Voltage-Gated Sodium Channel in Neurodegenerative Diseases

Subjects: Neurosciences

Contributor: Raffaella Barbieri , Mario Nizzari , Ilaria Zanardi , Michael Pusch , Paola Gavazzo

The pore-forming subunits (α subunits) of voltage-gated sodium channels (VGSC) are encoded in humans by a family of nine highly conserved genes. Among them, SCN1A, SCN2A, SCN3A, and SCN8A are primarily expressed in the central nervous system. The encoded proteins Nav1.1, Nav1.2, Nav1.3, and Nav1.6, respectively, are important players in the initiation and propagation of action potentials and in turn of the neural network activity. In the context of neurological diseases, mutations in the genes encoding Nav1.1, 1.2, 1.3 and 1.6 are responsible for many forms of genetic epilepsy and for Nav1.1 also of hemiplegic migraine. Conversely, VGSCs seem to have a modulatory role in the most common neurodegenerative diseases such as Alzheimer's, where SCN8A expression has been shown to be negatively correlated with disease severity.

neurodegeneration Alzheimer's disease Parkinson's disease amyotrophic lateral sclerosis Nav channels

1. Alzheimer's Disease

Alzheimer's disease (AD) is a heterogeneous neurodegenerative disorder with irreversible progression, characterized by the progressive loss of synapses and neurons and by the formation of amyloid plaques in the brain. Clinically, it is characterized by loss of memory, followed by deterioration of all mental functions, neuronal degeneration of both cerebral and limbic cortices, reactive gliosis and deposition in the brain parenchyma of amyloid aggregates (or plaques) closely associated with dystrophic neurons. Activated phagocytic microglia, and intraneuronal aggregates of disrupted microtubules, known as "neurofibrillary tangles" are also detectable [1]. The molecular mechanisms underlying the development of AD are not well known so far and also the physiological functions of the crucial proteins the amyloid precursor protein (APP) and the presenilins 1 and 2 (PS1 and PS2) are unclear. The toxic extracellular amyloid oligomers detectable in AD plaques are composed of amyloid-Aß peptides (Aß) derived from the sequential proteolytic cleavage of APP by the ß-secretase BACE1 and of the "ß-secretase-complex" in which PS1 has a regulatory role. Mutations of the *APP* gene are responsible for AD as well. In addition, intracellular neurofibrillary tangles, composed of filaments of hyper-phosphorylated Tau protein, are neuropathological hallmarks of AD. Furthermore, presenilins, which are part of the molecular machinery that processes APP, when mutated are responsible for most of the cases of familial AD; more than 70 different mutations in presenilin 1 (PS1) have been associated with inherited early onset Alzheimer's disease [2]. The phenotypical heterogeneity among patients, and even among familial patients with the same genetic mutation, implies that other proteins might have a role in regulating the onset and severity of the neurodegeneration. Recent

findings suggest that APP and PSs are the center of a complex network of interactions with many different intracellular adaptors, but the role of these proteins in the physiology or pathology is still unknown [3]. APP contains a YENPTY motif that has been previously described as an internalization motif, which now has been recognized to be involved as a key player in the regulation of multiple interactions with intracellular proteins [4]. The significance of the motif, which is typical of the receptor (TKR) and non-receptor tyrosine kinases (TK), in amyloid formation and in general for AD development is under investigation. Furthermore, the cytoplasmic tail of APP undergoes post-translational modifications; in particular, one of the mechanisms which may regulate APP cleavage and protein–protein interactions is linked to the occurrence of phosphorylation at Ser, Thr and Tyr residues. For example, Thr 668 can be phosphorylated by c-Jun N-terminal kinase-3 [5]. Thus APP is a tightly regulated protein, post-translationally modified by kinases. The pathophysiological significance of APP phosphorylation is unclear and there are even contrasting opinions about the effective influence of such post-translational modifications on APP cleavage, amyloid formation and AD development. Indeed in this context, it has to be underlined that APP and APP-related proteins, APLP1 and APLP2, can interact with several proteins such as X11 and Fe65 [6], c-Abl [7], mDab [8], JIP-1 [9] independently of the phosphorylation of the tyrosine residues of the YENPTY motif.

Interestingly, several studies suggest that the physical interaction of APP and its related proteins, Aß oligomers and BACE1 enzyme with various isoforms of Nav could interfere with neural physiological processes and be involved in the development of the AD.

