesis, deficiency in glycine synthesis (a serine hydroxymethyltransferase null mutant) does not seem to have many overt effects [129].

VGAT is highly influential on in utero development, with marked cleft palate, omphalocele and abnormal spine curvature, of a greater extent than those of GAD mutants [117,123,130,131]. These gross developmental morphology defects are likely due to altered foetal movements [117,118,125], in a similar manner to how lung development is impaired when foetal diaphragm muscle or breathing activity is reduced [117,118,132]. In support, despite excess GABA and glycine (i.e., an abundance of "trophic" inhibitory amino acid signalling) in VGAT mice, there is an almost total absence of GABAergic and glycinergic neurotransmission [124,125], with marked effects on MN survival, morphology and muscular innervation [124,133].

GABA receptor subunit knockout mutations have explored the role of GABA-A receptor-mediated synaptic influences on morphology, with β_3, during embryonic development leading to cleft palate deformities [134,135], while γ_2 exhibits a postnatal developmental growth retardation and sensorimotor dysfunction [136]. However, as many of the major α and β subunits exhibit differential expression following postnatal development, in utero effects are not as common as in most other mutations [137]. With regard to the glycine receptors, there are some human hyperekplexia conditions directly tied to mutations in α_1 glycine receptor subunits [138,139]. Knockouts of the α_2 glycine receptors do not exhibit gross morphological deformities or growth restrictions and following the establishment of mature glycine signalling synaptic differences are absent, indicating compensation by other subunits [138,140]. Similarly, knockouts of glycine receptors do not exhibit gross morphological alterations [138,141].

Altered synaptic stabilization molecules are noted for their influence on development. At GABAergic synapses, Neuroligin-2 is predominantly associated with neurobehavioural disorders, including autism and attention deficit hyperactivity disorder and reduced GABAergic inhibitory neurotransmission [142–144]. By contrast, the gephyrin mutant, which lacks the glycine receptor binding and destabilization has a phenotype at birth, with marked startle responses and death from respiratory muscle dysfunction [145,146]. In gephyrin deficient mice, there is an almost total absence of glycinergic neurotransmission, which is not compensated for by GABAergic transmission (which remains functional) [17,133,147] alongside severe effects on MN survival, morphology and muscular innervation [133]. These results are also suggestive of different postsynaptic roles for gephyrin at GABAergic and glycinergic synapses, which may also depend on neural region [148,149] and pathophysiological factors [150]. Additional roles for gephyrin impairment in various behavioural brain disorders have also been postulated [151].

Altered ligand reuptake by GABA transporters (GAT1) for GABA, and ASC1 for glycine have impaired inhibitory neurotransmission, with the motor phenotype more pronounced in GlyT2 and ASC1 mutants than in the GABA reuptake mutants [152–157]. Notably, the severity of the phenotypes of many of these reuptake mutants is dependent on developmental timing, with different transporter expression and differential salience of GABA and glycinergic neurotransmission at different ages [71,105,158,159].

2.4. Developmental Aspects of Chloride Channel Expression

In utero, and during early postnatal development the ionotropic neurotransmitter actions of GABA and glycine are depolarizing, rather than hyperpolarizing [160,161]. This is due to the differential regulation of chloride cotransporters. In immature neurons, the expression of Na$^+$-K$^+$-Cl$^-$ cotransporter 1 (NKCC1) is elevated compared to K$^+$-Cl$^-$ cotransporter 2 (KCC2) [161,162]. NKCC1 increased intracellular chloride, thus when the ligand binding opens the chloride pore at GABAergic and glycinergic synapse, chloride efflux occurs, depolarizing the neuron [163] (Figure 3). By contrast, in mature neurons, KCC2 transporters are highly expressed, with a relatively low intracellular chloride concentration resulting in the influx of chloride following ligand binding at GABAergic and glycinergic synapses and neuronal hyperpolarisation [163,164] (Figure 3).

The temporal and spatial nature of NKCC1 to KCC2 maturation has been a topic of intense interest and may be different between GABAergic and glycinergic systems [112, 160,165]. For GABA, maturation seems to occur in a caudo-rostral fashion, with maturation occurring first in the spinal cord [166], followed by the brainstem [167], cerebellum [168], hippocampus [169,170] and then the cortex [171]. At glycinergic synapses, maturation seems to occur at similar times throughout the neuraxis [112,160,165–167,172–174].
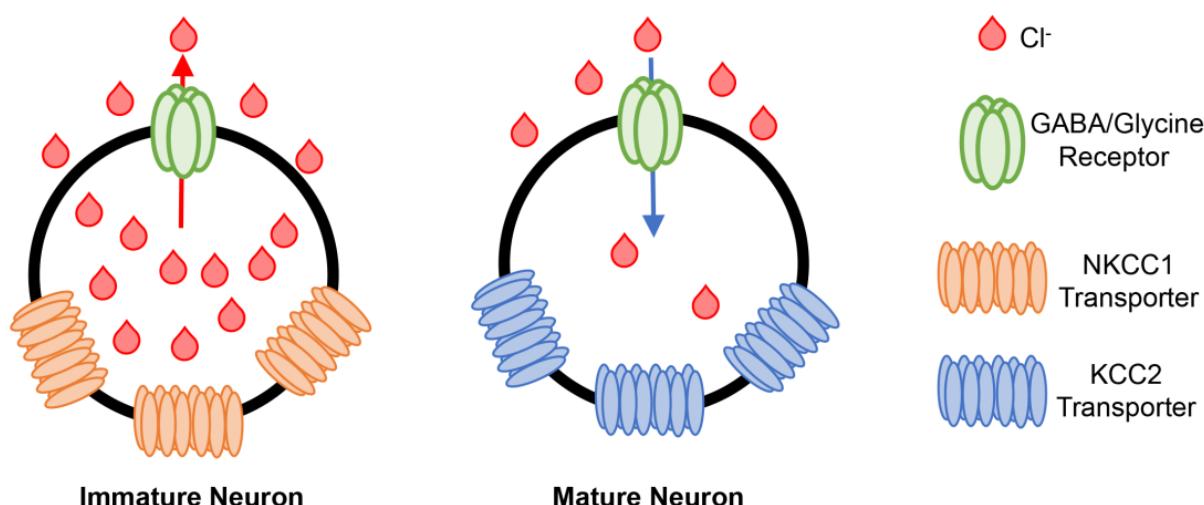
Figure 3. Maturation of neuronal chloride transporters. In immature neurons, chloride (Cl⁻, red drops) concentrations are higher intracellularly due to the expression of immature NKCC2 transporter (orange). When the ion pore of GABAergic or glycinergic synapses is opened (green), chloride efflux (red arrow) occurs depolarizing the neuron. In mature neurons, intracellular chloride concentration is low, due to the expression of the mature KCC2 transporter (blue). When the ion pore of GABAergic of glycinergic synapses is opened chloride influx occurs (blue arrow), hyperpolarizing the neuron.

Intriguingly, from a pathophysiological perspective, a variety of conditions alter the expression of these chloride transporters, including Alzheimer's disease [175,176], anaesthesia [177], autism [175,178,179], epilepsy [167,175,180–183], Huntington's disease [175,184–187], Rett syndrome [178,188], schizophrenia [175,189,190] and traumatic brain and spinal cord injury [181,191–195].

In addition to chloride, GABAergic receptor channels are permeable to bicarbonate (HCO_3^-), generated as part of the cellular carbon dioxide (CO_2) conversion [196]. When the GABA ionic pore is open, this causes bicarbonate efflux, depolarizing the neuron [197]. Under standard conditions, the permeability of chloride is ~4–5 times greater than that of bicarbonate [198]. Under certain conditions, such as seizures or when there is an excessive period of chloride permeable channel opening, there may be a dissipation [199,200] or reversal [201] of the chloride gradient, leading to depolarization of the neuron due to the bicarbonate efflux [197,202]. In the context of many neurodevelopmental disorders, bicarbonate action is understudied and may be a fruitful direction of investigation in conditions of intractable excitation/inhibition imbalance.

3. Inhibitory Influences on Rett Syndrome

3.1. Rett Syndrome

Rett syndrome is an early-onset neurological disorder that commences between 6–18 months of age [203,204]. These children exhibit typical neural motor and language development until this period, with the stark arrest of typical developmental milestones and the onset of symptoms including hand-stereotypies, breathing and gait abnormalities coinciding with growth reduction—particularly of the head [203]. By 4–7 years old, children with Rett syndrome have motor and cognitive deficits that will continue throughout their lifespan [203] in addition to a variety of neurobehavioural issues consistent with autism [203]. There is a direct genetic link for Rett syndrome, a mutation in the X-linked *MECP2* gene [205], with females overwhelmingly more likely to be affected [203,206]. The *MECP2* gene is highly expressed in neurons and is essential for neuronal development and in the establishment of synaptic connections [207], with normal function involving both repression (via binding to methylated DNA) or activation of gene transcription [208]. Mutated *MECP2* results in impaired *MECP2* protein synthesis and a lack of repression/promotion

activities. The developmental onset of *MECP2* expression during the postnatal period is contemporaneous with central nervous system maturation [209,210], and closely matched the timing of initial Rett syndrome symptoms [207]. However, in Rett syndrome there are many individual *MECP2* mutations, neither necessary nor sufficient for diagnosis [211,212]. Males that are affected develop the syndrome extremely rapidly (within a few days post-partum) and die within 2 years [206,213]. Recently, there have been major advancements in the amelioration of Rett syndrome via growth factors (IGF1), *MECP2* gene transfer, genetic corrections and approaches focusing on downstream targets in rodent models and human trials [207,214–219]. Despite these promising advances targeting *MECP2* and its related downstream protein, there remains an influence on Rett syndrome symptoms of altered inhibitory neurotransmission on the motor phenotypes and altered chloride homeostasis [220]. A richer understanding of the involvement of inhibitory neurotransmission and altered chloride homeostasis may pave the way for alternative therapeutic interventions in cases where genetic approaches are precluded or the nature of specific individual patient mutations are unknown.

3.2. Limb and Respiratory Neuromotor Deficits in Rett Syndrome and Their Relationships to Inhibitory Neurotransmission

As noted above, even in a simplified context, there are many mediators of motor control prior to their convergence on the motor unit as the final common pathway (Figure 1). In addition, much of respiratory neuromotor control is misattributed to the autonomic nervous system. Insights into the specific movement dysfunctions of the limb, respiratory and respiratory associated (including speech, cough [1,221,222]) neuromotor behaviours may uncover overlooked aspects of inhibitory influences on Rett syndrome. Indeed, in Rett syndrome patients and in *MECP2* models, reduced GABA-A receptor expression is evident [223,224], although excitation/inhibition imbalances appear to be region specific [220]. Curiously, mutation of *MECP2* in exclusively VGAT-expressing cells (i.e., inhibitory interneurons—see above), recapitulates the Rett syndrome phenotype [225]. When *MECP2*-deficient mice have *MECP2* rescued in exclusively VGAT-expressing cells a substantial improvement of Rett syndrome related symptoms ensues [226]. In patient neurons derived from induced pleuripotent stem cells, GABAergic dysfunction is also evident, further underscoring the importance of inhibitory deficits in Rett syndrome [225].

Limb associated motor dysfunctions may be under greater influence by corticospinal pathways than those of respiratory or respiratory associated motor dysfunctions [10] (Figure 1). Excessive inhibition in the motor cortex in *MECP2* models [216,227,228] is not found in patients, which exhibit cortical hyperexcitability [229,230]. Despite there being difficulties in localizing specific pathophysiologies of motor stereotypies, reduced GABA in cingulate and striatal regions were associated with a patient population with complex motor stereotypies [231]. Motor stereotypies in mice have been associated with altered Neuroligin-2 expression, further underscoring the importance of inhibitory neurotransmission and the motor dysfunctions [232]. Overall, despite some differences between *MECP2* models and the human scenario, therapeutic approaches involving inhibitory modulation may prove beneficial in the limb dysfunctions observed in Rett syndrome.

The potent influence of inhibitory neurotransmission underlies many aspects of the rhythmic nature of breathing [72,99,233–236] and the coordination of breathing with other activities [2,10,237]. Considerable attention has been paid to respiratory neuromotor dysfunction in Rett syndrome, with breathing disturbances, alongside coordination of breathing problems (i.e., swallowing, speech, etcetera) common across patients and *MECP2* models [37,203,238–246]. Importantly, breathing dysfunctions occur during periods of wakefulness and sleep, with cessation of breathing during awake states not necessarily apnoeas [37,247,248], but prolonged breath-holds [37,240,246,248] that more closely resembling Valsalva manoeuvres [37]. By contrast, during sleep, obstructive sleep apnoeas are more prevalent [245,249–254]. It is not currently known as to whether the intensity of the Valsalva-like activation of the diaphragm muscle mirrors the maximum magnitudes of

pressure generation observed in adults [37], which exhibit transdiaphragmatic pressures ~10 times that of eupnoea [10,255–257], but if it is of sufficient magnitude, it may indicate that activation of type S, type FR and type FF motor units is altered in an arousal-dependent manner in Rett syndrome. Studies in *MECP2* mice indicate that these breathing abnormalities may be related to post-inspiratory phase of breathing via altering the activity of the Kölliker-Fuse nucleus, the nucleus tractus solitarius and the ventrolateral medulla (see [37] for an excellent summary of the *MECP2* discoveries of breathing circuit abnormalities) and reduced inhibitory inputs to various respiratory associated brainstem regions [220,258–261]. Of particular relevance to inhibitory pathways, a discoordinated relationship between hypoglossal MNs and the post-inspiratory phase and disinhibition of related circuits is observed in *MECP2* models [262,263] and is consistent with altered speech and swallowing control [264] in Rett syndrome [37,265–267]. Improvement of GABAergic signalling in *MECP2* mice appears to restore normal breathing [258,268,269].

Alongside the major limitations for speech when discoordination of the lingual and oropharyngeal muscles and the post-inspiratory phase occur, dysphagia and aspiration present major health concerns for Rett syndrome patients [267,270,271]. Indeed, pneumonias are the primary morbidity and mortality indicated in Rett [271–273]. Rett syndrome is not coupled to ineffective airway clearance reflexes [267], although no evaluation of airway clearance pressures has been performed.

In summary, despite clear evidence of inhibitory influences on the pathophysiology of Rett neuromotor dysfunctions, specific interventions remain few and far between. With time, evaluation of a variety of GABAergic and glycinergic agents aimed at improving the regularity of respiratory and oromotor associated neuromotor circuit discharge (Figure 1) may yield major advances for patient quality of life.

3.3. Chloride Homeostasis in Rett Syndrome

Due to the developmental nature and the large degree of symptomatic heterogeneity observed in Rett syndrome, various mechanisms of spatio-temporal governing of neural circuit function have been proposed as disease-influencing. One such mechanism is the shift in neuronal intracellular chloride concentration from high to low via the mature expression of KCC2. Notably, KCC2-deficient mice exhibit similar pathologies of breathing abnormalities, lower body mass and impaired cognition and memory to those of *MECP2* models [274–276]. In Rett syndrome, KCC2 levels are altered in patients, neurons derived from patient induced pluripotent stem cells and the *MECP*2 model [178,188,277–279], with suggestions that KCC2 is downstream of *MECP2* [280], or reduced *MECP2*-influenced BDNF signalling [281–283] suppresses KCC2 [284], which is reduced in patient neurons derived from induced pluripotent stem cells [278]. Rescuing or enhancing KCC2 in *MECP2* mice or patient induced pluripotent stem cells using a variety of treatments has been shown to be a feasible approach [285,286]. Overall, aside from the major genetic contribution (~80%) of *MECP2* to Rett Syndrome, patients with and without the mutation have a reduction in the abundance and perhaps the maturation of inhibitory neurotransmission, independent and dependent of *MECP2*.

4. Inhibitory Influences on Spastic Cerebral Palsy

4.1. Spastic Cerebral Palsy

Cerebral palsy is the most common childhood motor disability [287–290], with ~80% of clinical presentations involving spasticity (sCP) [38,290,291]. Despite the aetiology of sCP being a topic of intense debate [38,292–299], the symptoms, therapeutic interventions and the timing of syndrome onset is consistent with a major influence of inhibitory neurotransmission on sCP [300,301]. Symptomatically, cerebral palsy is characterized by spasticity (sCP), dyskinesias, ataxia, hyper-reflexia and occasionally hypotonia [290,302,303]. Notably, spasticity and hypertonia, defined clinically as the resistance of a muscle to stretch [304–306]. and hyper-reflexia, increased stretch reflex responses, are thought to involve specific disinhibitory mechanisms [300,301,307,308]. Moreover, the timing of the development

of the sCP syndrome is concomitant with the postnatal maturation of chloride channels (NKCC1 to KCC2—see above) throughout the neuraxis [163,309,310]. Motor control is hindered in limb muscles [38,311], with the respiratory muscles and speech often affected due to either weakness or post-inspiratory motor control problems [312,313]. Despite the empirical evidence of inhibitory neurotransmission being a potential key player in the development and symptoms of sCP, an implacable focus of many preclinical studies has remained on perinatal injury and hypoxia, which are neither predictive nor specific for sCP [38,295,299,314]. Nonetheless, an emerging body of evidence in a variety of animal models, with some supporting clues from clinical investigations and therapeutic interventions has uncovered an involvement for inhibitory neurotransmission defects within the spinal cord (and upon MNs) in sCP.

4.2. Animal Models of Cerebral Palsy and Criteria for Validation

By contrast to the highly successful *MECP2* model for Rett syndrome, models of cerebral palsy in general, and sCP in particular, are not widely adopted and most have little resemblance to the clinical scenario. Importantly, a diversity of clinical presentations in Rett syndrome has not hindered the adoption of the *MECP2* model, while the diversity of sCP presentations seems to have spurred a multitude of animal models, all with different goals—from modelling risk factors to modelling symptoms.

As mentioned, models of cerebral palsy fall into two broad categories, namely, models of risk factors and models of symptoms. Some mooted risk factors include perinatal anoxia, perinatal brain injury, perinatal infection, congenital deformity and genetic factors [38, 296,315]. However, some of these risk factors are neither sensitive nor specific to cerebral palsy, for example, brain injury may be present without cerebral palsy, and cerebral palsy may be present without brain injury per se, perhaps due to lack of uniform assessment standards [295,299,316]. Indeed, all the known risk factors besides birth prematurity (with ~75% of cerebral palsy patients having been born premature), display rates of cerebral palsy in <15% of all cases (in utero ischemia/infection/inflammation 12%, stroke < 1%, hypoxia-ischemia encephalopathy 15% and asphyxia 2–10%) [38]. Nonetheless, hypoxia, ischemia, in utero infections and combinations of these have been modelled in rabbits, rats and many other species [38,315,317]. Unsurprisingly, due to the low risk-association with cerebral palsy, most of these models do not recapitulate motor dysfunctions [38,318], spasticity or hypertona [38,318,319], have an excessive mortality rate or deaths shortly following experiments (unlike the clinical scenario, where mortality in associated with symptom severity) [292,319–321] and lack spasticity [38,292,318]. One exception to this general lack of suitability is the rat model of transient occlusion of uterine arteries and intra-amniotic injection of lipopolysaccharide [317,322], which despite high experimental mortality [317], the surviving offspring exhibit locomotor and postural deficits and some indications of spasticity [317], although there seems to be ventriculomegaly, other white and grey matter lesions and cognitive declines that do not match some aspects of clinical sCP [317]. Overall, the risk factor models succeed in providing information about the impact of various lesions on brain development but do little to move the needle of sCP translation.

One model of sCP that has been guided by the natural history of the clinical syndrome is the *Spa* mutant mouse. The *Spa* mice have a mutation in the β subunit of the glycine receptor gene resulting in a splicing error prevalent in the brain and spinal cord [323]. *Spa* mice develop spasticity and hypertonia ~2–4 weeks postnatal [319,323,324], have motor deficits [256,325–329] and restricted growth [319], with mild to moderate mortality rates [319]. Despite this surface suitability, the majority of the sCP research community seems fixated on in utero surgical approaches modelling the poorly defined "brain injury" that has captured much of the clinical imagination [292].

If one considers the major tenets of an animal model to exhibit: (i) the behavioural phenotype; (ii) the pathological phenotype; (iii) the temporal phenotype and (iv) the aetiological mechanism of a particular disease, the *Spa* mouse exemplifies sCP in points i, ii

and iii. Despite this, there is no major association of glycinergic mutations with cerebral palsy, point iv. However, if we expand our definition of aetiology to include disease manipulating mechanisms, then the *Spa* model is clearly one of the better options in our arsenal. Of course, an animal model based on a known risk factor that recapitulates tenets i–iii would be a major breakthrough in sCP research. The remainder of this section of the review will focus on the importance of inhibition, specifically inhibition and its influence on the neuromotor system and symptomatic treatment in clinical sCP and in experimental model approaches.

4.3. Evidence for Inhibitory Deficits in Spastic Cerebral Palsy

As mentioned previously, inhibitory neurotransmission dysfunction in developmental behavioural and psychiatric disorders is well-established [36]. Clinical studies and animal models have shown that dysfunction may involve reduced levels of inhibitory neurotransmitters in cerebro-spinal fluid [330,331], the GABA and/or glycine receptors (reduced expression levels or loss-of-function mutations) [332–334], reduced inhibitory circuit inputs [335–337] and altered chloride channel expression [338–341]. In cerebral palsy, there is evidence of decreased GABA-A receptors in the cerebrospinal fluid [342] and reduced GABA receptor expression in the brainstem, but not the cortex (a further nail in the coffin of the cerebral primacy of the aetiology) [343], deficits in reciprocal inhibition [344–346], suggestions of reduced cortical inhibition [347,348] and a relationship between the of loss of inhibition and the degree of physical motor dysfunction [349]. Together, these scraps of information in sCP patients and in spasticity more generally led to the trial of a various strategies to enhance or compensate for inhibitory dysfunctions.

4.4. Enhancing Inhibition as Therapies in Spastic Cerebral Palsy

Response to treatment has historically been important in the de facto understanding the pathophysiology of many neurological defects. Indeed, in sCP, a multitude of treatments aimed at improving inhibitory neurotransmission or compensating for reduced inhibitory neurotransmission, provide some ersatz mechanistic understanding of the syndrome. These treatments that hint at inhibitory involvement include intrathecal baclofen and benzodiazepines [290,350]. Intrathecal baclofen, a GABA-B receptor agonist [351,352] and mediate some GABA-A activation [353,354] has been used to treat spasticity in general [355] and sCP [356] since the 1980s. It has been shown to reduce spasticity and improve the quality of life of sCP patients, both children and adults, in a variety of trials an meta analyses [357,358], although hypotonicity in unaffected limbs remains a concern [358]. Curiously, despite the recent use of *Spa* mice with a glycine receptor mutation closely mirroring the natural history of sCP [256,292,319,329,359], glycine therapy (which crosses the blood–brain barrier) has not been more widely adopted, despite some promising preliminary studies in sCP patients and other spastic conditions [360].

Benzodiazepines (most notably diazepam) bind to GABA-A receptors [361] and reduce muscle spasticity via inhibiting MNs in patients with sCP [350]. Clinically, improvement post diazepam treatment has been demonstrated [362–364], with nocturnal dosing helping to avoid daytime sedation [364]. Longer-term use of diazepam is somewhat hindered by a building up of tolerance and consequent dosage escalations [365], severe withdrawal effects [365] and concerns regarding dependence and abuse [365,366].

Importantly, the efficacy (although modest in many cases [290]) of these interventions can be interpreted as being consistent with sCP being a disorder of inhibition. Secondly, and perhaps most importantly, the underlying pathophysiology of sCP may reside in the impairments of inhibitory neurotransmission throughout the motor neuraxis; and are valid regardless of the prism through which one views the aetiology of sCP (i.e., brain injury, hypoxia/ischemia and maternal age).

4.5. Motor Neurons and the Spinal Cord as a Locus of Pathophysiology in Spastic Cerebral Palsy

Other clues to the importance of the spinal cord in sCP are in the original description as a cerebro-spinal syndrome (named Little's disease) [367]. Indeed, the inclusion of the spinal cord is evident by descriptions of MN degeneration in patient autopsy [368], reduced motor unit number estimates [369] and a reduction in the grey and white matter of the spinal cord [290,293,370,371]. Notably, in the *Spa* model of early onset spasticity, MN loss is prevalent in the spinal cord, disproportionately afflicting the larger MNs of the phrenic and tibialis anterior motor pools [325–327]. In the rabbit ischemia/hypoxia model, generalized lumbar MN loss was evident, without equivalent loss in the cervical spinal cord [372] was observed perinatally. In this particular study, no attempt was made to determine the size-dependence of loss. Regardless, in leporidae MN size in the first postnatal week is not indicative of motor unit types, as motor unit type dependent expansion of MN and muscle fibre size, in addition to the expression of the full gamut of mature myosin heavy chain isoforms occurs later in development in rodents (which leporidae were once classified) [373–376] and leporidae themselves [377–380]. Interestingly, reducing excitatory AMPA receptor activation in this model restores some function in rabbit ischemia-hypoxia models [381].

The importance of the MN in sCP is not solely related to the rostro-caudal neuroanatomical locus of pathology. As the final common pathway in the motor system, MNs may serve as the ideal site for therapeutic interventions. Indeed, four major therapeutic interventions baclofen injection, dorsal rhizotomy, botulinum toxin type A (BoNTA) and dantrolene are localized to the spinal cord (spinal baclofen and dorsal rhizotomy) and/or motor unit (baclofen and dorsal rhizotomy affecting MNs directly or indirectly, with BoNTA at the NMJ and dantrolene at the skeletal muscle). Perhaps the central nature of the motor unit to the symptoms of sCP is evident in the use of BoNTA as a therapeutic to reduce spasticity in spinal cord injury, stroke and sCP [290,382,383]. Although BoNTA does not influence the inhibition of MNs, it does make use of the motor unit as a final common pathway by blocking the acetylcholine release at the NMJ. Although widely used for sCP [290,383–385], the nature of any developmental effects (on MNs and muscle) that decoupling MN firing from skeletal muscle excitation–contraction coupling is a concern [383], albeit one with a very little mechanistic valuation. In addition, whether repeated dosing of BoNTA leads to exaggerated muscle weakness and atrophy is a source of controversy [383]. Regardless, studies in animals are not performed under conditions of MN loss, nor at stages where developmental myosin is still being expressed in muscle, which represents a major knowledge gap. Dantrolene directly limits skeletal muscle contractility by inhibiting excitation–contraction coupling [351,386] and is advised for those whom centrally acting agents or general sedation may be contraindicated [350]. Improvements in reduced hypertonicity, range of motion, strength (likely due to reduced joint torque) and spasticity are noted [350,387], although outcomes and side-effects, including longer-term weakness remain understudied [290,388].

4.6. Prospects for Progress in Understanding the Pathogenesis and Improving Patient Outcomes in Spastic Cerebral Palsy

Despite cerebral palsy being the most common early onset movement disorder, there has been a remarkable lack of innovation in the therapeutic arena—likely due to the preponderance of the (little) research attention paid to cerebral palsy fixated on modelling perinatal risk factors rather than symptoms. Some attention paid to the pathophysiology of weakness and the roles MN loss or dysfunction may play in the development and progression of sCP is long overdue.

Intriguingly, a size-dependent loss of MNs hints at motor unit specific effects on muscle contractility and fatigue with type FF motor units likely to bear the major phenotypic and symptomatic burden, with type S and FR motor units relatively preserved. This contention holds in the *Spa* mice, where neuromuscular transmission failures and behavioural assessments show deficits or overt weakness, reflective of the action and/or recruitment of

FF motor units [256,327–329]. These findings are consistent with some human investigations, where overt muscle weakness is readily demonstrated [389–391], particularly with increased symptom severity [392] with a conservation of muscular fatigue and endurance properties [390,393,394]. Notably, the integrated muscular function during activities such as walking may be impaired in cerebral palsy due to constant co-activation of antagonistic muscles and/or cardiovascular or respiratory factors [312,391,394,395].

Currently, a "cure" for sCP remains a pipe dream, fuelled by desperation and thwarted by both the heterogeneous nature of the syndrome and perhaps more importantly by ethical considerations amongst the adult398 cerebral palsy community that (rightly) demand a focus in improving their quality of life (see [396,397] for a detailed discussion on this topic). By contrast, a resetting of some research priorities towards maximizing the efficacy and safety of existing therapies (with two major interventions directly involving inhibitory inputs to MNs) or developing uncovering new targets or pharmacological agents that improve inhibitory neurotransmission or neural circuitry within the brain and spinal cord is well past due. Finally, in the absence of a widely adopted and validated (i.e., symptomatic) model of sCP that recapitulates the natural history of the syndrome, we remain incredibly limited in our abilities to rationally test any new interventions. Until we have the creation of a new model or the adoption of the "least-worst" symptomatic proxy (perhaps the *Spa* mouse) any new therapy will be untested and captive to the (quite rightly) risk averse proclivities of clinicians. These approaches we suggest here are agnostic as to disease aetiology and serve to improve the lives of those currently living with cerebral palsy as well as those yet to be born.

5. Conclusions

The abundance of transporter and receptor subtypes of the structures involved in GABAergic and glycinergic neurotransmission should be seen by researchers as an opportunity as opposed to a drawback. The diversity of isoforms, and differences in ligand affinities may prove to multiply the potential therapeutic approaches and targets designed to arrest excitation/inhibition imbalance and disorders of inhibition. In two developmental neuromotor disease contexts, Rett and sCP, intuitive approaches to limiting disinhibition or more mechanistic approaches aimed at restoring the correct maturational factor involved in inhibitory neurotransmission show promise. Despite these advances, in sCP symptomatic therapies remain a matter of guesswork without a widely adopted and validated symptomatic model. By contrast, great strides in Rett syndrome have been made despite the imperfections of the *MECP2* model, due to the fields focus on the restoration of a clear clinically important phenotype—namely breathing. It is this author's opinion that the clarity that we have regarding the circuit control of the respiratory neuromotor system provides a stable backdrop for the evaluation of the pathophysiology and potential therapies for a variety of developmental and degenerative neuromotor diseases.

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References

1. Fogarty, M.J.; Sieck, G.C. Diaphragm muscle adaptations in health and disease. *Drug Discov. Today Dis. Model.* **2019**, *in press*. [CrossRef] [PubMed]
2. Pitts, T.; Iceman, K.E. Deglutition and the Regulation of the Swallow Motor Pattern. *Physiology* **2023**, *38*, 10–24. [CrossRef] [PubMed]
3. Bennett, M.R.; Hacker, P.M. The motor system in neuroscience: A history and analysis of conceptual developments. *Prog. Neurobiol.* **2002**, *67*, 1–52. [CrossRef] [PubMed]

4. Hultborn, H.; Nielsen, J.B. Spinal control of locomotion—from cat to man. *Acta Physiol.* **2007**, *189*, 111–121. [CrossRef]

5. Kiehn, O. Decoding the organization of spinal circuits that control locomotion. *Nat. Rev. Neurosci.* **2016**, *17*, 224–238. [CrossRef]

6. Grillner, S.; Wallen, P.; Saitoh, K.; Kozlov, A.; Robertson, B. Neural bases of goal-directed locomotion in vertebrates–an overview. *Brain Res. Rev.* **2008**, *57*, 2–12. [CrossRef]

7. Maas, E. Speech and nonspeech: What are we talking about? *Int. J. Speech Lang. Pathol.* **2017**, *19*, 345–359. [CrossRef]

8. Eccles, J.C.; Sherrington, C.S. Numbers and contraction values of individual motor units examined in some muscles of the limb. *Am. J. Physiol.* **1930**, *253*, 210–218.

9. Schiaffino, S.; Reggiani, C. Fiber types in mammalian skeletal muscles. *Physiol. Rev.* **2011**, *91*, 1447–1531. [CrossRef]

10. Fogarty, M.J.; Sieck, G.C. Evolution and Functional Differentiation of the Diaphragm Muscle of Mammals. *Compr. Physiol.* **2019**, *9*, 715–766.

11. Henneman, E.; Somjen, G.; Carpenter, D.O. Functional significance of cell size in spinal motoneurons. *J. Neurophysiol.* **1965**, *28*, 560–580. [CrossRef] [PubMed]

12. Powers, R.K.; Elbasiouny, S.M.; Rymer, W.Z.; Heckman, C.J. Contribution of intrinsic properties and synaptic inputs to motoneuron discharge patterns: A simulation study. *J. Neurophysiol.* **2012**, *107*, 808–823. [CrossRef] [PubMed]

13. Powers, R.K.; Heckman, C.J. Synaptic control of the shape of the motoneuron pool input-output function. *J. Neurophysiol.* **2017**, *117*, 1171–1184. [CrossRef] [PubMed]

14. Yokota, K.; Kubota, K.; Kobayakawa, K.; Saito, T.; Hara, M.; Kijima, K.; Maeda, T.; Katoh, H.; Ohkawa, Y.; Nakashima, Y.; et al. Pathological changes of distal motor neurons after complete spinal cord injury. *Mol. Brain* **2019**, *12*, 4. [CrossRef] [PubMed]

15. Rana, S.; Mantilla, C.B.; Sieck, G.C. Glutamatergic Input Varies with Phrenic Motor Neuron Size. *J. Neurophysiol.* **2019**, *122*, 1518–1529. [CrossRef] [PubMed]

16. Fogarty, M.J.; Hammond, L.A.; Kanjhan, R.; Bellingham, M.C.; Noakes, P.G. A method for the three-dimensional reconstruction of Neurobiotin-filled neurons and the location of their synaptic inputs. *Front. Neural. Circuits* **2013**, *7*, 153. [CrossRef] [PubMed]

17. Fogarty, M.J.; Kanjhan, R.; Bellingham, M.C.; Noakes, P.G. Glycinergic Neurotransmission: A Potent Regulator of Embryonic Motor Neuron Dendritic Morphology and Synaptic Plasticity. *J. Neurosci.* **2016**, *36*, 80–87. [CrossRef]

18. Rozani, I.; Tsapara, G.; Witts, E.C.; Deaville, S.J.; Miles, G.B.; Zagoraiou, L. Pitx2 cholinergic interneurons are the source of C bouton synapses on brainstem motor neurons. *Sci. Rep.* **2019**, *9*, 4936. [CrossRef]

19. Buls Wollman, L.; Clarke, J.; DeLucia, C.M.; Levine, R.B.; Fregosi, R.F. Developmental Nicotine Exposure Alters Synaptic Input to Hypoglossal Motoneurons and Is Associated with Altered Function of Upper Airway Muscles. *eNeuro* **2019**, *6*, 1–17. [CrossRef]

20. Thakre, P.P.; Bellingham, M.C. Capsaicin Enhances Glutamatergic Synaptic Transmission to Neonatal Rat Hypoglossal Motor Neurons via a TRPV1-Independent Mechanism. *Front. Cell. Neurosci.* **2017**, *11*, 383. [CrossRef]

21. Lau, C.; Thakre, P.P.; Bellingham, M.C. Alfaxalone Causes Reduction of Glycinergic IPSCs, but Not Glutamatergic EPSCs, and Activates a Depolarizing Current in Rat Hypoglossal Motor Neurons. *Front. Cell. Neurosci.* **2019**, *13*, 100. [CrossRef]

22. Thakre, P.P.; Bellingham, M.C. Capsaicin causes robust reduction in glycinergic transmission to rat hypoglossal motor neurons via a TRPV1-independent mechanism. *J. Neurophysiol.* **2019**, *121*, 1535–1542. [CrossRef]

23. Bellingham, M.C. Synaptic inhibition of cat phrenic motoneurons by internal intercostal nerve stimulation. *J. Neurophysiol.* **1999**, *82*, 1224–1232. [CrossRef] [PubMed]

24. Ireland, M.F.; Funk, G.D.; Bellingham, M.C. Muscarinic acetylcholine receptors enhance neonatal mouse hypoglossal motoneuron excitability in vitro. *J. Appl. Physiol.* **2012**, *113*, 1024–1039. [CrossRef] [PubMed]

25. Bellingham, M.C.; Berger, A.J. Presynaptic depression of excitatory synaptic inputs to rat hypoglossal motoneurons by muscarinic M2 receptors. *J. Neurophysiol.* **1996**, *76*, 3758–3770. [CrossRef] [PubMed]

26. Singer, J.H.; Bellingham, M.C.; Berger, A.J. Presynaptic inhibition of glutamatergic synaptic transmission to rat motoneurons by serotonin. *J. Neurophysiol.* **1996**, *76*, 799–807. [CrossRef]