1.1. Alzheimer Disease and Nav Involvement: APP Phosphorylation

Even if a causative dependence of AD from VGSC mutations has not been assessed so far, it has been recently hypothesized that several isoforms may be modulated from APP. In a paper published in 2015, Liu and collaborators demonstrated that in murine cortical neurons, APP co-localizes and interacts with Nav1.6 and that knocking down APP provokes a decrease in Nav1.6 cell surface expression and function [10]. Conversely, APP-induced increases of Nav1.6 cell surface expression have been shown to be dependent on Go protein, the most abundant G protein in the CNS, being enhanced by a constitutively-active mutant Go protein and blocked by a dominant negative mutant Go protein. Interestingly, Nav1.6 sodium channel surface expression was shown to be increased by T668E and decreased by T668A mutations of APP, mimicking and preventing Thr-668 phosphorylation, respectively. In agreement phosphorylation of APP at Thr-668 enhanced its interaction with Nav1.6. Furthermore, APP regulates JNK activity in a Go protein-dependent manner and JNK, in turn, phosphorylates APP. Therefore, APP enhances Nav1.6 sodium channel cell surface expression through a Go-coupled JNK pathway [10]. The interaction between APP and Nav1.6 sodium channel was further studied by Shao li and colleagues. From studies in APP knockout mice they observed that APP molecules aggregated at nodes of Ranvier (NORs) in CNS myelinated axons and interacted with Nav1.6 and described a reduction of sodium current density in hippocampal neurons as well. Coexpression of APP or its intracellular domains (AICD) with Nav1.6 in *Xenopus laevis* oocytes resulted in an increase of peak sodium currents, which also in this case was enhanced by constitutively-active Go mutant and blocked by a Go dominant negative mutant. Similarly to the results of Liu and colleagues, Nav1.6 current was increased by APP mutation T668E and decreased by T668A. Accordingly, the cell surface expression of Nav1.6 sodium channels in the white matter of the spinal cord and the spinal conduction

velocity was decreased in APP/JNK3/knockout mice. Thus also in this research, the conclusion was that APP modulates Nav1.6 sodium channels through a Go-coupled JNK pathway and that this modulation is dependent on the phosphorylation of the Thr668 residue of APP [11].

1.2. Alzheimer's Disease and Nav Involvement: Aß Oligomers

The correlation among AD pathophysiology, seizures and increased neuronal excitability was established by Busche and colleagues examining an AD mouse model. Indeed in the CA1 hippocampal region of young APP/PS1 mice, they observed an increased number of hyperactive neurons associated with the high level of Aβ oligomers produced, and therefore speculated that soluble Aβ oligomers might directly induce neuronal hyperactivity [12]. Several lines of evidence indicated that amyloid-β1–42 (Aβ1–42) induced neuronal hyperactivity may give rise to cognitive deficits and memory dysfunction in AD. Indeed recent studies on primary hippocampal neurons of another AD mouse model (Tg2576) exposed to Aβ1–42 oligomers, demonstrated that the overexpression of Nav1.6 contributes to membrane depolarization and to the increase of spike frequency, thereby resulting in neuronal hyperexcitability. These findings identify the Nav1.6 channel as a determinant of hippocampal neuronal hyperexcitability induced by Aβ1–42 oligomers [13].

1.3. Alzheimer's Disease and Nav Involvement: BACE1

Another relevant molecule for the sequential proteolytic cleavage of APP and plaques formation is the ß-secretase BACE1. Some authors describe a correlation between BACE1 and sodium channel expression. A recent study performed by De-Juan Yuan and colleagues on WT mice and on the APP/PS1 AD mouse model has shown that Nav1.6 is overexpressed in old AD mice. The high expression of Nav1.6 in APP/PS1 mice enhances BACE1 transcription through activation of the NFAT1 factor regulated by the Na(+)/Ca(2+)exchanger (NCX). Interestingly, the authors demonstrated that knocking down Nav1.6 with a bilateral injection of adeno-associated viruses (serotype 8, AAV8) encoding shRNA of Nav1.6 in the hippocampus significantly reduced the density of Aβ plaques through the suppression of the β-secretase-mediated cleavage of APP. As a consequence, the cognitive deficit of the mice and the neural network hyper excitability were both remarkably reduced [14]. The authors went further in defining the molecular mechanisms underlying the role of Nav1.6 in AD pathogenesis. Treating Nav1.6 overexpressing HEK cells with TTX, an unspecific blocker of CNS VGSC, they observed a remarkable reduction of BACE1 expression; the same reduction was less evident when Nav1.6 channel was knocked down by shRNA transfection and TTX was applied, unveiling a molecular mechanism dependent on Na ion flux and not only the presence of the channel itself. Thus for the first time, Nav1.6 has been indicated as a new target to be considered to slow down AD evolution.

Other authors suggest that Nav1.1 and 1.2 might also be involved to some extent in AD; indeed the results of their investigations indicated a reduction of Nav1.1, 1.2 and Nav1.6 α-subunits protein in primary neurons in a culture of wild type BACE1-null mice. They propose an underlying mechanism involving BACE1 activity regulating mRNA levels of the Nav1.1 α-subunit through the cleavage of the Navβ2 subunit expressed on the surface. Interestingly in the hippocampus of the same murine model, Nav1.1 expression appeared significantly reduced, while Nav1.2,

perhaps as a compensatory mechanism, was remarkably increased. Thus endogenous BACE1 activity seems to regulate total and surface levels of VGSC in mouse brains [15].

2. Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor disabilities that affects predominantly the dopaminergic neurons of the substantia nigra causing a decrease in dopamine levels in the striatum [16]. The main symptoms are bradykinesia, akinesia, muscle rigidity, postural instability, stiffness and resting tremor which may be due to the high levels of synchronous oscillations in the basal ganglia neurons [17][18]. The causes of PD are unknown, although it is speculated that there may be a contribution from genetic and environmental factors [19]. PD pathogenesis has been associated with a number of factors, including impairments linked to intracellular Ca^{2+} excess, mitochondrial malfunction, oxidative or metabolic stress, and, in particular, a small number of neurotoxins that render neuronal cells more susceptible to death. VGSCs have an important role in the abnormal electrical activity of neurons in the globus pallidus and the subthalamic nucleus in PD [20] and are involved in cognitive impairments. By using the rat PD model infused with 6-OHDA (6-hyroxydopamine), Wang and colleagues showed that the expression of Nav1.1, 1.3 and 1.6 in the hippocampus was dynamically increased at different time points after dopamine depletion [21]. In contrast, treating rats with phenytoin, a sodium channel blocker that slows down the recovery from inactivation [22], remarkably improved cognitive impairments. In MPTP (1-metyl-4-fenyl-1,2,3,6-tetrahydropyridin)-treated PD mice it was found that Nav1.1 expression was increased in the external globus pallidus [23]. Globus pallidus is a central nucleus of the basal ganglia; it receives the majority of the inhibitory GABAergic inputs from the striatum and plays a key role in the propagation of synchronized oscillatory activity of basal ganglia [18]. In particular, the increase of Nav1.1 expression in MPTP-treated mice was evident in parvalbumin (PV) positive GABAergic interneurons that exhibit fast-firing spontaneous activity, and exert their inhibitory control on the activity of innervated neurons in the subthalamic nucleus, substantia nigra and in the striatum [24]. In these cells, Nav1.1 is a determinant for the maintenance of sustained fast spiking more than for its onset [25][26]. Additionally, in this research phenytoin was used to test the effectiveness of blocking VGSCs in reducing PD symptoms. Indeed both motor disability and high synchronous oscillations were reduced in MPTP-treated mice, thus confirming the potential therapeutic role of this compound in PD. Even if the role of GABAergic transmission in PD is still unknown, it is possible to speculate that the observed effect of phenytoin could result from blocking the increased activity of Nav1.1 in the globus pallidus thus restoring the physiological GABAergic activity. Probably, the upregulation of Nav1.1 expression in globus pallidus may be a compensatory molecular mechanism aimed to enhance inhibitory response in the basal ganglia and counteract the abnormal neural activity of PD animals. Nav1.3 seems to be involved in PD as well. This VGSC isoform generally is robustly expressed during the fetal period and is downregulated after birth. By using the rat PD model infused with 6-OHDA, it has been demonstrated that 49 days after infusion Nav1.3 is re-expressed in dopaminergic neurons of the substantia nigra [21]. Additionally, in this case the authors suggest that the re-expression of Nav1.3 could be a compensatory mechanism for the degeneration of dopaminergic neurons caused by PD progression. Current therapies treat only PD symptoms, but several investigations have also been carried out in order to find putative neuroprotective drugs for dopaminergic neurons. In particular, Sadeghian and colleagues have examined the effects of safinamide on

microglial activation and dopaminergic neurons degeneration in a rat model of PD in vivo. In the PD rat model, safinamide reduced the number of activated microglial cells and increased survival of dopaminergic neurons [27]. Safinamide is a sodium and calcium channels modulator and inhibits glutamate release induced by abnormal neuronal activity, promoting its neuroprotective effect [28]. Specifically safinamide interacts with the inactivated state of the VGSCs, keeping most of the channels in the inactive state and preventing their activation. This effect induces a selective depression of the pathological high-frequency firing, leaving physiologic activity unaffected and thus avoiding CNS depressant effects [29].

3. Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic Lateral Sclerosis (ALS) is an unknown etiology disease, caused by the progressive neurodegeneration of motor neurons [30]. The degenerative process induces a progressive atrophy of the neuromuscular system which causes death from paralysis 3–5 years after the onset of the disease [31]. At the moment there is no effective therapy for ALS on slowing down or arresting the neurodegenerative process [32]. To date, there are two main drugs for the treatment of ALS aimed to prolong the patient's life expectancy: riluzole [30][33] and edaravone [33][34]. Although the mechanisms by which these drugs exert their effects are not well known, various hypotheses have been formulated. Riluzole is believed to modulate the release of glutamate [35][36] and sodium channel activity. In particular, this drug is able to down-regulate neuronal firing and inhibit the persistent current of VGSC [37][38]. Persistent current is caused by a particular kinetics of VGSC characterized by a rapid activation followed by a subsequent slow inactivation which maintains the channel in the activated state for hundreds of milliseconds [39]. It is generally more evident in various pathological conditions, when the ionic environment is altered or when a mutation modifies functional properties of VGSCs and contributes to maintaining the neuronal membrane potential near the threshold value triggering spontaneous action potentials [40]. Vucic and Kiernan using the transcranial magnetic stimulation technique on ALS patients have demonstrated that cortical excitability is abnormally increased in an early state of the disease [41]. Similarly experiments performed on ASL animal models have confirmed that a neuronal hyperexcitability of the motor cortex activating the glutamate excitotoxic cascade via trans-synaptic mechanism is at the route of the neurodegenerative process of the motor neuron [42][43].

Although the molecular mechanisms underlying ALS are still not well understood, several pieces of evidence indicate that Nav1.6 channels could be a potential therapeutic target. Using G93A mice, Saba and collaborators showed that the expression levels of the Nav1.6 channels during ASL progression are modified in the primary motor cortex but not in other cortical areas with consequent alteration of the excitability and of persistent current of this neural district [44].

While it is assumed that Nav1.6 dysfunction may be linked to ALS, evidence has recently been provided of the existence of sporadic ALS forms caused by heterozygous point mutations in the *SCN4A* gene that precede the development of the disease. In this context, two mutations, Arg672His and Ser1159Pro, which have opposite effects on neuromuscular excitability have been identified in two different patients. In both cases, the authors hypothesize that the abnormal Nav1.4 channels predisposed to depolarization-induced cellular excitotoxicity,

leading to the development of ALS [45]. Whole genome sequencing analysis of ALS patients identified the presence of missense mutations in the *SCN7A* gene, which codes for NaX, a type II sodium channel sensitive to the extracellular [Na^+] [46]. Mutations in this channel result in a loss of function phenotype which provokes a dysregulation of sodium homeostasis and neuronal hyperexcitability. Overall, the findings described above support the hypothesis of the role of VGSC dysfunction in ALS development. Gaining more insights into the molecular mechanisms related to VGSC underlying the disease could lead to the identification of new therapeutic targets and even pave the way for personalized gene therapy.

4. Multiple Sclerosis

Multiple sclerosis (MS) is a multifactorial neurodegenerative disease of the central nervous system whose etiology is still mostly unknown. It is a chronic demyelinating disease characterized by an autoimmune response against the tissues of the central nervous system with lymphocytic and macrophage infiltration [47]. The pathological hallmarks of MS are demyelinated plaques in the CNS with inflammation, gliosis, and neurodegeneration [48]. At the beginning of the disease, the lymphocyte infiltration that triggers the axonal and myelin damage can be recovered. Later the inflammatory episodes occur repeatedly and microglia activation causes extensive and chronic neurodegeneration leading to disability.

An experimental autoimmune encephalomyelitis (EAE) mouse model is used to study MS. In this murine model, T cells infiltrate the CNS, initiate demyelination and cause loss of axons [49]. VGSCs have an important role in axonal loss in MS. It has been shown that in demyelinated axons there is a particular distribution of sodium channels, with Nav1.2 and Nav1.6 present in the plaques together with the Na^+/Ca^{2+} exchanger whereas in non-demyelinated control axons Nav1.6 is located only in Ranvier nodes [50]. High sodium flux along Nav1.6 reverses the Na^+/Ca^{2+} exchanger and increases axonal calcium finally leading to axonal damage through the activation Ca^{2+} dependent proteases [50]. Upregulation of Nav1.8 detected in cerebellar Purkinje neurons of MS patients and in the experimental EAE mouse model appears to be a determinant for the cerebellar dysfunction observed in this disease [51][52]. Indeed the administration of a selective Nav1.8 blocker in the cerebrospinal fluid of EAE mice partially improved symptomatology [53]. Overexpression of Nav1.5 has been detected in astrocytes of post-mortem MS brain tissue. It has been suggested that its upregulation is necessary to restore physiological ATPase-dependent Na^+/K^+ homeostasis in damaged neural areas [51]. Experiments performed on an in vitro model of glial injury [54] have assessed that Nav1.5 in non-excitable cells plays the main role of reversing the NCX function. It has been proposed that the application of sodium channel blockers could attenuate the inflammatory effects provoked by microglia injury and activation such as phagocytosis, the release of cytokines interleukin-1 and tumor necrosis factor-α [55]. In vitro studies have shown that Nav1.5 is present in the membrane of maturing endosomes of macrophages suggesting a possible role of the channel in the phagocytic pathway of myelin degradation within MS lesions [56]. The main neurological and neurodegenerative diseases correlated with Nav channel dysfunctions in the **Table 1**.