27. Lorier, A.R.; Funk, G.D.; Greer, J.J. Opiate-induced suppression of rat hypoglossal motoneuron activity and its reversal by ampakine therapy. *PLoS ONE* **2010**, *5*, e8766. [CrossRef]

28. Parkis, M.A.; Dong, X.; Feldman, J.L.; Funk, G.D. Concurrent inhibition and excitation of phrenic motoneurons during inspiration: Phase-specific control of excitability. *J. Neurosci.* **1999**, *19*, 2368–2380. [CrossRef]

29. Rekling, J.C.; Funk, G.D.; Bayliss, D.A.; Dong, X.W.; Feldman, J.L. Synaptic control of motoneuronal excitability. *Physiol. Rev.* **2000**, *80*, 767–852. [CrossRef]

30. Flynn, J.R.; Conn, V.L.; Boyle, K.A.; Hughes, D.I.; Watanabe, M.; Velasquez, T.; Goulding, M.D.; Callister, R.J.; Graham, B.A. Anatomical and Molecular Properties of Long Descending Propriospinal Neurons in Mice. *Front Neuroanat* **2017**, *11*, 5. [CrossRef]

31. Smith, J.C.; Ellenberger, H.H.; Ballanyi, K.; Richter, D.W.; Feldman, J.L. Pre-Botzinger complex: A brainstem region that may generate respiratory rhythm in mammals. *Science* **1991**, *254*, 726–729. [CrossRef]

32. Leiras, R.; Cregg, J.M.; Kiehn, O. Brainstem Circuits for Locomotion. *Ann. Rev. Neurosci.* **2022**, *45*, 63–85. [CrossRef]

33. Grillner, S.; Kozlov, A. The CPGs for Limbed Locomotion-Facts and Fiction. *Int. J. Mol. Sci.* **2021**, *22*, 5882. [CrossRef] [PubMed]

34. Grillner, S. The execution of movement: A spinal affair. *J. Neurophysiol.* **2021**, *125*, 693–698. [CrossRef] [PubMed]

35. Grillner, S.; El Manira, A. Current Principles of Motor Control, with Special Reference to Vertebrate Locomotion. *Physiol. Rev.* **2020**, *100*, 271–320. [CrossRef] [PubMed]

36. Bolneo, E.; Chau, P.Y.S.; Noakes, P.G.; Bellingham, M.C. Investigating the Role of GABA in Neural Development and Disease Using Mice Lacking GAD67 or VGAT Genes. *Int. J. Mol. Sci.* **2022**, *23*, 7965. [CrossRef] [PubMed]

37. Ramirez, J.M.; Karlen-Amarante, M.; Wang, J.J.; Bush, N.E.; Carroll, M.S.; Weese-Mayer, D.E.; Huff, A. The Pathophysiology of Rett Syndrome With a Focus on Breathing Dysfunctions. *Physiology* **2020**, *35*, 375–390. [CrossRef] [PubMed]

38. Brandenburg, J.E.; Fogarty, M.J.; Sieck, G.C. A Critical Evaluation of Current Concepts in Cerebral Palsy. *Physiology* **2019**, *34*, 216–229. [CrossRef] [PubMed]

39. Shaye, H.; Stauch, B.; Gati, C.; Cherezov, V. Molecular mechanisms of metabotropic GABA(B) receptor function. *Sci. Adv.* **2021**, *7*, eabg3362. [CrossRef]

40. Bowery, N.G.; Smart, T.G. GABA and glycine as neurotransmitters: A brief history. *Br. J. Pharmacol.* **2006**, *147*, S109–S119. [CrossRef] [PubMed]

41. Misgeld, U.; Bijak, M.; Jarolimek, W. A physiological role for GABAB receptors and the effects of baclofen in the mammalian central nervous system. *Prog. Neurobiol.* **1995**, *46*, 423–462. [CrossRef] [PubMed]

42. Dutar, P.; Nicoll, R.A. A physiological role for GABAB receptors in the central nervous system. *Nature* **1988**, *332*, 156–158. [CrossRef]

43. Mueller, A.L.; Taube, J.S.; Schwartzkroin, P.A. Development of Hyperpolarizing Inhibitory Postsynaptic Potentials and Hyperpolarizing Response to Gamma-Aminobutyric Acid in Rabbit Hippocampus Studied Invitro. *J. Neurosci.* **1984**, *4*, 860–867. [CrossRef] [PubMed]

44. Obata, K. The inhibitory action of -aminobutyric acid, a probable synaptic transmitter. *Int. Rev. Neurobiol.* **1972**, *15*, 167–187. [CrossRef] [PubMed]

45. Obata, K.; Ito, M.; Ochi, R.; Sato, N. Pharmacological properties of the postsynaptic inhibition by Purkinje cell axons and the action of gamma-aminobutyric acid on deiters NEURONES. *Exp. Brain Res.* **1967**, *4*, 43–57. [CrossRef] [PubMed]

46. Kasarello, K.; Cudnoch-Jedrzejewska, A.; Czarzasta, K. Communication of gut microbiota and brain via immune and neuroendocrine signaling. *Front. Microbiol.* **2023**, *14*, 1118529. [CrossRef] [PubMed]

47. Auteri, M.; Zizzo, M.G.; Serio, R. GABA and GABA receptors in the gastrointestinal tract: From motility to inflammation. *Pharmacol. Res.* **2015**, *93*, 11–21. [CrossRef] [PubMed]

48. Barragan, A.; Weidner, J.M.; Jin, Z.; Korpi, E.R.; Birnir, B. GABAergic signalling in the immune system. *Acta Physiol.* **2015**, *213*, 819–827. [CrossRef]

49. Hyland, N.P.; Cryan, J.F. A gut feeling about GABA: Focus on GABA(B) receptors. *Front. Pharmacol.* **2010**, *1*, 124. [CrossRef]

50. Ben-Othman, N.; Vieira, A.; Courtney, M.; Record, F.; Gjernes, E.; Avolio, F.; Hadzic, B.; Druelle, N.; Napolitano, T.; Navarro-Sanz, S.; et al. Long-Term GABA Administration Induces Alpha Cell-Mediated Beta-like Cell Neogenesis. *Cell* **2017**, *168*, 73–85.e11. [CrossRef]

51. Hagan, D.W.; Ferreira, S.M.; Santos, G.J.; Phelps, E.A. The role of GABA in islet function. *Front. Endocrinol.* **2022**, *13*. [CrossRef] [PubMed]

52. Sorenson, R.L.; Garry, D.G.; Brelje, T.C. Structural and Functional Considerations of Gaba in Islets of Langerhans—Beta-Cells and Nerves. *Diabetes* **1991**, *40*, 1365–1374. [CrossRef] [PubMed]

53. Shan, Y.; Zhao, J.; Zheng, Y.; Guo, S.; Schrodi, S.J.; He, D. Understanding the function of the GABAergic system and its potential role in rheumatoid arthritis. *Front. Immunol.* **2023**, *14*, 1114350. [CrossRef] [PubMed]

54. Pin, J.P.; Bettler, B. Organization and functions of mGlu and GABA(B) receptor complexes. *Nature* **2016**, *540*, 60–68. [CrossRef]

55. Tremblay, R.; Lee, S.; Rudy, B. GABAergic Interneurons in the Neocortex: From Cellular Properties to Circuits. *Neuron* **2016**, *91*, 260–292. [CrossRef] [PubMed]

56. Benes, F.M.; Berretta, S. GABAergic interneurons: Implications for understanding schizophrenia and bipolar disorder. *Neuropsychopharmacology* **2001**, *25*, 1–27. [CrossRef]

57. Kelsom, C.; Lu, W. Development and specification of GABAergic cortical interneurons. *Cell. Biosci.* **2013**, *3*, 19. [CrossRef]

58. Anwyl, R. Modulation of vertebrate neuronal calcium channels by transmitters. *Brain Res. Brain Res. Rev.* **1991**, *16*, 265–281. [CrossRef]

59. Kaufman, D.L.; Houser, C.R.; Tobin, A.J. Two forms of the gamma-aminobutyric acid synthetic enzyme glutamate decarboxylase have distinct intraneuronal distributions and cofactor interactions. *J. Neurochem.* **1991**, *56*, 720–723. [CrossRef]

60. Eaton, M.J.; Plunkett, J.A.; Karmally, S.; Martinez, M.A.; Montanez, K. Changes in GAD- and GABA- immunoreactivity in the spinal dorsal horn after peripheral nerve injury and promotion of recovery by lumbar transplant of immortalized serotonergic precursors. *J. Chem. Neuroanat.* **1998**, *16*, 57–72. [CrossRef]

61. Chaudhry, F.A.; Reimer, R.J.; Bellocchio, E.E.; Danbolt, N.C.; Osen, K.K.; Edwards, R.H.; Storm-Mathisen, J. The vesicular GABA transporter, VGAT, localizes to synaptic vesicles in sets of glycinergic as well as GABAergic neurons. *J. Neurosci.* **1998**, *18*, 9733–9750. [CrossRef] [PubMed]

62. McIntire, S.L.; Reimer, R.J.; Schuske, K.; Edwards, R.H.; Jorgensen, E.M. Identification and characterization of the vesicular GABA transporter. *Nature* **1997**, *389*, 870–876. [CrossRef] [PubMed]

63. Dumoulin, A.; Rostaing, P.; Bedet, C.; Levi, S.; Isambert, M.F.; Henry, J.P.; Triller, A.; Gasnier, B. Presence of the vesicular inhibitory amino acid transporter in GABAergic and glycinergic synaptic terminal boutons. *J. Cell Sci.* **1999**, *112 Pt 6*, 811–823. [CrossRef]

64. Jin, X.T.; Galvan, A.; Wichmann, T.; Smith, Y. Localization and Function of GABA Transporters GAT-1 and GAT-3 in the Basal Ganglia. *Front. Syst. Neurosci.* **2011**, *5*, 63. [CrossRef] [PubMed]

65. Motiwala, Z.; Aduri, N.G.; Shaye, H.; Han, G.W.; Lam, J.H.; Katritch, V.; Cherezov, V.; Gati, C. Structural basis of GABA reuptake inhibition. *Nature* **2022**, *606*, 820–826. [CrossRef] [PubMed]

66. Zhou, Y.; Danbolt, N.C. GABA and Glutamate Transporters in Brain. *Front. Endocrinol.* **2013**, *4*, 165. [CrossRef] [PubMed]
67. Daemen, M.A.; Hoogland, G.; Cijntje, J.M.; Spincemaille, G.H. Upregulation of the GABA-transporter GAT-1 in the spinal cord contributes to pain behaviour in experimental neuropathy. *Neurosci. Lett.* **2008**, *444*, 112–115. [CrossRef]
68. Guo, H.; Yuan, X.S.; Zhou, J.C.; Chen, H.; Li, S.Q.; Qu, W.M.; Huang, Z.L. Whole-Brain Monosynaptic Inputs to Hypoglossal Motor Neurons in Mice. *Neurosci. Bull.* **2020**, *36*, 585–597. [CrossRef]
69. Curtis, D.R.; Felix, D. GABA and prolonged spinal inhibition. *Nat. New Biol.* **1971**, *231*, 187–188. [CrossRef]
70. Goulding, M.; Bourane, S.; Garcia-Campmany, L.; Dalet, A.; Koch, S. Inhibition downunder: An update from the spinal cord. *Curr. Opin. Neurobiol.* **2014**, *26*, 161–166. [CrossRef]
71. Gamlin, C.R.; Yu, W.Q.; Wong, R.O.L.; Hoon, M. Assembly and maintenance of GABAergic and Glycinergic circuits in the mammalian nervous system. *Neural. Dev.* **2018**, *13*, 12. [CrossRef] [PubMed]
72. Baertsch, N.A.; Baertsch, H.C.; Ramirez, J.M. The interdependence of excitation and inhibition for the control of dynamic breathing rhythms. *Nat. Commun.* **2018**, *9*, 843. [CrossRef] [PubMed]
73. Jiang, J.; Alstermark, B. Not GABA but glycine mediates segmental, propriospinal, and bulbospinal postsynaptic inhibition in adult mouse spinal forelimb motor neurons. *J. Neurosci.* **2015**, *35*, 1991–1998. [CrossRef] [PubMed]
74. Betley, J.N.; Wright, C.V.; Kawaguchi, Y.; Erdelyi, F.; Szabo, G.; Jessell, T.M.; Kaltschmidt, J.A. Stringent specificity in the construction of a GABAergic presynaptic inhibitory circuit. *Cell* **2009**, *139*, 161–174. [CrossRef]
75. Fink, A.J.; Croce, K.R.; Huang, Z.J.; Abbott, L.F.; Jessell, T.M.; Azim, E. Presynaptic inhibition of spinal sensory feedback ensures smooth movement. *Nature* **2014**, *509*, 43–48. [CrossRef]
76. Rudomin, P.; Schmidt, R.F. Presynaptic inhibition in the vertebrate spinal cord revisited. *Exp. Brain Res.* **1999**, *129*, 1–37. [CrossRef]
77. Caron, G.; Bilchak, J.N.; Cote, M.P. Direct evidence for decreased presynaptic inhibition evoked by PBSt group I muscle afferents after chronic SCI and recovery with step-training in rats. *J. Physiol.* **2020**, *598*, 4621–4642. [CrossRef]
78. Glykys, J.; Mody, I. Activation of GABA(A) receptors: Views from outside the synaptic cleft. *Neuron* **2007**, *56*, 763–770. [CrossRef]
79. Bryson, A.; Reid, C.; Petrou, S. Fundamental Neurochemistry Review: GABA(A) receptor neurotransmission and epilepsy: Principles, disease mechanisms and pharmacotherapy. *J. Neurochem.* **2023**. [CrossRef] [PubMed]
80. Sigel, E.; Steinmann, M.E. Structure, function, and modulation of GABA(A) receptors. *J. Biol. Chem.* **2012**, *287*, 40224–40231. [CrossRef]
81. Sigel, E.; Buhr, A. The benzodiazepine binding site of GABAA receptors. *Trends Pharmacol. Sci.* **1997**, *18*, 425–429. [CrossRef]
82. Sigel, E.; Luscher, B.P. A closer look at the high affinity benzodiazepine binding site on GABAA receptors. *Curr. Top Med. Chem.* **2011**, *11*, 241–246. [CrossRef]
83. Benke, D.; Fakitsas, P.; Roggenmoser, C.; Michel, C.; Rudolph, U.; Mohler, H. Analysis of the presence and abundance of GABAA receptors containing two different types of alpha subunits in murine brain using point-mutated alpha subunits. *J. Biol. Chem.* **2004**, *279*, 43654–43660. [CrossRef] [PubMed]
84. Fritschy, J.M.; Brunig, I. Formation and plasticity of GABAergic synapses: Physiological mechanisms and pathophysiological implications. *Pharmacol. Ther.* **2003**, *98*, 299–323. [CrossRef] [PubMed]
85. Carunchio, I.; Mollinari, C.; Pieri, M.; Merlo, D.; Zona, C. GAB(A) receptors present higher affinity and modified subunit composition in spinal motor neurons from a genetic model of amyotrophic lateral sclerosis. *Eur. J. Neurosci.* **2008**, *28*, 1275–1285. [CrossRef]
86. Davenport, C.M.; Rajappa, R.; Katchan, L.; Taylor, C.R.; Tsai, M.C.; Smith, C.M.; de Jong, J.W.; Arnold, D.B.; Lammel, S.; Kramer, R.H. Relocation of an Extrasynaptic GABA(A) Receptor to Inhibitory Synapses Freezes Excitatory Synaptic Strength and Preserves Memory. *Neuron* **2021**, *109*, 123–134.e4. [CrossRef] [PubMed]
87. Varoqueaux, F.; Jamain, S.; Brose, N. Neuroligin 2 is exclusively localized to inhibitory synapses. *Eur. J. Cell. Biol.* **2004**, *83*, 449–456. [CrossRef]
88. Ali, H.; Marth, L.; Krueger-Burg, D. Neuroligin-2 as a central organizer of inhibitory synapses in health and disease. *Sci. Signal* **2020**, *13*, eabd8379. [CrossRef] [PubMed]
89. Takazawa, T.; Choudhury, P.; Tong, C.K.; Conway, C.M.; Scherrer, G.; Flood, P.D.; Mukai, J.; MacDermott, A.B. Inhibition Mediated by Glycinergic and GABAergic Receptors on Excitatory Neurons in Mouse Superficial Dorsal Horn Is Location-Specific but Modified by Inflammation. *J. Neurosci.* **2017**, *37*, 2336–2348. [CrossRef]
90. Legendre, P. The glycinergic inhibitory synapse. *Cell. Mol. Life Sci.* **2001**, *58*, 760–793. [CrossRef]
91. Gradwell, M.A.; Boyle, K.A.; Callister, R.J.; Hughes, D.I.; Graham, B.A. Heteromeric alpha/beta glycine receptors regulate excitability in parvalbumin-expressing dorsal horn neurons through phasic and tonic glycinergic inhibition. *J. Physiol.* **2017**, *595*, 7185–7202. [CrossRef]
92. Anderson, W.B.; Graham, B.A.; Beveridge, N.J.; Tooney, P.A.; Brichta, A.M.; Callister, R.J. Different forms of glycine- and GABA(A)-receptor mediated inhibitory synaptic transmission in mouse superficial and deep dorsal horn neurons. *Mol. Pain* **2009**, *5*, 65. [CrossRef] [PubMed]
93. Takahashi, T.; Momiyama, A. Single-Channel Currents Underlying Glycinergic Inhibitory Postsynaptic Responses in Spinal Neurons. *Neuron* **1991**, *7*, 965–969. [CrossRef]
94. Schneider, S.P.; Fyffe, R.E. Involvement of GABA and glycine in recurrent inhibition of spinal motoneurons. *J. Neurophysiol.* **1992**, *68*, 397–406. [CrossRef] [PubMed]

95. Oleskevich, S.; Alvarez, F.J.; Walmsley, B. Glycinergic miniature synaptic currents and receptor cluster sizes differ between spinal cord interneurons. *J. Neurophysiol.* **1999**, *82*, 312–319. [CrossRef] [PubMed]
96. O'Brien, J.A.; Berger, A.J. Cotransmission of GABA and glycine to brain stem motoneurons. *J. Neurophysiol.* **1999**, *82*, 1638–1641. [CrossRef]
97. Moore, M.J.; Caspary, D.M. Strychnine blocks binaural inhibition in lateral superior olivary neurons. *J. Neurosci.* **1983**, *3*, 237–242. [CrossRef]
98. Tadros, M.A.; Farrell, K.E.; Schofield, P.R.; Brichta, A.M.; Graham, B.A.; Fuglevand, A.J.; Callister, R.J. Intrinsic and synaptic homeostatic plasticity in motoneurons from mice with glycine receptor mutations. *J. Neurophysiol.* **2014**, *111*, 1487–1498. [CrossRef] [PubMed]
99. Hulsmann, S.; Hagos, L.; Eulenburg, V.; Hirrlinger, J. Inspiratory Off-Switch Mediated by Optogenetic Activation of Inhibitory Neurons in the preBotzinger Complex In Vivo. *Int. J. Mol. Sci.* **2021**, *22*, 2019. [CrossRef]
100. Fortuna, M.G.; Kugler, S.; Hulsmann, S. Probing the function of glycinergic neurons in the mouse respiratory network using optogenetics. *Respir. Physiol. Neurobiol.* **2019**, *265*, 141–152. [CrossRef] [PubMed]
101. Shevtsova, N.A.; Busselberg, D.; Molkov, Y.I.; Bischoff, A.M.; Smith, J.C.; Richter, D.W.; Rybak, I.A. Effects of glycinergic inhibition failure on respiratory rhythm and pattern generation. *Prog. Brain Res.* **2014**, *209*, 25–38. [CrossRef] [PubMed]
102. Lynch, J.W. Molecular structure and function of the glycine receptor chloride channel. *Physiol. Rev.* **2004**, *84*, 1051–1095. [CrossRef] [PubMed]
103. Mahendrasingam, S.; Wallam, C.A.; Hackney, C.M. Two approaches to double post-embedding immunogold labeling of freeze-substituted tissue embedded in low temperature Lowicryl HM20 resin. *Brain Res. Brain Res. Protoc.* **2003**, *11*, 134–141. [CrossRef]
104. Poyatos, I.; Ponce, J.; Aragon, C.; Gimenez, C.; Zafra, F. The glycine transporter GLYT2 is a reliable marker for glycine-immunoreactive neurons. *Mol. Brain Res.* **1997**, *49*, 63–70. [CrossRef]
105. Eulenburg, V.; Huelsmann, S. Synergistic Control of Transmitter Turnover at Glycinergic Synapses by GlyT1, GlyT2, and ASC-1. *Int. J. Mol. Sci.* **2022**, *23*, 2561. [CrossRef] [PubMed]
106. Ehmsen, J.T.; Liu, Y.; Wang, Y.; Paladugu, N.; Johnson, A.E.; Rothstein, J.D.; du Lac, S.; Mattson, M.P.; Hoke, A. The astrocytic transporter SLC7A10 (Asc-1) mediates glycinergic inhibition of spinal cord motor neurons. *Sci. Rep.* **2016**, *6*, 35592. [CrossRef] [PubMed]
107. Mesuret, G.; Khabbazzadeh, S.; Bischoff, A.M.; Safory, H.; Wolosker, H.; Hulsmann, S. A neuronal role of the Alanine-Serine-Cysteine-1 transporter (SLC7A10, Asc-1) for glycine inhibitory transmission and respiratory pattern. *Sci. Rep.* **2018**, *8*, 8536. [CrossRef] [PubMed]
108. Jonas, P.; Bischofberger, J.; Sandkuhler, J. Corelease of two fast neurotransmitters at a central synapse. *Science* **1998**, *281*, 419–424. [CrossRef]
109. Russier, M.; Kopysova, I.L.; Ankri, N.; Ferrand, N.; Debanne, D. GABA and glycine co-release optimizes functional inhibition in rat brainstem motoneurons in vitro. *J. Physiol.* **2002**, *541*, 123–137. [CrossRef]
110. Sagne, C.; El Mestikawy, S.; Isambert, M.F.; Hamon, M.; Henry, J.P.; Giros, B.; Gasnier, B. Cloning of a functional vesicular GABA and glycine transporter by screening of genome databases. *FEBS Lett.* **1997**, *417*, 177–183. [CrossRef]
111. Kuhse, J.; Betz, H.; Kirsch, J. The inhibitory glycine receptor: Architecture, synaptic localization and molecular pathology of a postsynaptic ion-channel complex. *Curr. Opin. Neurobiol.* **1995**, *5*, 318–323. [CrossRef] [PubMed]
112. Avila, A.; Nguyen, L.; Rigo, J.M. Glycine receptors and brain development. *Front. Cell. Neurosci.* **2013**, *7*, 184. [CrossRef] [PubMed]
113. Kirsch, J.; Betz, H. The postsynaptic localization of the glycine receptor-associated protein gephyrin is regulated by the cytoskeleton. *J. Neurosci.* **1995**, *15*, 4148–4156. [CrossRef] [PubMed]
114. Kneussel, M.; Betz, H. Receptors, gephyrin and gephyrin-associated proteins: Novel insights into the assembly of inhibitory postsynaptic membrane specializations. *J. Physiol.* **2000**, *525 Pt 1*, 1–9. [CrossRef]
115. Pless, S.A.; Dibas, M.I.; Lester, H.A.; Lynch, J.W. Conformational variability of the glycine receptor M2 domain in response to activation by different agonists. *J. Biol. Chem.* **2007**, *282*, 36057–36067. [CrossRef]
116. Lewis, T.M.; Schofield, P.R.; McClellan, A.M.L. Kinetic determinants of agonist action at the recombinant human glycine receptor. *J. Physiol.* **2003**, *549*, 361–374. [CrossRef] [PubMed]
117. Oh, W.J.; Westmoreland, J.J.; Summers, R.; Condie, B.G. Cleft Palate Is Caused by CNS Dysfunction in Gad1 and Viaat Knockout Mice. *PLoS ONE* **2010**, *5*, e9758. [CrossRef]
118. Tsunekawa, N.; Arata, A.; Obata, K. Development of spontaneous mouth/tongue movement and related neural activity, and their repression in fetal mice lacking glutamate decarboxylase 67. *Eur. J. Neurosci.* **2005**, *21*, 173–178. [CrossRef] [PubMed]
119. Asada, H.; Kawamura, Y.; Maruyama, K.; Kume, H.; Ding, R.G.; Kanbara, N.; Kuzume, H.; Sanbo, M.; Yagi, T.; Obata, K. Cleft palate and decreased brain gamma-aminobutyric acid in mice lacking the 67-kDa isoform of glutamic acid decarboxylase. *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 6496–6499. [CrossRef] [PubMed]
120. Walls, A.B.; Eyjolfsson, E.M.; Smeland, O.B.; Nilsen, L.H.; Schousboe, I.; Schousboe, A.; Sonnewald, U.; Waagepetersen, H.S. Knockout of GAD65 has major impact on synaptic GABA synthesized from astrocyte-derived glutamine. *J. Cerebr. Blood F Met.* **2011**, *31*, 494–503. [CrossRef]
121. Asada, H.; Kawamura, Y.; Maruyama, K.; Kume, H.; Ding, R.; Ji, F.Y.; Kanbara, N.; Kuzume, H.; Sanbo, M.; Yagi, T.; et al. Mice lacking the 65 kDa isoform of glutamic acid decarboxylase (GAD65) maintain normal levels of GAD67 and GABA in their brains but are susceptible to seizures. *Biochem. Biophys. Res. Commun.* **1996**, *229*, 891–895. [CrossRef] [PubMed]

122. Jiang, W.; Kakizaki, T.; Fujihara, K.; Miyata, S.; Zhang, Y.; Suto, T.; Kato, D.; Saito, S.; Shibasaki, K.; Ishizaki, Y.; et al. Impact of GAD65 and/or GAD67 deficiency on perinatal development in rats. *FASEB J.* **2022**, *36*, e22123. [CrossRef] [PubMed]

123. Kakizaki, T.; Oriuchi, N.; Yanagawa, Y. Gad65/Gad67 Double Knockout Mice Exhibit Intermediate Severity in Both Cleft Palate and Omphalocele Compared with Gad67 Knockout and Vgat Knockout Mice. *Neuroscience* **2015**, *288*, 86–93. [CrossRef]

124. Fogarty, M.J.; Kanjhan, R.; Yanagawa, Y.; Noakes, P.G.; Bellingham, M.C. Alterations in hypoglossal motor neurons due to GAD67 and VGAT deficiency in mice. *Exp. Neurol.* **2017**, *289*, 117–127. [CrossRef] [PubMed]

125. Fujii, M.; Arata, A.; Kanbara-Kume, N.; Saito, K.; Yanagawa, Y.; Obata, K. Respiratory activity in brainstem of fetal mice lacking glutamate decarboxylase 65/67 and vesicular GABA transporter. *Neuroscience* **2007**, *146*, 1044–1052. [CrossRef]

126. Fogarty, M.J.; Smallcombe, K.L.; Yanagawa, Y.; Obata, K.; Bellingham, M.C.; Noakes, P.G. Genetic deficiency of GABA differentially regulates respiratory and non-respiratory motor neuron development. *PLoS ONE* **2013**, *8*, e56257. [CrossRef]

127. Muller, I.; Caliskan, G.; Stork, O. The GAD65 knock out mouse—A model for GABAergic processes in fear- and stress-induced psychopathology. *Genes Brain Behav.* **2015**, *14*, 37–45. [CrossRef] [PubMed]

128. Stork, O.; Ji, F.Y.; Kaneko, K.; Stork, S.; Yoshinobu, Y.; Moriya, T.; Shibata, S.; Obata, K. Postnatal development of a GABA deficit and disturbance of neural functions in mice lacking GAD65. *Brain Res.* **2000**, *865*, 45–58. [CrossRef]

129. MacFarlane, A.J.; Liu, X.W.; Perry, C.A.; Flodby, P.; Allen, R.H.; Stabler, S.P.; Stover, P.J. Cytoplasmic serine hydroxymethyltransferase regulates the metabolic partitioning of methylenetetrahydrofolate but is not essential in mice. *J. Biol. Chem.* **2008**, *283*, 25846–25853. [CrossRef]

130. Saito, K.; Kakizaki, T.; Hayashi, R.; Nishimaru, H.; Furukawa, T.; Nakazato, Y.; Takamori, S.; Ebihara, S.; Uematsu, M.; Mishina, M.; et al. The physiological roles of vesicular GABA transporter during embryonic development: A study using knockout mice. *Mol. Brain* **2010**, *3*, 40. [CrossRef]

131. Wojcik, S.M.; Katsurabayashi, S.; Guillemin, I.; Friauf, E.; Rosenmund, C.; Brose, N.; Rhee, J.S. A shared vesicular carrier allows synaptic corelease of GABA and glycine. *Neuron* **2006**, *50*, 575–587. [CrossRef] [PubMed]

132. Inanlou, M.R.; Kablar, B. Contractile activity of skeletal musculature involved in breathing is essential for normal lung cell differentiation, as revealed in Myf5-/-: MyoD-/- embryos. *Dev. Dyn.* **2005**, *233*, 772–782. [CrossRef] [PubMed]

133. Banks, G.B.; Kanjhan, R.; Wiese, S.; Kneussel, M.; Wong, L.M.; O'Sullivan, G.; Sendtner, M.; Bellingham, M.C.; Betz, H.; Noakes, P.G. Glycinergic and GABAergic synaptic activity differentially regulate motoneuron survival and skeletal muscle innervation. *J. Neurosci.* **2005**, *25*, 1249–1259, Erratum in *J. Neurosci.* **2005**, *25*, 3018–3021. [CrossRef] [PubMed]

134. Homanics, G.E.; DeLorey, T.M.; Firestone, L.L.; Quinlan, J.J.; Handforth, A.; Harrison, N.L.; Krasowski, M.D.; Rick, C.E.M.; Korpi, E.R.; Makela, R.; et al. Mice devoid of gamma-aminobutyrate type A receptor beta 3 subunit have epilepsy, cleft palate, and hypersensitive behavior. *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 4143–4148. [CrossRef]

135. Culiat, C.T.; Stubbs, L.J.; Woychik, R.P.; Russell, L.B.; Johnson, D.K.; Rinchik, E.M. Deficiency of the Beta-3 Subunit of the Type-a Gamma-Aminobutyric-Acid Receptor Causes Cleft-Palate in Mice. *Nat. Genet.* **1995**, *11*, 344–346. [CrossRef] [PubMed]

136. Gunther, U.; Benson, J.; Benke, D.; Fritschy, J.M.; Reyes, G.; Knoflach, F.; Crestani, F.; Aguzzi, A.; Arigoni, M.; Lang, Y.; et al. Benzodiazepine-insensitive mice generated by targeted disruption of the gamma 2 subunit gene of gamma-aminobutyric acid type A receptors. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 7749–7753. [CrossRef]

137. Sur, C.; Wafford, K.A.; Reynolds, D.S.; Hadingham, K.L.; Bromidge, F.; Macaulay, A.; Collinson, N.; O'Meara, G.; Howell, O.; Newman, R.; et al. Loss of the major GABA(A) receptor subtype in the brain is not lethal in mice. *J. Neurosci.* **2001**, *21*, 3409–3418. [CrossRef] [PubMed]

138. Schaefer, N.; Vogel, N.; Villmann, C. Glycine receptor mutants of the mouse: What are possible routes of inhibitory compensation? *Front. Mol. Neurosci.* **2012**, *5*, 98. [CrossRef]

139. Shiang, R.; Ryan, S.G.; Zhu, Y.Z.; Hahn, A.F.; Oconnell, P.; Wasmuth, J.J. Mutations in the Alpha-1 Subunit of the Inhibitory Glycine Receptor Cause the Dominant Neurologic Disorder, Hyperekplexia. *Nat. Genet.* **1993**, *5*, 351–358. [CrossRef] [PubMed]

140. Young-Pearse, T.L.; Ivic, L.; Kriegstein, A.R.; Cepko, C.L. Characterization of mice with targeted deletion of glycine receptor alpha 2. *Mol. Cell. Biol.* **2006**, *26*, 5728–5734. [CrossRef]

141. Harvey, R.J.; Depner, U.B.; Wassle, H.; Ahmadi, S.; Heindl, C.; Reinold, H.; Smart, T.G.; Harvey, K.; Schutz, B.; Abo-Salem, O.M.; et al. GlyR alpha3: An essential target for spinal PGE2-mediated inflammatory pain sensitization. *Science* **2004**, *304*, 884–887. [CrossRef] [PubMed]

142. Gibson, J.R.; Huber, K.M.; Sudhof, T.C. Neuroligin-2 deletion selectively decreases inhibitory synaptic transmission originating from fast-spiking but not from somatostatin-positive interneurons. *J. Neurosci.* **2009**, *29*, 13883–13897. [CrossRef] [PubMed]

143. Pohl, T.T.; Hornberg, H. Neuroligins in neurodevelopmental conditions: How mouse models of de novo mutations can help us link synaptic function to social behavior. *Neuronal Signal* **2022**, *6*, NS20210030. [CrossRef] [PubMed]

144. Blundell, J.; Tabuchi, K.; Bolliger, M.F.; Blaiss, C.A.; Brose, N.; Liu, X.; Sudhof, T.C.; Powell, C.M. Increased anxiety-like behavior in mice lacking the inhibitory synapse cell adhesion molecule neuroligin 2. *Genes Brain Behav.* **2009**, *8*, 114–126. [CrossRef]

145. Grosskreutz, Y.; Betz, H.; Kneussel, M. Rescue of molybdenum cofactor biosynthesis in gephyrin-deficient mice by a Cnx1 transgene. *Biochem. Biophys. Res. Commun.* **2003**, *301*, 450–455. [CrossRef] [PubMed]

146. Feng, G.; Tintrup, H.; Kirsch, J.; Nichol, M.C.; Kuhse, J.; Betz, H.; Sanes, J.R. Dual requirement for gephyrin in glycine receptor clustering and molybdoenzyme activity. *Science* **1998**, *282*, 1321–1324. [CrossRef]

147. Levi, S.; Logan, S.M.; Tovar, K.R.; Craig, A.M. Gephyrin is critical for glycine receptor clustering but not for the formation of functional GABAergic synapses in hippocampal neurons. *J. Neurosci.* **2004**, *24*, 207–217. [CrossRef] [PubMed]

148. Liebsch, F.; Eggersmann, F.R.; Merkler, Y.; Kloppenburg, P.; Schwarz, G. Automated Image Analysis Reveals Different Localization of Synaptic Gephyrin C4 Splice Variants. *eNeuro* **2023**, *10*. [CrossRef] [PubMed]

149. Kuljis, D.A.; Micheva, K.D.; Ray, A.; Wegner, W.; Bowman, R.; Madison, D.V.; Willig, K.I.; Barth, A.L. Gephyrin-Lacking PV Synapses on Neocortical Pyramidal Neurons. *Int. J. Mol. Sci.* **2021**, *22*, 10032. [CrossRef]

150. Garcia, J.D.; Gookin, S.E.; Crosby, K.C.; Schwartz, S.L.; Tiemeier, E.; Kennedy, M.J.; Dell'Acqua, M.L.; Herson, P.S.; Quillinan, N.; Smith, K.R. Stepwise disassembly of GABAergic synapses during pathogenic excitotoxicity. *Cell Rep.* **2021**, *37*, 110142. [CrossRef]

151. Tyagarajan, S.K.; Fritschy, J.M. Gephyrin: A master regulator of neuronal function? *Nat. Rev. Neurosci.* **2014**, *15*, 141–156. [CrossRef] [PubMed]

152. Safory, H.; Neame, S.; Shulman, Y.; Zubedat, S.; Radzishevsky, I.; Rosenberg, D.; Sason, H.; Engelender, S.; Avital, A.; Hulsmann, S.; et al. The alanine-serine-cysteine-1 (Asc-1) transporter controls glycine levels in the brain and is required for glycinergic inhibitory transmission. *EMBO Rep.* **2015**, *16*, 590–598. [CrossRef]

153. Yang, P.; Cai, G.; Cai, Y.; Fei, J.; Liu, G. Gamma aminobutyric acid transporter subtype 1 gene knockout mice: A new model for attention deficit/hyperactivity disorder. *Acta Biochim. Biophys. Sin.* **2013**, *45*, 578–585. [CrossRef]