Table 1. List of the main neurological and neurodegenerative diseases correlated with Nav channel dysfunctions.

Nav Isoform	Gene	Neurological Disorder	References	Neurodegenerative Disorder	References
Nav1.1	*SCN1A*				
		Dravet Syndrome	[57][58]	Alzheimer's Disease	[15]
		GEFS+ (genetic epilepsy with febrile seizures plus)	[58][59][60]	Parkinson's Disease	[24]
		Epilepsy of infancy with migrating focal seizures	[58][59]		
		Myoclonic-atonic epilepsy	[58][59]		
		Familial hemiplegic migraine	[61]		
Nav1.2	*SCN2A*				
		Developmental and epileptic encephalopathy (DEE).	[58][62]	Alzheimer's disease	[15]
		Benign Familial Neonatal-Infantile Seizures (BFNIS)	[58][62]		
		West syndrome	[63][64]		
		Epilepsy of infancy with migrating focal seizures (EIMFS)	[58][59]		
		Autism Syndrome Disorder (ASD)	[64]		
		Intellectual Disability	[64]		
		Episodic ataxia	[65]		
Nav1.3	*SCN3A*				
		Developmental and Epileptic Encephalopathy (DEE)	[66]	Parkinson's Disease	[21]
		Polymicrogyria	[66]		
		Intellectual Disability	[66]		
Nav1.4	*SCN4A*				
				Amyotrophic Lateral	[45]

Nav Isoform	Gene	Neurological Disorder	References	Neurodegenerative Disorder	References
				Sclerosis	
				Huntington's Disease	[67]
Nav1.5	*SCN5A*				
				Multiple Sclerosis	[51][56]
NaX	*SCN7A*				
				Amyotrophic Lateral Sclerosis	[46]
Nav1.6	*SCN8A*				
		Developmental and epileptic encephalopathy (DEE).	[58]	Alzheimer Disease	[11][14]
		Autism Syndrome Disorder (ASD)	[58]	Amyotrophic Lateral Sclerosis	[44]
		Intellectual Disability	[68][69]	Multiple Sclerosis	[50]
Nav1.8	*SCN10A*				
				Multiple Sclerosis	[51][52]

References

1. Selkoe, D.J. Deciphering the genesis and fate of amyloid beta-protein yields novel therapies for Alzheimer disease. J. Clin. Investig. 2002, 110, 1375–1381.
2. Gandy, S.; Naslund, J.; Nordstedt, C. Alzheimer's disease. Molecular consequences of presenilin-1 mutation. Nature 2001, 411, 654–656.
3. Zhang, Y.-W.; Thompson, R.; Zhang, H.; Xu, H. APP processing in Alzheimer's disease. Mol. Brain 2011, 4, 3.
4. Cao, X.; Sudhof, T.C. A transcriptionally active complex of APP with Fe65 and histone acetyltransferase Tip60. Science 2001, 293, 115–120.
5. Inomata, H.; Nakamura, Y.; Hayakawa, A.; Takata, H.; Suzuki, T.; Miyazawa, K.; Kitamura, N. A scaffold protein JIP-1b enhances amyloid precursor protein phosphorylation by JNK and its association with kinesin light chain 1. J. Biol. Chem. 2003, 278, 22946–22955.