154. Fischer, F.P.; Kasture, A.S.; Hummel, T.; Sucic, S. Molecular and Clinical Repercussions of GABA Transporter 1 Variants Gone Amiss: Links to Epilepsy and Developmental Spectrum Disorders. *Front. Mol. Biosci.* **2022**, *9*, 834498. [CrossRef] [PubMed]

155. Chen, L.; Yang, X.; Zhou, X.; Wang, C.; Gong, X.; Chen, B.; Chen, Y. Hyperactivity and impaired attention in Gamma aminobutyric acid transporter subtype 1 gene knockout mice. *Acta Neuropsychiatr.* **2015**, *27*, 368–374. [CrossRef]

156. Gomeza, J.; Ohno, K.; Hulsmann, S.; Armsen, W.; Eulenburg, V.; Richter, D.W.; Laube, B.; Betz, H. Deletion of the mouse glycine transporter 2 results in a hyperekplexia phenotype and postnatal lethality. *Neuron* **2003**, *40*, 797–806. [CrossRef] [PubMed]

157. Gomeza, J.; Hulsmann, S.; Ohno, K.; Eulenburg, V.; Szoke, K.; Richter, D.; Betz, H. Inactivation of the glycine transporter 1 gene discloses vital role of glial glycine uptake in glycinergic inhibition. *Neuron* **2003**, *40*, 785–796. [CrossRef] [PubMed]

158. Eulenburg, V.; Retiounskaia, M.; Papadopoulos, T.; Gomeza, J.; Betz, H. Glial Glycine Transporter 1 Function Is Essential for Early Postnatal Survival but Dispensable in Adult Mice. *Glia* **2010**, *58*, 1066–1073. [CrossRef] [PubMed]

159. Gao, B.X.; Stricker, C.; Ziskind-Conhaim, L. Transition from GABAergic to glycinergic synaptic transmission in newly formed spinal networks. *J. Neurophysiol.* **2001**, *86*, 492–502. [CrossRef]

160. Ehrlich, I.; Lohrke, S.; Friauf, E. Shift from depolarizing to hyperpolarizing glycine action in rat auditory neurones is due to age-dependent Cl- regulation. *J. Physiol.* **1999**, *520*, 121–137. [CrossRef]

161. Ben-Ari, Y. Excitatory actions of gaba during development: The nature of the nurture. *Nat. Rev. Neurosci.* **2002**, *3*, 728–739. [CrossRef] [PubMed]

162. Owens, D.F.; Kriegstein, A.R. Is there more to GABA than synaptic inhibition? *Nat. Rev. Neurosci.* **2002**, *3*, 715–727. [CrossRef] [PubMed]

163. Delpy, A.; Allain, A.E.; Meyrand, P.; Branchereau, P. NKCC1 cotransporter inactivation underlies embryonic development of chloride-mediated inhibition in mouse spinal motoneuron. *J. Physiol.* **2008**, *586*, 1059–1075. [CrossRef]

164. Baccei, M.L.; Fitzgerald, M. Development of GABAergic and glycinergic transmission in the neonatal rat dorsal horn. *J. Neurosci.* **2004**, *24*, 4749–4757. [CrossRef] [PubMed]

165. Ben-Ari, Y.; Gaiarsa, J.L.; Tyzio, R.; Khazipov, R. GABA: A pioneer transmitter that excites immature neurons and generates primitive oscillations. *Physiol. Rev.* **2007**, *87*, 1215–1284. [CrossRef]

166. Wu, W.L.; Ziskind-Conhaim, L.; Sweet, M.A. Early development of glycine- and GABA-mediated synapses in rat spinal cord. *J. Neurosci.* **1992**, *12*, 3935–3945. [CrossRef]

167. Singer, J.H.; Talley, E.M.; Bayliss, D.A.; Berger, A.J. Development of glycinergic synaptic transmission to rat brain stem motoneurons. *J. Neurophysiol.* **1998**, *80*, 2608–2620. [CrossRef]

168. Brickley, S.G.; Cull-Candy, S.G.; Farrant, M. Development of a tonic form of synaptic inhibition in rat cerebellar granule cells resulting from persistent activation of GABAA receptors. *J. Physiol.* **1996**, *497 Pt 3*, 753–759. [CrossRef]

169. Tyzio, R.; Holmes, G.L.; Ben-Ari, Y.; Khazipov, R. Timing of the developmental switch in GABA(A) mediated signaling from excitation to inhibition in CA3 rat hippocampus using gramicidin perforated patch and extracellular recordings. *Epilepsia* **2007**, *48* (Suppl. S5), 96–105. [CrossRef]

170. Rivera, C.; Voipio, J.; Payne, J.A.; Ruusuvuori, E.; Lahtinen, H.; Lamsa, K.; Pirvola, U.; Saarma, M.; Kaila, K. The K+/Cl- co-transporter KCC2 renders GABA hyperpolarizing during neuronal maturation. *Nature* **1999**, *397*, 251–255. [CrossRef]

171. Owens, D.F.; Boyce, L.H.; Davis, M.B.; Kriegstein, A.R. Excitatory GABA responses in embryonic and neonatal cortical slices demonstrated by gramicidin perforated-patch recordings and calcium imaging. *J. Neurosci.* **1996**, *16*, 6414–6423. [CrossRef] [PubMed]

172. Backus, K.H.; Deitmer, J.W.; Friauf, E. Glycine-activated currents are changed by coincident membrane depolarization in developing rat auditory brainstem neurons. *J. Physiol.* **1998**, *507 Pt 3*, 783–794. [CrossRef]

173. Ito, S.; Cherubini, E. Strychnine-sensitive glycine responses of neonatal rat hippocampal neurones. *J. Physiol.* **1991**, *440*, 67–83. [CrossRef] [PubMed]

174. Song, W.; Chattipakorn, S.C.; McMahon, L.L. Glycine-gated chloride channels depress synaptic transmission in rat hippocampus. *J. Neurophysiol.* **2006**, *95*, 2366–2379. [CrossRef]

175. Lam, P.; Newland, J.; Faull, R.L.M.; Kwakowsky, A. Cation-Chloride Cotransporters KCC2 and NKCC1 as Therapeutic Targets in Neurological and Neuropsychiatric Disorders. *Molecules* **2023**, *28*, 1344. [CrossRef]

176. Lam, P.; Vinnakota, C.; Guzman, B.C.; Newland, J.; Peppercorn, K.; Tate, W.P.; Waldvogel, H.J.; Faull, R.L.M.; Kwakowsky, A. Beta-Amyloid (Abeta(1-42)) Increases the Expression of NKCC1 in the Mouse Hippocampus. *Molecules* **2022**, *27*, 2440. [CrossRef] [PubMed]
177. Cabrera, O.H.; Tesic, V.; Tat, Q.L.; Chastain, S.; Quillinan, N.; Jevtovic-Todorovic, V. Sevoflurane-Induced Dysregulation of Cation-Chloride Cotransporters NKCC1 and KCC2 in Neonatal Mouse Brain. *Mol. Neurobiol.* **2020**, *57*, 1–10. [CrossRef]
178. Duarte, S.T.; Armstrong, J.; Roche, A.; Ortez, C.; Perez, A.; O'Callaghan Mdel, M.; Pereira, A.; Sanmarti, F.; Ormazabal, A.; Artuch, R.; et al. Abnormal expression of cerebrospinal fluid cation chloride cotransporters in patients with Rett syndrome. *PLoS ONE* **2013**, *8*, e68851. [CrossRef]
179. Tyzio, R.; Nardou, R.; Ferrari, D.C.; Tsintsadze, T.; Shahrokhi, A.; Eftekhari, S.; Khalilov, I.; Tsintsadze, V.; Brouchoud, C.; Chazal, G.; et al. Oxytocin-mediated GABA inhibition during delivery attenuates autism pathogenesis in rodent offspring. *Science* **2014**, *343*, 675–679. [CrossRef] [PubMed]
180. Loscher, W.; Puskarjov, M.; Kaila, K. Cation-chloride cotransporters NKCC1 and KCC2 as potential targets for novel antiepileptic and antiepileptogenic treatments. *Neuropharmacology* **2013**, *69*, 62–74. [CrossRef]
181. Kahle, K.T.; Staley, K.J.; Nahed, B.V.; Gamba, G.; Hebert, S.C.; Lifton, R.P.; Mount, D.B. Roles of the cation-chloride cotransporters in neurological disease. *Nat. Clin. Pract. Neurol.* **2008**, *4*, 490–503. [CrossRef] [PubMed]
182. Palma, E.; Amici, M.; Sobrero, F.; Spinelli, G.; Di Angelantonio, S.; Ragozzino, D.; Mascia, A.; Scoppetta, C.; Esposito, V.; Miledi, R.; et al. Anomalous levels of Cl^- transporters in the hippocampal subiculum from temporal lobe epilepsy patients make GABA excitatory. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 8465–8468. [CrossRef]
183. Sen, A.; Martinian, L.; Nikolic, M.; Walker, M.C.; Thom, M.; Sisodiya, S.M. Increased NKCC1 expression in refractory human epilepsy. *Epilepsy Res* **2007**, *74*, 220–227. [CrossRef] [PubMed]
184. Serranilla, M.; Woodin, M.A. Striatal Chloride Dysregulation and Impaired GABAergic Signaling Due to Cation-Chloride Cotransporter Dysfunction in Huntington's Disease. *Front. Cell. Neurosci.* **2022**, *15*, 817013. [CrossRef] [PubMed]
185. Andrews, K.; Josiah, S.S.; Zhang, J. The Therapeutic Potential of Neuronal K-Cl Co-Transporter KCC2 in Huntington's Disease and Its Comorbidities. *Int. J. Mol. Sci.* **2020**, *21*, 9142. [CrossRef]
186. Hsu, Y.T.; Chang, Y.G.; Liu, Y.C.; Wang, K.Y.; Chen, H.M.; Lee, D.J.; Yang, S.S.; Tsai, C.H.; Lien, C.C.; Chern, Y. Enhanced $Na^{(+)}$-$K^{(+)}$-$2Cl^{(-)}$ cotransporter 1 underlies motor dysfunction in huntington's disease. *Mov. Disord.* **2019**, *34*, 845–857. [CrossRef]
187. Dargaei, Z.; Bang, J.Y.; Mahadevan, V.; Khademullah, C.S.; Bedard, S.; Parfitt, G.M.; Kim, J.C.; Woodin, M.A. Restoring GABAergic inhibition rescues memory deficits in a Huntington's disease mouse model. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, E1618–E1626. [CrossRef]
188. Hinz, L.; Torrella Barrufet, J.; Heine, V.M. KCC2 expression levels are reduced in post mortem brain tissue of Rett syndrome patients. *Acta Neuropathol. Commun.* **2019**, *7*, 196. [CrossRef]
189. Arion, D.; Lewis, D.A. Altered expression of regulators of the cortical chloride transporters NKCC1 and KCC2 in schizophrenia. *Arch Gen. Psychiatry* **2011**, *68*, 21–31. [CrossRef]
190. Tao, R.; Li, C.; Newburn, E.N.; Ye, T.; Lipska, B.K.; Herman, M.M.; Weinberger, D.R.; Kleinman, J.E.; Hyde, T.M. Transcript-specific associations of SLC12A5 (KCC2) in human prefrontal cortex with development, schizophrenia, and affective disorders. *J. Neurosci.* **2012**, *32*, 5216–5222. [CrossRef]
191. Talifu, Z.; Pan, Y.; Gong, H.; Xu, X.; Zhang, C.; Yang, D.; Gao, F.; Yu, Y.; Du, L.; Li, J. The role of KCC2 and NKCC1 in spinal cord injury: From physiology to pathology. *Front. Physiol.* **2022**, *13*, 1045520. [CrossRef] [PubMed]
192. Allen, L.L.; Seven, Y.B.; Baker, T.L.; Mitchell, G.S. Cervical spinal contusion alters $Na^{(+)}$-$K(+)$-$2Cl-$ and $K^{(+)}$-$Cl-$ cation-chloride cotransporter expression in phrenic motor neurons. *Respir. Physiol. Neurobiol.* **2019**, *261*, 15–23. [CrossRef] [PubMed]
193. Beverungen, H.; Klaszky, S.C.; Klaszky, M.; Cote, M.P. Rehabilitation Decreases Spasticity by Restoring Chloride Homeostasis through the Brain-Derived Neurotrophic Factor-KCC2 Pathway after Spinal Cord Injury. *J. Neurotraum.* **2020**, *37*, 846–859. [CrossRef] [PubMed]
194. Cote, M.P.; Gandhi, S.; Zambrotta, M.; Houle, J.D. Exercise modulates chloride homeostasis after spinal cord injury. *J. Neurosci.* **2014**, *34*, 8976–8987. [CrossRef] [PubMed]
195. Bilchak, J.N.; Yeakle, K.; Caron, G.; Malloy, D.; Cote, M.P. Enhancing KCC2 activity decreases hyperreflexia and spasticity after chronic spinal cord injury. *Exp Neurol* **2021**, *338*, 113605. [CrossRef] [PubMed]
196. Chesler, M. Regulation and modulation of pH in the brain. *Physiol. Rev.* **2003**, *83*, 1183–1221. [CrossRef]
197. Sallard, E.; Letourneur, D.; Legendre, P. Electrophysiology of ionotropic GABA receptors. *Cell. Mol. Life Sci.* **2021**, *78*, 5341–5370. [CrossRef] [PubMed]
198. Voipio, J.; Kaila, K. GABAergic excitation and $K^{(+)}$-mediated volume transmission in the hippocampus. *Prog. Brain Res.* **2000**, *125*, 329–338. [CrossRef]
199. Staley, K.J.; Proctor, W.R. Modulation of mammalian dendritic GABA(A) receptor function by the kinetics of Cl- and HCO3- transport. *J. Physiol.* **1999**, *519 Pt 3*, 693–712. [CrossRef]
200. Staley, K.J.; Soldo, B.L.; Proctor, W.R. Ionic mechanisms of neuronal excitation by inhibitory GABAA receptors. *Science* **1995**, *269*, 977–981. [CrossRef]
201. Kim, D.Y.; Fenoglio, K.A.; Kerrigan, J.F.; Rho, J.M. Bicarbonate contributes to GABAA receptor-mediated neuronal excitation in surgically resected human hypothalamic hamartomas. *Epilepsy Res.* **2009**, *83*, 89–93. [CrossRef] [PubMed]

202. Cherubini, E.; Gaiarsa, J.L.; Ben-Ari, Y. GABA: An excitatory transmitter in early postnatal life. *Trends Neurosci.* **1991**, *14*, 515–519. [CrossRef] [PubMed]

203. Hagberg, B.; Aicardi, J.; Dias, K.; Ramos, O. A progressive syndrome of autism, dementia, ataxia, and loss of purposeful hand use in girls: Rett's syndrome: Report of 35 cases. *Ann. Neurol.* **1983**, *14*, 471–479. [CrossRef] [PubMed]

204. Rett, A. On a unusual brain atrophy syndrome in hyperammonemia in childhood. *Wien Med Wochenschr* **1966**, *116*, 723–726. [PubMed]

205. Amir, R.E.; Van den Veyver, I.B.; Wan, M.; Tran, C.Q.; Francke, U.; Zoghbi, H.Y. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nat. Genet.* **1999**, *23*, 185–188. [CrossRef]

206. Pascual-Alonso, A.; Martinez-Monseny, A.F.; Xiol, C.; Armstrong, J. MECP2-Related Disorders in Males. *Int. J. Mol. Sci.* **2021**, *22*, 9610. [CrossRef]

207. Luikenhuis, S.; Giacometti, E.; Beard, C.F.; Jaenisch, R. Expression of MeCP2 in postmitotic neurons rescues Rett syndrome in mice. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 6033–6038. [CrossRef]

208. Chahrour, M.; Jung, S.Y.; Shaw, C.; Zhou, X.; Wong, S.T.; Qin, J.; Zoghbi, H.Y. MeCP2, a key contributor to neurological disease, activates and represses transcription. *Science* **2008**, *320*, 1224–1229. [CrossRef] [PubMed]

209. Mullaney, B.C.; Johnston, M.V.; Blue, M.E. Developmental expression of methyl-CpG binding protein 2 is dynamically regulated in the rodent brain. *Neuroscience* **2004**, *123*, 939–949. [CrossRef]

210. Shahbazian, M.D.; Antalffy, B.; Armstrong, D.L.; Zoghbi, H.Y. Insight into Rett syndrome: MeCP2 levels display tissue- and cell-specific differences and correlate with neuronal maturation. *Hum. Mol. Genet.* **2002**, *11*, 115–124. [CrossRef]

211. Percy, A.K.; Lane, J.B.; Childers, J.; Skinner, S.; Annese, F.; Barrish, J.; Caeg, E.; Glaze, D.G.; MacLeod, P. Rett syndrome: North American database. *J. Child. Neurol.* **2007**, *22*, 1338–1341. [CrossRef]

212. Neul, J.L.; Kaufmann, W.E.; Glaze, D.G.; Christodoulou, J.; Clarke, A.J.; Bahi-Buisson, N.; Leonard, H.; Bailey, M.E.; Schanen, N.C.; Zappella, M.; et al. Rett syndrome: Revised diagnostic criteria and nomenclature. *Ann. Neurol.* **2010**, *68*, 944–950. [CrossRef]

213. Schule, B.; Armstrong, D.D.; Vogel, H.; Oviedo, A.; Francke, U. Severe congenital encephalopathy caused by MECP2 null mutations in males: Central hypoxia and reduced neuronal dendritic structure. *Clin. Genet.* **2008**, *74*, 116–126. [CrossRef] [PubMed]

214. Collins, B.E.; Merritt, J.K.; Erickson, K.R.; Neul, J.L. Safety and efficacy of genetic MECP2 supplementation in the R294X mouse model of Rett syndrome. *Genes. Brain Behav.* **2022**, *21*, e12739. [CrossRef] [PubMed]

215. Vermudez, S.A.D.; Gogliotti, R.G.; Arthur, B.; Buch, A.; Morales, C.; Moxley, Y.; Rajpal, H.; Conn, P.J.; Niswender, C.M. Profiling beneficial and potential adverse effects of MeCP2 overexpression in a hypomorphic Rett syndrome mouse model. *Genes. Brain Behav.* **2022**, *21*, e12752. [CrossRef]

216. Tropea, D.; Giacometti, E.; Wilson, N.R.; Beard, C.; McCurry, C.; Fu, D.D.; Flannery, R.; Jaenisch, R.; Sur, M. Partial reversal of Rett Syndrome-like symptoms in MeCP2 mutant mice. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 2029–2034. [CrossRef] [PubMed]

217. Panayotis, N.; Ehinger, Y.; Felix, M.S.; Roux, J.C. State-of-the-art therapies for Rett syndrome. *Dev. Med. Child. Neurol.* **2023**, *65*, 162–170. [CrossRef]

218. Glaze, D.G.; Neul, J.L.; Kaufmann, W.E.; Berry-Kravis, E.; Condon, S.; Stoms, G.; Oosterholt, S.; Della Pasqua, O.; Glass, L.; Jones, N.E.; et al. Double-blind, randomized, placebo-controlled study of trofinetide in pediatric Rett syndrome. *Neurology* **2019**, *92*, e1912–e1925. [CrossRef]

219. Glaze, D.G.; Neul, J.L.; Percy, A.; Feyma, T.; Beisang, A.; Yaroshinsky, A.; Stoms, G.; Zuchero, D.; Horrigan, J.; Glass, L.; et al. A Double-Blind, Randomized, Placebo-Controlled Clinical Study of Trofinetide in the Treatment of Rett Syndrome. *Pediatr. Neurol.* **2017**, *76*, 37–46. [CrossRef]

220. Li, W. Excitation and Inhibition Imbalance in Rett Syndrome. *Front. Neurosci.* **2022**, *16*, 825063. [CrossRef]

221. Fogarty, M.J.; Sieck, G.C. Tongue muscle contractile, fatigue, and fiber type properties in rats. *J. Appl. Physiol.* **2021**, *131*, 1043–1055. [CrossRef]

222. Holstege, G. The periaqueductal gray controls brainstem emotional motor systems including respiration. *Prog. Brain Res.* **2014**, *209*, 379–405. [CrossRef] [PubMed]

223. Samaco, R.C.; Hogart, A.; LaSalle, J.M. Epigenetic overlap in autism-spectrum neurodevelopmental disorders: MECP2 deficiency causes reduced expression of UBE3A and GABRB3. *Hum. Mol. Genet.* **2005**, *14*, 483–492. [CrossRef] [PubMed]

224. Minh, V.C.N.; Du, F.; Felice, C.A.; Shan, X.W.; Nigam, A.; Mandel, G.; Robinson, J.K.; Ballas, N. MeCP2 Is Critical for Maintaining Mature Neuronal Networks and Global Brain Anatomy during Late Stages of Postnatal Brain Development and in the Mature Adult Brain. *J. Neurosci.* **2012**, *32*, 10021–10034. [CrossRef]

225. Chao, H.T.; Chen, H.M.; Samaco, R.C.; Xue, M.S.; Chahrour, M.; Yoo, J.; Neul, J.L.; Gong, S.C.; Lu, H.C.; Heintz, N.; et al. Dysfunction in GABA signalling mediates autism-like stereotypies and Rett syndrome phenotypes. *Nature* **2010**, *468*, 263–269. [CrossRef]

226. Ure, K.; Lui, H.; Wang, W.; Ito-Ishida, A.; Wu, Z.Y.; He, L.J.; Sztainberg, Y.; Chen, W.; Tang, J.R.; Zoghbi, H.Y. Restoration of Mecp2 expression in GABAergic neurons is sufficient to rescue multiple disease features in a mouse model of Rett syndrome. *Elife* **2016**, *5*, e14198. [CrossRef]

227. Wood, L.; Gray, N.W.; Zhou, Z.; Greenberg, M.E.; Shepherd, G.M. Synaptic circuit abnormalities of motor-frontal layer 2/3 pyramidal neurons in an RNA interference model of methyl-CpG-binding protein 2 deficiency. *J. Neurosci.* **2009**, *29*, 12440–12448. [CrossRef] [PubMed]

228. Li, J.W.; Kells, P.A.; Osgood, A.C.; Gautam, S.H.; Shew, W.L. Collapse of complexity of brain and body activity due to excessive inhibition and MeCP2 disruption. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2106378118. [CrossRef]

229. Bernardo, P.; Cobb, S.; Coppola, A.; Tomasevic, L.; Di Lazzaro, V.; Bravaccio, C.; Manganelli, F.; Dubbioso, R. Neurophysiological Signatures of Motor Impairment in Patients with Rett Syndrome. *Ann. Neurol.* **2020**, *87*, 763–773. [CrossRef]

230. Eyre, J.A.; Kerr, A.M.; Miller, S.; O'Sullivan, M.C.; Ramesh, V. Neurophysiological observations on corticospinal projections to the upper limb in subjects with Rett syndrome. *J. Neurol. Neurosurg. Psychiatry* **1990**, *53*, 874–879. [CrossRef] [PubMed]

231. Harris, A.D.; Singer, H.S.; Horska, A.; Kline, T.; Ryan, M.; Edden, R.A.; Mahone, E.M. GABA and Glutamate in Children with Primary Complex Motor Stereotypies: An 1H-MRS Study at 7T. *AJNR Am. J. Neuroradiol.* **2016**, *37*, 552–557. [CrossRef]

232. Hines, R.M.; Wu, L.; Hines, D.J.; Steenland, H.; Mansour, S.; Dahlhaus, R.; Singaraja, R.R.; Cao, X.; Sammler, E.; Hormuzdi, S.G.; et al. Synaptic imbalance, stereotypies, and impaired social interactions in mice with altered neuroligin 2 expression. *J. Neurosci.* **2008**, *28*, 6055–6067. [CrossRef] [PubMed]

233. Harris, K.D.; Dashevskiy, T.; Mendoza, J.; Garcia, A.J., 3rd; Ramirez, J.M.; Shea-Brown, E. Different roles for inhibition in the rhythm-generating respiratory network. *J. Neurophysiol.* **2017**, *118*, 2070–2088. [CrossRef] [PubMed]

234. Marchenko, V.; Koizumi, H.; Mosher, B.; Koshiya, N.; Tariq, M.F.; Bezdudnaya, T.G.; Zhang, R.; Molkov, Y.I.; Rybak, I.A.; Smith, J.C. Perturbations of Respiratory Rhythm and Pattern by Disrupting Synaptic Inhibition within Pre-Botzinger and Botzinger Complexes. *eNeuro* **2016**, *3*, 1–24. [CrossRef]

235. Baertsch, N.A.; Severs, L.J.; Anderson, T.M.; Ramirez, J.M. A spatially dynamic network underlies the generation of inspiratory behaviors. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 7493–7502. [CrossRef]

236. Fogarty, M.J.; Mantilla, C.B.; Sieck, G.C. Breathing: Motor Control of Diaphragm Muscle. *Physiology* **2018**, *33*, 113–126. [CrossRef] [PubMed]

237. Huff, A.; Karlen-Amarante, M.; Pitts, T.; Ramirez, J.M. Optogenetic stimulation of pre-Botzinger complex reveals novel circuit interactions in swallowing-breathing coordination. *Proc. Natl. Acad. Sci. USA* **2022**, *119*, e2121095119. [CrossRef]

238. d'Orsi, G.; Trivisano, M.; Luisi, C.; Demaio, V.; Di Claudio, M.T.; Pascarella, M.G.; Sciruicchio, V.; Galeone, D.; La Neve, A.; Scarpelli, F.; et al. Epileptic seizures, movement disorders, and breathing disturbances in Rett syndrome: Diagnostic relevance of video-polygraphy. *Epilepsy Behav.* **2012**, *25*, 401–407. [CrossRef]

239. Mesuret, G.; Dannenberg, J.; Arnoldt, M.; Grutzner, A.A.; Niebert, M.; Hulsmann, S. Breathing disturbances in a model of Rett syndrome: A potential involvement of the glycine receptor alpha3 subunit? *Respir. Physiol. Neurobiol.* **2018**, *248*, 43–47. [CrossRef]

240. Ramirez, J.M.; Karlen-Amarante, M.; Wang, J.J.; Huff, A.; Burgraff, N. Breathing disturbances in Rett syndrome. *Handb. Clin. Neurol.* **2022**, *189*, 139–151. [CrossRef]

241. Stettner, G.M.; Huppke, P.; Gartner, J.; Richter, D.W.; Dutschmann, M. Disturbances of breathing in Rett syndrome: Results from patients and animal models. *Adv. Exp. Med. Biol.* **2008**, *605*, 503–507. [CrossRef]

242. Tarquinio, D.C.; Hou, W.; Neul, J.L.; Berkmen, G.K.; Drummond, J.; Aronoff, E.; Harris, J.; Lane, J.B.; Kaufmann, W.E.; Motil, K.J.; et al. The course of awake breathing disturbances across the lifespan in Rett syndrome. *Brain Dev.* **2018**, *40*, 515–529. [CrossRef]

243. Voituron, N.; Zanella, S.; Menuet, C.; Dutschmann, M.; Hilaire, G. Early breathing defects after moderate hypoxia or hypercapnia in a mouse model of Rett syndrome. *Respir. Physiol. Neurobiol.* **2009**, *168*, 109–118. [CrossRef]

244. Voituron, N.; Zanella, S.; Menuet, C.; Lajard, A.M.; Dutschmann, M.; Hilaire, G. Early abnormalities of post-sigh breathing in a mouse model of Rett syndrome. *Respir. Physiol. Neurobiol.* **2010**, *170*, 173–182. [CrossRef] [PubMed]

245. Katz, D.M.; Dutschmann, M.; Ramirez, J.M.; Hilaire, G. Breathing disorders in Rett syndrome: Progressive neurochemical dysfunction in the respiratory network after birth. *Respir. Physiol. Neurobiol.* **2009**, *168*, 101–108. [CrossRef] [PubMed]

246. Ramirez, J.M.; Ward, C.S.; Neul, J.L. Breathing challenges in Rett syndrome: Lessons learned from humans and animal models. *Respir. Physiol. Neurobiol.* **2013**, *189*, 280–287. [CrossRef] [PubMed]

247. Carroll, M.S.; Ramirez, J.M.; Weese-Mayer, D.E. Diurnal variation in autonomic regulation among patients with genotyped Rett syndrome. *J. Med. Genet.* **2020**, *57*, 786–793. [CrossRef] [PubMed]

248. Weese-Mayer, D.E.; Lieske, S.P.; Boothby, C.M.; Kenny, A.S.; Bennett, H.L.; Silvestri, J.M.; Ramirez, J.M. Autonomic nervous system dysregulation: Breathing and heart rate perturbation during wakefulness in young girls with Rett syndrome. *Pediatr. Res.* **2006**, *60*, 443–449. [CrossRef]

249. Bassett, E.; Heinle, R.; Johnston, D. Sleep Apnea in Patients With Rett Syndrome: Roles for Polysomnography and Adenotonsillectomy. *J. Child. Neurol.* **2016**, *31*, 1633–1634. [CrossRef] [PubMed]

250. Sarber, K.M.; Howard, J.J.M.; Dye, T.J.; Pascoe, J.E.; Simakajornboon, N. Sleep-Disordered Breathing in Pediatric Patients With Rett Syndrome. *J. Clin. Sleep Med.* **2019**, *15*, 1451–1457. [CrossRef]

251. Amaddeo, A.; De Sanctis, L.; Arroyo, J.O.; Khirani, S.; Bahi-Buisson, N.; Fauroux, B. Polysomnographic findings in Rett syndrome. *Eur. J. Paediatr. Neuro.* **2019**, *23*, 214–221. [CrossRef] [PubMed]

252. Carotenuto, M.; Esposito, M.; D'Aniello, A.; Rippa, C.D.; Precenzano, F.; Pascotto, A.; Bravaccio, C.; Elia, M. Polysomnographic findings in Rett syndrome: A case-control study. *Sleep Breath.* **2013**, *17*, 93–98. [CrossRef] [PubMed]

253. Hagebeuk, E.E.O.; Bijlmer, R.P.G.M.; Koelman, J.H.T.M.; Poll-The, B.T. Respiratory Disturbances in Rett Syndrome: Don't Forget to Evaluate Upper Airway Obstruction. *J. Child. Neurol.* **2012**, *27*, 888–892. [CrossRef] [PubMed]

254. Leoncini, S.; Signorini, C.; Boasiako, L.; Scandurra, V.; Hayek, J.; Ciccoli, L.; Rossi, M.; Canitano, R.; De Felice, C. Breathing Abnormalities During Sleep and Wakefulness in Rett Syndrome: Clinical Relevance and Paradoxical Relationship With Circulating Pro-oxidant Markers. *Front. Neurol.* **2022**, *13*, 833239. [CrossRef] [PubMed]

255. Fogarty, M.J.; Zhan, W.-Z.; Simmon, V.F.; Vanderklish, P.W.; Sarraf, S.T.; Sieck, G.C. Novel Regenerative Drug, SPG302 Promotes Functional Recovery of Diaphragm Muscle Activity After Cervical Spinal Cord Injury. *J. Physiol.* 2023; *in press*. [CrossRef] [PubMed]

256. Fogarty, M.J.; Brandenburg, J.E.; Zhan, W.Z.; Sieck, G.C. Diaphragm Muscle Function in a Mouse Model of Early Onset Spasticity. *J. Appl. Physiol.* **2022**, *133*, 60–68. [CrossRef]

257. Khurram, O.U.; Fogarty, M.J.; Sarrafian, T.L.; Bhatt, A.; Mantilla, C.B.; Sieck, G.C. Impact of aging on diaphragm muscle function in male and female Fischer 344 rats. *Physiol. Rep.* **2018**, *6*, e13786. [CrossRef]

258. Wu, Y.; Cui, N.; Xing, H.; Zhong, W.; Arrowood, C.; Johnson, C.M.; Jiang, C. In vivo evidence for the cellular basis of central hypoventilation of Rett syndrome and pharmacological correction in the rat model. *J. Cell Physiol.* **2021**, *236*, 8082–8098. [CrossRef]

259. Medrihan, L.; Tantalaki, E.; Aramuni, G.; Sargsyan, V.; Dudanova, I.; Missler, M.; Zhang, W. Early defects of GABAergic synapses in the brain stem of a MeCP2 mouse model of Rett syndrome. *J. Neurophysiol.* **2008**, *99*, 112–121. [CrossRef]

260. Xing, H.; Cui, N.; Johnson, C.M.; Faisthalab, Z.; Jiang, C. Dual synaptic inhibitions of brainstem neurons by GABA and glycine with impact on Rett syndrome. *J. Cell Physiol.* **2021**, *236*, 3615–3628. [CrossRef]

261. Chen, C.Y.; Di Lucente, J.; Lin, Y.C.; Lien, C.C.; Rogawski, M.A.; Maezawa, I.; Jin, L.W. Defective GABAergic neurotransmission in the nucleus tractus solitarius in Mecp2-null mice, a model of Rett syndrome. *Neurobiol. Dis.* **2018**, *109*, 25–32. [CrossRef] [PubMed]

262. Abdala, A.P.; Toward, M.A.; Dutschmann, M.; Bissonnette, J.M.; Paton, J.F. Deficiency of GABAergic synaptic inhibition in the Kolliker-Fuse area underlies respiratory dysrhythmia in a mouse model of Rett syndrome. *J. Physiol.* **2016**, *594*, 223–237. [CrossRef] [PubMed]

263. Dhingra, R.R.; Zhu, Y.; Jacono, F.J.; Katz, D.M.; Galan, R.F.; Dick, T.E. Decreased Hering-Breuer input-output entrainment in a mouse model of Rett syndrome. *Front. Neural Circuits* **2013**, *7*, 42. [CrossRef] [PubMed]

264. Dutschmann, M.; Herbert, H. The Kolliker-Fuse nucleus gates the postinspiratory phase of the respiratory cycle to control inspiratory off-switch and upper airway resistance in rat. *Eur. J. Neurosci.* **2006**, *24*, 1071–1084. [CrossRef]

265. Stettner, G.M.; Huppke, P.; Brendel, C.; Richter, D.W.; Gartner, J.; Dutschmann, M. Breathing dysfunctions associated with impaired control of postinspiratory activity in Mecp2-/y knockout mice. *J. Physiol.* **2007**, *579*, 863–876. [CrossRef]

266. Didden, R.; Korzilius, H.; Smeets, E.; Green, V.A.; Lang, R.; Lancioni, G.E.; Curfs, L.M. Communication in Individuals with Rett Syndrome: An Assessment of Forms and Functions. *J. Dev. Phys. Disabil.* **2010**, *22*, 105–118. [CrossRef]

267. Mezzedimi, C.; Livi, W.; De Felice, C.; Cocca, S. Dysphagia in Rett Syndrome: A Descriptive Study. *Ann. Otol. Rhinol. Laryngol.* **2017**, *126*, 640–645. [CrossRef]

268. Johnson, C.M.; Cui, N.; Xing, H.; Wu, Y.; Jiang, C. The antitussive cloperastine improves breathing abnormalities in a Rett Syndrome mouse model by blocking presynaptic GIRK channels and enhancing GABA release. *Neuropharmacology* **2020**, *176*, 108214. [CrossRef]

269. Abdala, A.P.; Dutschmann, M.; Bissonnette, J.M.; Paton, J.F. Correction of respiratory disorders in a mouse model of Rett syndrome. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 18208–18213. [CrossRef]

270. Martin, B.J.; Corlew, M.M.; Wood, H.; Olson, D.; Golopol, L.A.; Wingo, M.; Kirmani, N. The association of swallowing dysfunction and aspiration pneumonia. *Dysphagia* **1994**, *9*, 1–6. [CrossRef]

271. MacKay, J.; Leonard, H.; Wong, K.; Wilson, A.; Downs, J. Respiratory morbidity in Rett syndrome: An observational study. *Dev. Med. Child. Neurol.* **2018**, *60*, 951–957. [CrossRef] [PubMed]

272. Laurvick, C.L.; De Klerk, N.; Bower, C.; Christodoulou, J.; Ravine, D.; Ellaway, C.; Williamson, S.; Leonard, H. Rett syndrome in Australia: A review of the epidemiology. *J. Pediatr.* **2006**, *148*, 347–352. [CrossRef] [PubMed]

273. Anderson, A.; Wong, K.; Jacoby, P.; Downs, J.; Leonard, H. Twenty years of surveillance in Rett syndrome: What does this tell us? *Orphanet J. Rare Dis.* **2014**, *9*, 87. [CrossRef]