6. Borg, J.P.; Ooi, J.; Levy, E.; Margolis, B. The phosphotyrosine interaction domains of X11 and FE65 bind to distinct sites on the YENPTY motif of amyloid precursor protein. Mol. Cell Biol. 1996, 16, 6229–6241.
7. Zambrano, N.; Bruni, P.; Minopoli, G.; Mosca, R.; Molino, D.; Russo, C.; Schettini, G.; Sudol, M.; Russo, T. The beta-amyloid precursor protein APP is tyrosine-phosphorylated in cells expressing a constitutively active form of the Abl protoncogene. J. Biol. Chem. 2001, 276, 19787–19792.
8. Howell, B.W.; Lanier, L.M.; Frank, R.; Gertler, F.B.; Cooper, J.A. The disabled 1 phosphotyrosine-binding domain binds to the internalization signals of transmembrane glycoproteins and to phospholipids. Mol. Cell Biol. 1999, 19, 5179–5188.
9. Roncarati, R.; Sestan, N.; Scheinfeld, M.H.; Berechid, B.E.; Lopez, P.A.; Meucci, O.; McGlade, J.C.; Rakic, P.; D'Adamio, L. The gamma-secretase-generated intracellular domain of beta-amyloid precursor protein binds Numb and inhibits Notch signaling. Proc. Natl. Acad. Sci. USA 2002, 99, 7102–7107.
10. Liu, C.; Tan, F.C.K.; Xiao, Z.-C.; Dawe, G.S. Amyloid precursor protein enhances Nav1.6 sodium channel cell surface expression. J. Biol. Chem. 2015, 8, 12048.
11. Li, S.; Wang, X.; Ma, Q.; Yang, W.-L.; Zhang, X.-G.; Dawe, G.S.; Xiao, Z.-C. Amyloid precursor protein modulates Nav1.6 sodium channel currents through a Go-coupled JNK pathway. Sci. Rep. 2016, 6, 39320.
12. Busche, M.A.; Chen, X.; Henning, H.A.; Reichwald, J.; Staufenbiel, M.; Sakmann, B.; Konnerth, A. Henning, +3, and Arthur Konnerth Critical role of soluble amyloid-β for early hippocampal hyperactivity in a mouse model of Alzheimer's disease. Proc. Natl. Acad. Sci. USA 2012, 109, 8740–8745.
13. Ciccone, R.; Franco, C.; Piccialli, I.; Boscia, F.; Casamassa, A.; de Rosa, V.; Cepparulo, P.; Cataldi, M.; Annunziato, L.; Pannaccione, A. Amyloid β-Induced Upregulation of Nav1.6 Underlies Neuronal Hyperactivity in Tg2576 Alzheimer's Disease Mouse Model. Sci. Rep. 2019, 9, 13592.
14. Yuan, D.; Yang, G.; Wu, W.; Li, Q.; Xu, D.; Ntim, M.; Jiang, C.; Liu, J.; Zhang, Y.; Wang, Y.; et al. Reducing Nav1.6 expression attenuates the pathogenesis of Alzheimer's disease by suppressing BACE1 transcription. Aging Cell 2022, 21, e13593.
15. Kim, D.Y.; Gersbacher, M.T.; Inquimbert, P.; Kovacs, D.M. Reduced Sodium Channel Nav1.1 Levels in BACE1-null Mice. J Biol Chem. 2011, 286, 8106–8116.
16. Hammond, C.; Bergman, H.; Brown, P. Pathological synchronization in Parkinson's disease: Networks, models and treatments. Trends Neurosci. 2007, 30, 357–364.
17. Bergman, H.; Deuschl, G. Pathophysiology of Parkinson's disease: From clinical neurology to basic neuroscience and back. Mov. Disord. Off. J. Mov. Disord. Soc. 2002, 17 (Suppl. 3), S28–S40.

18. Schwab, B.C.; Heida, T.; Zhao, Y.; Marani, E.; van Gils, S.A.; van Wezel, R.J. Synchrony in Parkinson's disease: Importance of intrinsic properties of the external globus pallidus. Front. Syst. Neurosci. 2013, 7, 60.
19. Dolgacheva, L.P.; Zinchenko, V.P.; Goncharov, N.V. Molecular and Cellular Interactions in Pathogenesis of Sporadic Parkinson Disease. Int. J. Mol. Sci. 2022, 23, 13043.
20. Zhu, H.; Wang, Z.; Jin, J.; Pei, X.; Zhao, Y.; Wu, H.; Lin, W.; Tao, J.; Ji, Y. Parkinson's disease-like forelimb akinesia induced by BmK I, a sodium channel modulator. Behav. Brain Res. 2016, 308, 166–176.
21. Wang, Z.; Lin, Y.; Liu, W.; Kuang, P.; Lao, W.; Ji, Y.; Zhu, H. Voltage-Gated Sodium Channels Are Involved in Cognitive Impairments in Parkinson's Disease- like Rats. Neuroscience 2019, 418, 231–243.
22. Rogawski, M.A.; Loscher, W. The neurobiology of antiepileptic drugs. Nat. Rev. Neurosci. 2004, 5, 553–564.
23. Liu, W.; Lao, W.; Zhang, R.; Zhu, H. Altered expression of voltage gated sodium channel Nav1.1 is involved in motor ability in MPTP-treated mice. Brain Res. Bull. 2021, 170, 187–198.
24. Saunders, A.; Huang, K.W.; Sabatini, B.L. Globus Pallidus Externus Neurons Expressing parvalbumin Interconnect the Subthalamic Nucleus and Striatal Interneurons. PLoS ONE 2016, 11, e0149798.
25. Ogiwara, I.; Miyamoto, H.; Morita, N.; Atapour, N.; Mazaki, E.; Inoue, I.; Takeuchi, T.; Itohara, S.; Yanagawa, Y.; Obata, K.; et al. Nav1.1 localizes to axons of parvalbumin-positive inhibitory interneurons: A circuit basis for epileptic seizures in mice carrying an Scn1a gene mutation. J. Neurosci. Off. J. Soc. Neurosci. 2007, 27, 5903–5914.
26. Duflocq, A.; Le Bras, B.; Bullier, E.; Couraud, F.; Davenne, M. Nav1.1 is predominantly expressed in nodes of Ranvier and axon initial segments. Mol. Cell. Neurosci. 2008, 39, 180–192.
27. Sadeghian, M.; Mullali, G.; Pocock, J.M.; Piers, T.; Roach, A.; Smith, K.J. Neuroprotection by safinamide in the 6-hydroxydopamine model of Parkinson's disease. Neuropathol. Appl. Neurobiol. 2016, 42, 423–435.
28. Chazot, P.L. Safinamide (Newron Pharmaceuticals). Curr. Opin. Investig. Drugs 2001, 2, 809–813.
29. Caccia, C.; Maj, R.; Calabresi, M.; Maestroni, S.; Faravelli, L.; Curatolo, L.; Salvati, P.; Fariello, R.G. Safinamide: From molecular targets to a new anti-Parkinson drug. Neurology 2006, 67, S18–S23.
30. Mathis, S.; Couratier, P.; Julian, A.; Vallat, J.M.; Corcia, P.; Le Masson, G. Management and therapeutic perspectives in amyotrophic lateral sclerosis. Expert Rev. Neurother. 2017, 17, 263–

276.

31. Hardiman, O.; van den Berg, L.H. Edaravone: A new treatment for ALS on the horizon? Lancet. Neurol. 2017, 16, 490–491.
32. Petrov, D.; Mansfield, C.; Moussy, A.; Hermine, O. ALS Clinical Trials Review: 20 Years of Failure. Are We Any Closer to Registering a New Treatment? Front. Aging Neurosci. 2017, 9, 68.
33. Hinchcliffe, M.; Smith, A. Riluzole: Real-world evidence supports significant extension of median survival times in patients with amyotrophic lateral sclerosis. Degener. Neurol. Neuromuscul. Dis. 2017, 7, 61–70.
34. Silani, V. Therapy in Amyotrophic Lateral Sclerosis (ALS): An unexpected evolving scenario. Arch. Ital. De Biol. 2017, 155, 118–130.
35. Blasco, H.; Mavel, S.; Corcia, P.; Gordon, P.H. The glutamate hypothesis in ALS: Pathophysiology and drug development. Curr. Med. Chem. 2014, 21, 3551–3575.
36. Lazarevic, V.; Yang, Y.; Ivanova, D.; Fejtova, A.; Svenningsson, P. Riluzole attenuates the efficacy of glutamatergic transmission by interfering with the size of the readily releasable neurotransmitter pool. Neuropharmacology 2018, 143, 38–48.
37. Carunchio, I.; Curcio, L.; Pieri, M.; Pica, F.; Caioli, S.; Viscomi, M.T.; Molinari, M.; Canu, N.; Bernardi, G.; Zona, C. Increased levels of p70S6 phosphorylation in the G93A mouse model of Amyotrophic Lateral Sclerosis and in valine-exposed cortical neurons in culture. Exp. Neurol. 2010, 226, 218–230.
38. Lamanauskas, N.; Nistri, A. Riluzole blocks persistent Na+ and Ca2+ currents and modulates release of glutamate via presynaptic NMDA receptors on neonatal rat hypoglossal motoneurons in vitro. Eur. J. Neurosci. 2008, 27, 2501–2514.
39. Carter, B.C.; Giessel, A.J.; Sabatini, B.L.; Bean, B.P. Transient sodium current at subthreshold voltages: Activation by EPSP waveforms. Neuron 2012, 75, 1081–1093.
40. Ceballos, C.C.; Roque, A.C.; Leao, R.M. The role of negative conductances in neuronal subthreshold properties and synaptic integration. Biophys. Rev. 2017, 9, 827–834.
41. Vucic, S.; Kiernan, M.C. Transcranial Magnetic Stimulation for the Assessment of Neurodegenerative Disease. Neurother. J. Am. Soc. Exp. Neuro Ther. 2017, 14, 91–106.
42. Ozdinler, P.H.; Benn, S.; Yamamoto, T.H.; Guzel, M.; Brown, R.H., Jr.; Macklis, J.D. Corticospinal motor neurons and related subcerebral projection neurons undergo early and specific neurodegeneration in hSOD1G(9)(3)A transgenic ALS mice. J. Neurosci. Off. J. Soc. Neurosci. 2011, 31, 4166–4177.
43. Geevasinga, N.; Menon, P.; Ozdinler, P.H.; Kiernan, M.C.; Vucic, S. Pathophysiological and diagnostic implications of cortical dysfunction in ALS. Nat. Rev. Neurol. 2016, 12, 651–661.