274. Hubner, C.A.; Stein, V.; Hermans-Borgmeyer, I.; Meyer, T.; Ballanyi, K.; Jentsch, T.J. Disruption of KCC2 reveals an essential role of K-Cl cotransport already in early synaptic inhibition. *Neuron* **2001**, *30*, 515–524. [CrossRef]

275. Tornberg, J.; Voikar, V.; Savilahti, H.; Rauvala, H.; Airaksinen, M.S. Behavioural phenotypes of hypomorphic KCC2-deficient mice. *Eur. J. Neurosci.* **2005**, *21*, 1327–1337. [CrossRef]

276. Simonnet, C.; Sinha, M.; Goutierre, M.; Moutkine, I.; Daumas, S.; Poncer, J.C. Silencing KCC2 in mouse dorsal hippocampus compromises spatial and contextual memory. *Neuropsychopharmacology*, 2022; *in press*. [CrossRef]

277. Gogliotti, R.G.; Fisher, N.M.; Stansley, B.J.; Jones, C.K.; Lindsley, C.W.; Conn, P.J.; Niswender, C.M. Total RNA Sequencing of Rett Syndrome Autopsy Samples Identifies the M(4) Muscarinic Receptor as a Novel Therapeutic Target. *J. Pharmacol. Exp. Ther.* **2018**, *365*, 291–300. [CrossRef]

278. Tang, X.; Kim, J.; Zhou, L.; Wengert, E.; Zhang, L.; Wu, Z.; Carromeu, C.; Muotri, A.R.; Marchetto, M.C.; Gage, F.H.; et al. KCC2 rescues functional deficits in human neurons derived from patients with Rett syndrome. *Proc. Natl. Acad. Sci. USA* **2016**, *113*, 751–756. [CrossRef] [PubMed]

279. Banerjee, A.; Rikhye, R.V.; Breton-Provencher, V.; Tang, X.; Li, C.; Li, K.; Runyan, C.A.; Fu, Z.; Jaenisch, R.; Sur, M. Jointly reduced inhibition and excitation underlies circuit-wide changes in cortical processing in Rett syndrome. *Proc. Natl. Acad. Sci. USA* **2016**, *113*, E7287–E7296. [CrossRef]

280. Yeo, M.; Berglund, K.; Augustine, G.; Liedtke, W. Novel repression of Kcc2 transcription by REST-RE-1 controls developmental switch in neuronal chloride. *J. Neurosci.* **2009**, *29*, 14652–14662. [CrossRef]

281. Chang, Q.A.; Khare, G.; Dani, V.; Nelson, S.; Jaenisch, R. The disease progression mutant mice is affected of Mecp2 by the level of BDNF expression. *Neuron* **2006**, *49*, 341–348. [CrossRef] [PubMed]

282. Zhou, Z.; Hong, E.J.; Cohen, S.; Zhao, W.N.; Ho, H.Y.; Schmidt, L.; Chen, W.G.; Lin, Y.; Savner, E.; Griffith, E.C.; et al. Brain-specific phosphorylation of MeCP2 regulates activity-dependent Bdnf transcription, dendritic growth, and spine maturation. *Neuron* **2006**, *52*, 255–269. [CrossRef]

283. Ogier, M.; Wang, H.; Hong, E.; Wang, Q.; Greenberg, M.E.; Katz, D.M. Brain-derived neurotrophic factor expression and respiratory function improve after ampakine treatment in a mouse model of Rett syndrome. *J. Neurosci.* **2007**, *27*, 10912–10917. [CrossRef]

284. Rivera, C.; Li, H.; Thomas-Crusells, J.; Lahtinen, H.; Viitanen, T.; Nanobashvili, A.; Kokaia, Z.; Airaksinen, M.S.; Voipio, J.; Kaila, K.; et al. BDNF-induced TrkB activation down-regulates the K+-Cl- cotransporter KCC2 and impairs neuronal Cl- extrusion. *J. Cell. Biol.* **2002**, *159*, 747–752. [CrossRef]

285. Gigliucci, V.; Teutsch, J.; Woodbury-Smith, M.; Luoni, M.; Busnelli, M.; Chini, B.; Banerjee, A. Region-Specific KCC2 Rescue by rhIGF-1 and Oxytocin in a Mouse Model of Rett Syndrome. *Cereb. Cortex* **2022**, *32*, 2885–2894. [CrossRef]

286. Tang, X.; Drotar, J.; Li, K.; Clairmont, C.D.; Brumm, A.S.; Sullins, A.J.; Wu, H.; Liu, X.S.; Wang, J.; Gray, N.S.; et al. Pharmacological enhancement of KCC2 gene expression exerts therapeutic effects on human Rett syndrome neurons and Mecp2 mutant mice. *Sci. Transl. Med.* **2019**, *11*, eaau0164. [CrossRef]

287. Rosenbaum, P.; Paneth, N.; Leviton, A.; Goldstein, M.; Bax, M.; Damiano, D.; Dan, B.; Jacobsson, B. A report: The definition and classification of cerebral palsy April 2006. *Dev. Med. Child. Neurol.* **2007**, *109*, 8–14, Erratum in *Dev. Med. Child. Neurol.* **2007**, *49*, 480.

288. Yeargin-Allsopp, M.; Van Naarden Braun, K.; Doernberg, N.S.; Benedict, R.E.; Kirby, R.S.; Durkin, M.S. Prevalence of cerebral palsy in 8-year-old children in three areas of the United States in 2002: A multisite collaboration. *Pediatrics* **2008**, *121*, 547–554. [CrossRef]

289. Paneth, N.; Hong, T.; Korzeniewski, S. The descriptive epidemiology of cerebral palsy. *Clin. Perinatol.* **2006**, *33*, 251–267. [CrossRef]

290. Bekteshi, S.; Monbaliu, E.; McIntyre, S.; Saloojee, G.; Hilberink, S.R.; Tatishvili, N.; Dan, B. Towards functional improvement of motor disorders associated with cerebral palsy. *Lancet Neurol.* **2023**, *22*, 229–243. [CrossRef] [PubMed]

291. Christensen, D.; Van Naarden Braun, K.; Doernberg, N.S.; Maenner, M.J.; Arneson, C.L.; Durkin, M.S.; Benedict, R.E.; Kirby, R.S.; Wingate, M.S.; Fitzgerald, R.; et al. Prevalence of cerebral palsy, co-occurring autism spectrum disorders, and motor functioning—Autism and Developmental Disabilities Monitoring Network, USA, 2008. *Dev. Med. Child. Neurol.* **2014**, *56*, 59–65. [CrossRef] [PubMed]

292. Brandenburg, J.E.; Fogarty, M.J.; Sieck, G.C. Chapter 15—The spa transgenic mouse model of hypertonia and use for studying cerebral palsy. In *Handbook of Animal Models in Neurological Disorders*; Martin, C.R., Patel, V.B., Preedy, V.R., Eds.; Academic Press: Cambridge, MA, USA, 2023; pp. 183–192.

293. Back, S.A. Cerebral white and gray matter injury in newborns: New insights into pathophysiology and management. *Clin. Perinatol.* **2014**, *41*, 1–24. [CrossRef] [PubMed]

294. Back, S.A.; Riddle, A.; Dean, J.; Hohimer, A.R. The instrumented fetal sheep as a model of cerebral white matter injury in the premature infant. *Neurotherapeutics* **2012**, *9*, 359–370. [CrossRef]

295. Bax, M.; Tydeman, C.; Flodmark, O. Clinical and MRI correlates of cerebral palsy: The European Cerebral Palsy Study. *J. Am. Med. Assoc.* **2006**, *296*, 1602–1608. [CrossRef] [PubMed]

296. Van Steenwinckel, J.; Schang, A.L.; Sigaut, S.; Chhor, V.; Degos, V.; Hagberg, H.; Baud, O.; Fleiss, B.; Gressens, P. Brain damage of the preterm infant: New insights into the role of inflammation. *Biochem. Soc. Trans.* **2014**, *42*, 557–563. [CrossRef]

297. Ellenberg, J.H.; Nelson, K.B. The association of cerebral palsy with birth asphyxia: A definitional quagmire. *Dev. Med. Child. Neurol.* **2013**, *55*, 210–216. [CrossRef]

298. Nelson, K.B. Causative factors in cerebral palsy. *Clin. Obstet. Gynecol.* **2008**, *51*, 749–762. [CrossRef] [PubMed]

299. Woodward, L.J.; Anderson, P.J.; Austin, N.C.; Howard, K.; Inder, T.E. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. *New Engl. J. Med.* **2006**, *355*, 685–694. [CrossRef]

300. Katz, R.T.; Rymer, W.Z. Spastic hypertonia: Mechanisms and measurement. *Arch. Phys. Med. Rehabil.* **1989**, *70*, 144–155.

301. McGuire, J.; Rymer, W.Z. Spasticity: Mechanisms and Management. In *Medical Management of Long-Term Disability*; Green, D., Ed.; Butterworth-Heinemann: Newton, MA, USA, 1996.

302. Novak, I.; Morgan, C.; Adde, L.; Blackman, J.; Boyd, R.N.; Brunstrom-Hernandez, J.; Cioni, G.; Damiano, D.; Darrah, J.; Eliasson, A.C.; et al. Early, Accurate Diagnosis and Early Intervention in Cerebral Palsy: Advances in Diagnosis and Treatment. *JAMA Pediatr.* **2017**, *171*, 897–907. [CrossRef]

303. Shevell, M.; Dagenais, L.; Oskoui, M. The epidemiology of cerebral palsy: New perspectives from a Canadian registry. *Semin. Pediatr. Neurol.* **2013**, *20*, 60–64. [CrossRef] [PubMed]

304. Lance, J.W. Pathophysiology of spasticity and clinical experience with baclofen. In *Spasticity: Disordered Motor Control*; Feldman, R.G., Young, R.R., Koella, W.P., Eds.; Year Book Medical Publishers: Chicago, IL, USA, 1980; pp. 185–220.

305. Sanger, T.D.; Delgado, M.R.; Gaebler-Spira, D.; Hallett, M.; Mink, J.W.; Task Force on Childhood Motor, D. Classification and definition of disorders causing hypertonia in childhood. *Pediatrics* **2003**, *111*, e89–e97. [CrossRef] [PubMed]

306. Haberfehlner, H.; Jaspers, R.T.; Rutz, E.; Harlaar, J.; van der Sluijs, J.A.; Witbreuk, M.M.; van Hutten, K.; Romkes, J.; Freslier, M.; Brunner, R.; et al. Outcome of medial hamstring lengthening in children with spastic paresis: A biomechanical and morphological observational study. *PLoS ONE* **2018**, *13*, e0192573. [CrossRef]

307. Walker, H.K. Deep Tendon Reflexes. In *The History, Physical, and Laboratory Examinations*; Walker, H.K., Hall, W.D., Hurst, J.W., Eds.; Butterworths: Boston, MA, USA, 1990.

308. Nielsen, J.B.; Crone, C.; Hultborn, H. The spinal pathophysiology of spasticity—From a basic science point of view. *Acta Physiol.* **2007**, *189*, 171–180. [CrossRef] [PubMed]

309. Stein, V.; Hermans-Borgmeyer, I.; Jentsch, T.J.; Hubner, C.A. Expression of the KCl cotransporter KCC2 parallels neuronal maturation and the emergence of low intracellular chloride. *J. Comp. Neurol.* **2004**, *468*, 57–64. [CrossRef] [PubMed]

310. Stil, A.; Liabeuf, S.; Jean-Xavier, C.; Brocard, C.; Viemari, J.C.; Vinay, L. Developmental up-regulation of the potassium-chloride cotransporter type 2 in the rat lumbar spinal cord. *Neuroscience* **2009**, *164*, 809–821. [CrossRef] [PubMed]

311. Graham, H.K.; Rosenbaum, P.; Paneth, N.; Dan, B.; Lin, J.P.; Damiano, D.L.; Becher, J.G.; Gaebler-Spira, D.; Colver, A.; Reddihough, D.S.; et al. Cerebral palsy. *Nat. Rev. Dis. Prim.* **2016**, *2*, 15082. [CrossRef] [PubMed]

312. Brandenburg, J.E.; Fogarty, M.J.; Sieck, G.C. Why individuals with cerebral palsy are at higher risk for respiratory complications from COVID-19. *J. Pediatr. Rehabil. Med.* **2020**, *13*, 317–327. [CrossRef]

313. Kwon, Y.H.; Lee, H.Y. Differences of respiratory function in children with spastic diplegic and hemiplegic cerebral palsy, compared with normally developed children. *J. Pediatr. Rehabil. Med.* **2013**, *6*, 113–117. [CrossRef]

314. Lee, J.D.; Park, H.-J.; Park, E.S.; Oh, M.-K.; Park, B.; Rha, D.-W.; Cho, S.-R.; Kim, E.Y.; Park, J.Y.; Kim, C.H.; et al. Motor pathway injury in patients with periventricular leucomalacia and spastic diplegia. *Brain* **2011**, *134*, 1199–1210. [CrossRef] [PubMed]

315. Johnston, M.V.; Ferriero, D.M.; Vannucci, S.J.; Hagberg, H. Models of cerebral palsy: Which ones are best? *J. Child. Neurol.* **2005**, *20*, 984–987. [CrossRef] [PubMed]

316. Schiariti, V.; Fowler, E.; Brandenburg, J.E.; Levey, E.; Mcintyre, S.; Sukal-Moulton, T.; Ramey, S.L.; Rose, J.; Sienko, S.; Stashinko, E.; et al. A common data language for clinical research studies: The National Institute of Neurological Disorders and Stroke and American Academy for Cerebral Palsy and Developmental Medicine Cerebral Palsy Common Data Elements Version 1.0 recommendations. *Dev. Med. Child. Neurol.* **2018**, *60*, 976–986. [CrossRef] [PubMed]

317. Hamimi, S.; Robinson, S.; Jantzie, L.L. Chapter 16—Transient occlusion of uterine arteries and intra-amniotic injection of lipopolysaccharide in rats as a model of cerebral palsy. In *Handbook of Animal Models in Neurological Disorders*; Martin, C.R., Patel, V.B., Preedy, V.R., Eds.; Academic Press: Cambridge, MA, USA, 2023; pp. 193–204.

318. Cavarsan, C.F.; Gorassini, M.A.; Quinlan, K.A. Animal models of developmental motor disorders: Parallels to human motor dysfunction in cerebral palsy. *J. Neurophysiol.* **2019**, *122*, 1238–1253. [CrossRef] [PubMed]

319. Brandenburg, J.E.; Fogarty, M.J.; Sieck, G.C. Growth and survival characteristics of spa mice. *Anim. Model Exp. Med.* **2020**, *3*, 319–324. [CrossRef]

320. Hutton, J.L. Cerebral palsy life expectancy. *Clin. Perinatol.* **2006**, *33*, 545–555. [CrossRef]

321. Durufle-Tapin, A.; Colin, A.; Nicolas, B.; Lebreton, C.; Dauvergne, F.; Gallien, P. Analysis of the medical causes of death in cerebral palsy. *Ann. Phys. Rehabil. Med.* **2014**, *57*, 24–37. [CrossRef]

322. Jantzie, L.L.; Corbett, C.J.; Berglass, J.; Firl, D.J.; Flores, J.; Mannix, R.; Robinson, S. Complex pattern of interaction between in utero hypoxia-ischemia and intra-amniotic inflammation disrupts brain development and motor function. *J. Neuroinflammation* **2014**, *11*, 131. [CrossRef] [PubMed]

323. Simon, E.S. Phenotypic heterogeneity and disease course in three murine strains with mutations in genes encoding for alpha 1 and beta glycine receptor subunits. *Mov. Disord.* **1997**, *12*, 221–228. [CrossRef]

324. Chai, C.K. Hereditary Spasticity in Mice. *J. Hered.* **1961**, *52*, 241–243. [CrossRef]

325. Brandenburg, J.E.; Fogarty, M.J.; Brown, A.D.; Sieck, G.C. Phrenic motor neuron loss in an animal model of early onset hypertonia. *J. Neurophysiol.* **2020**, *123*, 1682–1690. [CrossRef]

326. Brandenburg, J.E.; Gransee, H.M.; Fogarty, M.J.; Sieck, G.C. Differences in Lumbar Motor Neuron Pruning in an Animal Model of Early Onset Spasticity. *J. Neurophysiol.* **2018**, *120*, 601–609. [CrossRef]

327. Fogarty, M.J.; Brandenburg, J.E.; Sieck, G.C. Diaphragm Neuromuscular Transmission Failure in a Mouse Model of an Early-Onset Neuromotor Disorder. *J. Appl. Physiol.* **2021**, *130*, 708–720. [CrossRef]

328. Fogarty, M.J.; Sieck, G.C.; Brandenburg, J.E. Impaired neuromuscular transmission of the tibialis anterior in a rodent model of hypertonia. *J. Neurophysiol.* **2020**, *123*, 1864–1869. [CrossRef]

329. Rivares, C.; Vignaud, A.; Noort, W.; Koopmans, B.; Loos, M.; Kalinichev, M.; Jaspers, R.T. Glycine receptor subunit-beta-deficiency in a mouse model of spasticity results in attenuated physical performance, growth, and muscle strength. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2022**, *322*, R368–R388. [CrossRef]

330. Petroff, O.A.C.; Rothman, D.L.; Behar, K.L.; Mattson, R.H. Low brain GABA level is associated with poor seizure control. *Ann. Neurol.* **1996**, *40*, 908–911. [CrossRef]

331. Wood, J.H.; Hare, T.A.; Glaeser, B.S.; Ballenger, J.C.; Post, R.M. Low cerebrospinal fluid gamma-aminobutyric acid content in seizure patients. *Neurology* **1979**, *29*, 1203–1208. [CrossRef]

332. Cediel, M.L.; Stawarski, M.; Blanc, X.; Noskova, L.; Magner, M.; Platzer, K.; Gburek-Augustat, J.; Baldridge, D.; Constantino, J.N.; Ranza, E.; et al. GABBR1 monoallelic de novo variants linked to neurodevelopmental delay and epilepsy. *Am. J. Hum. Genet.* **2022**, *109*, 1885–1893. [CrossRef]

333. Maillard, P.Y.; Baer, S.; Schaefer, E.; Desnous, B.; Villeneuve, N.; Lepine, A.; Fabre, A.; Lacoste, C.; El Chehadeh, S.; Piton, A.; et al. Molecular and clinical descriptions of patients with GABA(A) receptor gene variants (GABRA1, GABRB2, GABRB3, GABRG2): A cohort study, review of literature, and genotype-phenotype correlation. *Epilepsia* **2022**, *63*, 2519–2533. [CrossRef]

334. Vogel, F.D.; Krenn, M.; Westphal, D.S.; Graf, E.; Wagner, M.; Leiz, S.; Koniuszewski, F.; Auge-Stock, M.; Kramer, G.; Scholze, P.; et al. A de novo missense variant in GABRA4 alters receptor function in an epileptic and neurodevelopmental phenotype. *Epilepsia* **2022**, *63*, e35–e41. [CrossRef]

335. Bernardino, I.; Dionisio, A.; Violante, I.R.; Monteiro, R.; Castelo-Branco, M. Motor Cortex Excitation/Inhibition Imbalance in Young Adults With Autism Spectrum Disorder: A MRS-TMS Approach. *Front. Psychiatry* **2022**, *13*, 860448. [CrossRef]

336. Eisenberg, C.; Subramanian, D.; Afrasiabi, M.; Ziobro, P.; DeLucia, J.; Hirschberg, P.R.; Shiflett, M.W.; Santhakumar, V.; Tran, T.S. Reduced hippocampal inhibition and enhanced autism-epilepsy comorbidity in mice lacking neuropilin 2. *Transl. Psychiatry* **2021**, *11*, 537. [CrossRef]

337. Fontes-Dutra, M.; Righes Marafiga, J.; Santos-Terra, J.; Deckmann, I.; Brum Schwingel, G.; Rabelo, B.; Kazmierzak de Moraes, R.; Rockenbach, M.; Vendramin Pasquetti, M.; Gottfried, C.; et al. GABAergic synaptic transmission and cortical oscillation patterns in the primary somatosensory area of a valproic acid rat model of autism spectrum disorder. *Eur. J. Neurosci.* **2023**, *57*, 527–546. [CrossRef]

338. Chen, L.; Wan, L.; Wu, Z.; Ren, W.; Huang, Y.; Qian, B.; Wang, Y. KCC2 downregulation facilitates epileptic seizures. *Sci. Rep.* **2017**, *7*, 156. [CrossRef]

339. He, Q.; Nomura, T.; Xu, J.; Contractor, A. The Developmental Switch in GABA Polarity Is Delayed in Fragile X Mice. *J. Neurosci.* **2014**, *34*, 446–450. [CrossRef]

340. Pisella, L.I.; Gaiarsa, J.L.; Diabira, D.; Zhang, J.; Khalilov, I.; Duan, J.; Kahle, K.T.; Medina, I. Impaired regulation of KCC2 phosphorylation leads to neuronal network dysfunction and neurodevelopmental pathology. *Sci. Signal.* **2019**, *12*, eaay0300. [CrossRef]

341. Hyde, T.M.; Lipska, B.K.; Ali, T.; Mathew, S.V.; Law, A.J.; Metitiri, O.E.; Straub, R.E.; Ye, T.; Colantuoni, C.; Herman, M.M.; et al. Expression of GABA signaling molecules KCC2, NKCC1, and GAD1 in cortical development and schizophrenia. *J. Neurosci.* **2011**, *31*, 11088–11095. [CrossRef]

342. Yuan, H.B.; Cheng, L.Y.; Yin, F.; Zhang, G.X.; Peng, J.; Kang, M.X.; Xu, Y.M.; Chen, R.L.; Wang, L. Levels of amino acids in cerebral spinal fluid in children with cerebral palsy. *Zhongguo Dang Dai Er Ke Za Zhi* **2008**, *10*, 475–477.

343. Lee, J.D.; Park, H.J.; Park, E.S.; Kim, D.G.; Rha, D.W.; Kim, E.Y.; Kim, D.I.; Kim, J.J.; Yun, M.; Ryu, Y.H.; et al. Assessment of regional GABA(A) receptor binding using 18F-fluoroflumazenil positron emission tomography in spastic type cerebral palsy. *Neuroimage* **2007**, *34*, 19–25. [CrossRef]

344. Achache, V.; Roche, N.; Lamy, J.C.; Boakye, M.; Lackmy, A.; Gastal, A.; Quentin, V.; Katz, R. Transmission within several spinal pathways in adults with cerebral palsy. *Brain* **2010**, *133*, 1470–1483. [CrossRef]

345. Leonard, C.T.; Moritani, T.; Hirschfeld, H.; Forssberg, H. Deficits in Reciprocal Inhibition of Children with Cerebral-Palsy as Revealed by H-Reflex Testing. *Dev. Med. Child. Neurol.* **1990**, *32*, 974–984. [CrossRef]

346. Leonard, C.T.; Sandholdt, D.Y.; McMillan, J.A.; Queen, S. Short- and long-latency contributions to reciprocal inhibition during various levels of muscle contraction of individuals with cerebral palsy. *J. Child. Neurol.* **2006**, *21*, 240–246. [CrossRef]

347. Frisk, R.F.; Lorentzen, J.; Nielsen, J.B. Contribution of corticospinal drive to ankle plantar flexor muscle activation during gait in adults with cerebral palsy. *Exp. Brain Res.* **2019**, *237*, 1457–1467. [CrossRef]

348. Heinen, F.; Kirschner, J.; Fietzek, U.; Glocker, F.X.; Mall, V.; Korinthenberg, R. Absence of transcallosal inhibition in adolescents with diplegic cerebral palsy. *Muscle Nerve* **1999**, *22*, 255–257. [CrossRef]

349. Condliffe, E.G.; Jeffery, D.T.; Emery, D.J.; Gorassini, M.A. Spinal inhibition and motor function in adults with spastic cerebral palsy. *J. Physiol.* **2016**, *594*, 2691–2705. [CrossRef]

350. Reilly, M.; Liuzzo, K.; Blackmer, A.B. Pharmacological Management of Spasticity in Children With Cerebral Palsy. *J Pediatr Health Care* **2020**, *34*, 495–509. [CrossRef]

351. Davidoff, R.A. Antispasticity drugs: Mechanisms of action. *Ann. Neurol.* **1985**, *17*, 107–116. [CrossRef]

352. de Beaurepaire, R. A Review of the Potential Mechanisms of Action of Baclofen in Alcohol Use Disorder. *Front. Psychiatry* **2018**, *9*, 506. [CrossRef]

353. Gerrow, K.; Triller, A. GABA(A) receptor subunit composition and competition at synapses are tuned by GABA(B) receptor activity. *Mol. Cell. Neurosci.* **2014**, *60*, 97–107. [CrossRef]

354. Connelly, W.M.; Fyson, S.J.; Errington, A.C.; McCafferty, C.P.; Cope, D.W.; Di Giovanni, G.; Crunelli, V. GABAB Receptors Regulate Extrasynaptic GABAA Receptors. *J. Neurosci.* **2013**, *33*, 3780–3785. [CrossRef]

355. Penn, R.D.; Kroin, J.S. Continuous intrathecal baclofen for severe spasticity. *Lancet* **1985**, *2*, 125–127. [CrossRef]

356. Brandenburg, J.E. Is baclofen the least worst option for spasticity management in children? *J. Pediatr. Rehabil. Med.* **2023**. [CrossRef] [PubMed]

357. Yoon, Y.K.; Lee, K.C.; Cho, H.E.; Chae, M.; Chang, J.W.; Chang, W.S.; Cho, S.R. Outcomes of intrathecal baclofen therapy in patients with cerebral palsy and acquired brain injury. *Medicine* **2017**, *96*, e7472. [CrossRef] [PubMed]

358. Kudva, A.; Abraham, M.E.; Gold, J.; Patel, N.A.; Gendreau, J.L.; Herschman, Y.; Mammis, A. Intrathecal baclofen, selective dorsal rhizotomy, and extracorporeal shockwave therapy for the treatment of spasticity in cerebral palsy: A systematic review. *Neurosurg. Rev.* **2021**, *44*, 3209–3228. [CrossRef] [PubMed]

359. Quinlan, J.J.; Ferguson, C.; Jester, K.; Firestone, L.L.; Homanics, G.E. Mice with glycine receptor subunit mutations are both sensitive and resistant to volatile anesthetics. *Anesth. Analg.* **2002**, *95*, 578–582. [CrossRef]

360. Stern, P.; Bokonjic, R. Glycine therapy in 7 cases of spasticity. A pilot study. *Pharmacology* **1974**, *12*, 117–119. [CrossRef]

361. Nutt, D.J.; Malizia, A.L. New insights into the role of the GABA(A)-benzodiazepine receptor in psychiatric disorder. *Brit. J. Psychiat.* **2001**, *179*, 390–396. [CrossRef] [PubMed]

362. Holt, K.S. The use of diazepam in childhood cerebral palsy. Report of a small study including electromyographic observations. *Ann. Phys. Med.* **1964**, *7*, 16–24. [CrossRef]

363. Engle, H.A. The effect of diazepam (Valium) in children with cerebral palsy: A double-blind study. *Dev. Med. Child. Neurol.* **1966**, *8*, 661–667. [CrossRef]

364. Mathew, A.; Mathew, M.C. Bedtime diazepam enhances well-being in children with spastic cerebral palsy. *Pediatr. Rehabil.* **2005**, *8*, 63–66. [CrossRef]

365. Tickner, N.; Apps, J.R.; Keady, S.; Sutcliffe, A.G. An overview of drug therapies used in the treatment of dystonia and spasticity in children. *Arch. Dis. Child. Educ. Pract. Ed.* **2012**, *97*, 230–235. [CrossRef]

366. O'Brien, C.P. Benzodiazepine use, abuse, and dependence. *J. Clin. Psychiatry* **2005**, *66* (Suppl. S2), 28–33.

367. Panteliadis, C.; Panteliadis, P.; Vassilyadi, F. Hallmarks in the history of cerebral palsy: From antiquity to mid-20th century. *Brain Dev.* **2013**, *35*, 285–292. [CrossRef]

368. Christensen, E.; Melchior, J.C. *Cerebral Palsy A Clinical and Neuropathological Study*; Butterworth-Heinemann: Newton, MA, USA, 1967.

369. Marciniak, C.; Li, X.; Zhou, P. An examination of motor unit number index in adults with cerebral palsy. *J. Electromyogr. Kinesiol.* **2015**, *25*, 444–450. [CrossRef]

370. Trevarrow, M.P.; Baker, S.E.; Wilson, T.W.; Kurz, M.J. Microstructural changes in the spinal cord of adults with cerebral palsy. *Dev. Med. Child. Neurol.* **2021**, *63*, 998–1003. [CrossRef]

371. Trevarrow, M.P.; Reelfs, A.; Baker, S.E.; Hoffman, R.M.; Wilson, T.W.; Kurz, M.J. Spinal cord microstructural changes are connected with the aberrant sensorimotor cortical oscillatory activity in adults with cerebral palsy. *Sci. Rep.* **2022**, *12*, 4807. [CrossRef]

372. Drobyshevsky, A.; Quinlan, K.A. Spinal cord injury in hypertonic newborns after antenatal hypoxia-ischemia in a rabbit model of cerebral palsy. *Exp. Neurol.* **2017**, *293*, 13–26. [CrossRef]

373. Prakash, Y.S.; Mantilla, C.B.; Zhan, W.Z.; Smithson, K.G.; Sieck, G.C. Phrenic motoneuron morphology during rapid diaphragm muscle growth. *J. Appl. Physiol.* **2000**, *89*, 563–572. [CrossRef]

374. Fogarty, M.J.; Mu, E.W.H.; Lavidis, N.A.; Noakes, P.G.; Bellingham, M.C. Motor Areas Show Altered Dendritic Structure in an Amyotrophic Lateral Sclerosis Mouse Model. *Front. Neurosci.* **2017**, *11*, 609. [CrossRef]

375. Kanjhan, R.; Fogarty, M.J.; Noakes, P.G.; Bellingham, M.C. Developmental changes in the morphology of mouse hypoglossal motor neurons. *Brain Struct. Funct.* **2016**, *221*, 3755–3786. [CrossRef]

376. Williams, P.A.; Bellinger, D.L.; Wilson, C.G. Changes in the Morphology of Hypoglossal Motor Neurons in the Brainstem of Developing Rats. *Anat. Rec.* **2019**, *302*, 869–892. [CrossRef]

377. Korfage, J.A.M.; Van Wessel, T.; Langenbach, G.E.J.; Van Eijden, T.M.G.J. Heterogeneous postnatal transitions in myosin heavy chain isoforms within the rabbit temporalis muscle. *Anat. Rec. Part A* **2006**, *288a*, 1095–1104. [CrossRef]

378. Korfage, J.A.; van Wessel, T.; Langenbach, G.E.; Ay, F.; van Eijden, T.M. Postnatal transitions in myosin heavy chain isoforms of the rabbit superficial masseter and digastric muscle. *J. Anat.* **2006**, *208*, 743–751. [CrossRef]

379. Korfage, J.A.; Helmers, R.; Matignon Mde, G.; van Wessel, T.; Langenbach, G.E.; van Eijden, T.M. Postnatal development of fiber type composition in rabbit jaw and leg muscles. *Cells Tissues Organs* **2009**, *190*, 42–52. [CrossRef]

380. Saito, K.; Morita, T.; Takasu, H.; Kuroki, K.; Fujiwara, T.; Hiraba, K.; Goto, S. Histochemical study of rabbit medial pterygoid muscle during postnatal development. *Odontology* **2017**, *105*, 141–149. [CrossRef]

381. Dohare, P.; Zia, M.T.; Ahmed, E.; Ahmed, A.; Yadala, V.; Schober, A.L.; Ortega, J.A.; Kayton, R.; Ungvari, Z.; Mongin, A.A.; et al. AMPA-Kainate Receptor Inhibition Promotes Neurologic Recovery in Premature Rabbits with Intraventricular Hemorrhage. *J. Neurosci.* **2016**, *36*, 3363–3377. [CrossRef]

382. Palazon-Garcia, R.; Benavente-Valdepenas, A.M. Botulinum Toxin: From Poison to Possible Treatment for Spasticity in Spinal Cord Injury. *Int. J. Mol. Sci.* **2021**, *22*, 4886. [CrossRef]

383. Kaya Keles, C.S.; Ates, F. Botulinum Toxin Intervention in Cerebral Palsy-Induced Spasticity Management: Projected and Contradictory Effects on Skeletal Muscles. *Toxins* **2022**, *14*, 772. [CrossRef]

384. Klein, C.; Gouron, R.; Barbier, V. Effects of botulinum toxin injections in the upper limbs of children with cerebral palsy: A systematic review of the literature. *Orthop. Traumatol. Surg. Res.* **2023**, 103578. [CrossRef] [PubMed]

385. Koman, L.A.; Mooney, J.F., 3rd; Smith, B.P.; Goodman, A.; Mulvaney, T. Management of spasticity in cerebral palsy with botulinum-A toxin: Report of a preliminary, randomized, double-blind trial. *J. Pediatr. Orthop.* **1994**, *14*, 299–303. [CrossRef] [PubMed]

386. Britt, B.A. Dantrolene. *Can. Anaesth. Soc. J.* **1984**, *31*, 61–75. [CrossRef]

387. Pinder, R.M.; Brogden, R.N.; Speight, T.M.; Avery, G.S. Dantrolene sodium: A review of its pharmacological properties and therapeutic efficacy in spasticity. *Drugs* **1977**, *13*, 3–23. [CrossRef]

388. Ward, A.; Chaffman, M.O.; Sorkin, E.M. Dantrolene. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in malignant hyperthermia, the neuroleptic malignant syndrome and an update of its use in muscle spasticity. *Drugs* **1986**, *32*, 130–168. [CrossRef] [PubMed]
389. Wiley, M.E.; Damiano, D.L. Lower-extremity strength profiles in spastic cerebral palsy. *Dev. Med. Child Neurol.* **1998**, *40*, 100–107. [CrossRef] [PubMed]
390. Neyroud, D.; Armand, S.; De Coulon, G.; Sarah, R.D.D.S.; Maffiuletti, N.A.; Kayser, B.; Place, N. Plantar flexor muscle weakness and fatigue in spastic cerebral palsy patients. *Res. Dev. Disabil.* **2017**, *61*, 66–76. [CrossRef]
391. Eken, M.M.; Braendvik, S.M.; Bardal, E.M.; Houdijk, H.; Dallmeijer, A.J.; Roeleveld, K. Lower limb muscle fatigue during walking in children with cerebral palsy. *Dev. Med. Child. Neurol.* **2019**, *61*, 212–218. [CrossRef]
392. Eek, M.N.; Beckung, E. Walking ability is related to muscle strength in children with cerebral palsy. *Gait Posture* **2008**, *28*, 366–371. [CrossRef]
393. Eken, M.M.; Dallmeijer, A.J.; Houdijk, H.; Doorenbosch, C.A. Muscle fatigue during repetitive voluntary contractions: A comparison between children with cerebral palsy, typically developing children and young healthy adults. *Gait Posture* **2013**, *38*, 962–967. [CrossRef]
394. Puce, L.; Pallecchi, I.; Chamari, K.; Marinelli, L.; Innocenti, T.; Pedrini, R.; Mori, L.; Trompetto, C. Systematic Review of Fatigue in Individuals With Cerebral Palsy. *Front. Hum. Neurosci.* **2021**, *15*, 598800. [CrossRef]
395. Wass, C.T.; Warner, M.E.; Worrell, G.A.; Castagno, J.A.; Howe, M.; Kerber, K.A.; Palzkill, J.M.; Schroeder, D.R.; Cascino, G.D. Effect of general anesthesia in patients with cerebral palsy at the turn of the new millennium: A population-based study evaluating perioperative outcome and brief overview of anesthetic implications of this coexisting disease. *J. Child Neurol.* **2012**, *27*, 859–866. [CrossRef]
396. Honan, I.; Finch-Edmondson, M.; Imms, C.; Novak, I.; Hogan, A.; Clough, S.; Bonyhady, B.; McIntyre, S.; Elliott, C.; Wong, S.; et al. Is the search for cerebral palsy 'cures' a reasonable and appropriate goal in the 2020s? *Dev. Med. Child Neurol.* **2022**, *64*, 49–55. [CrossRef]
397. Turner, L. Hope, hype, cures, and persons with cerebral palsy. *Dev. Med. Child. Neurol.* **2022**, *64*, 8. [CrossRef]