44. Saba, L.; Viscomi, M.T.; Martini, A.; Caioli, S.; Mercuri, N.B.; Guatteo, E.; Zona, C. Modified age-dependent expression of NaV1.6 in an ALS model correlates with motor cortex excitability alterations. Neurobiol. Dis. 2019, 130, 104532.
45. Franklin, J.P.; Cooper-Knock, J.; Baheerathan, A.; Moll, T.; Mannikko, R.; Heverin, M.; Hardiman, O.; Shaw, P.J.; Hanna, M.G. Concurrent sodium channelopathies and amyotrophic lateral sclerosis supports shared pathogenesis. Amyotroph. Lateral Scler. Front. Degener. 2020, 21, 627–630.
46. Hiyama, T.Y.; Watanabe, E.; Ono, K.; Inenaga, K.; Tamkun, M.M.; Yoshida, S.; Noda, M. Na(x) channel involved in CNS sodium-level sensing. Nat. Neurosci. 2002, 5, 511–512.
47. Compston, A.; Coles, A. Multiple sclerosis. Lancet 2008, 372, 1502–1517.
48. Popescu, B.F.; Pirko, I.; Lucchinetti, C.F. Pathology of multiple sclerosis: Where do we stand? Contin 2013, 19, 901–921.
49. t Hart, B.A.; Luchicchi, A.; Schenk, G.J.; Stys, P.K.; Geurts, J.J.G. Mechanistic underpinning of an inside-out concept for autoimmunity in multiple sclerosis. Ann. Clin. Transl. Neurol. 2021, 8, 1709–1719.
50. Craner, M.J.; Newcombe, J.; Black, J.A.; Hartle, C.; Cuzner, M.L.; Waxman, S.G. Molecular changes in neurons in multiple sclerosis: Altered axonal expression of Nav1.2 and Nav1.6 sodium channels and Na+/Ca2+ exchanger. Proc. Natl. Acad. Sci. USA 2004, 101, 8168–8173.
51. Black, J.A.; Newcombe, J.; Waxman, S.G. Astrocytes within multiple sclerosis lesions upregulate sodium channel Nav1.5. Brain J. Neurol. 2010, 133, 835–846.
52. Damarjian, T.G.; Craner, M.J.; Black, J.A.; Waxman, S.G. Upregulation and colocalization of p75 and Nav1.8 in Purkinje neurons in experimental autoimmune encephalomyelitis. Neurosci. Lett. 2004, 369, 186–190.
53. Shields, S.D.; Ahn, H.S.; Yang, Y.; Han, C.; Seal, R.P.; Wood, J.N.; Waxman, S.G.; Dib-Hajj, S.D. Nav1.8 expression is not restricted to nociceptors in mouse peripheral nervous system. Pain 2012, 153, 2017–2030.
54. Pappalardo, L.W.; Samad, O.A.; Black, J.A.; Waxman, S.G. Voltage-gated sodium channel Nav 1.5 contributes to astrogliosis in an in vitro model of glial injury via reverse Na+/Ca2+ exchange. Glia 2014, 62, 1162–1175.
55. Black, J.A.; Liu, S.; Waxman, S.G. Sodium channel activity modulates multiple functions in microglia. Glia 2009, 57, 1072–1081.
56. Black, J.A.; Newcombe, J.; Waxman, S.G. Nav1.5 sodium channels in macrophages in multiple sclerosis lesions. Mult. Scler. 2013, 19, 532–542.

57. Meng, H.; Xu, H.Q.; Yu, L.; Lin, G.W.; He, N.; Su, T.; Shi, Y.W.; Li, B.; Wang, J.; Liu, X.R.; et al. The SCN1A mutation database: Updating information and analysis of the relationships among genotype, functional alteration, and phenotype. Hum. Mutat. 2015, 36, 573–580.
58. Meisler, M.H.; Hill, S.F.; Yu, W. Sodium channelopathies in neurodevelopmental disorders. Nat. Rev. Neurosci. 2021, 22, 152–166.
59. Scheffer, I.E.; Nabbout, R. SCN1A-related phenotypes: Epilepsy and beyond. Epilepsia 2019, 60 (Suppl. 3), S17–S24.
60. Escayg, A.; Goldin, A.L. Sodium channel SCN1A and epilepsy: Mutations and mechanisms. Epilepsia 2010, 51, 1650–1658.
61. Dichgans, M.; Freilinger, T.; Eckstein, G.; Babini, E.; Lorenz-Depiereux, B.; Biskup, S.; Ferrari, M.D.; Herzog, J.; van den Maagdenberg, A.M.; Pusch, M.; et al. Mutation in the neuronal voltage-gated sodium channel SCN1A in familial hemiplegic migraine. Lancet 2005, 366, 371–377.
62. Begemann, A.; Acuna, M.A.; Zweier, M.; Vincent, M.; Steindl, K.; Bachmann-Gagescu, R.; Hackenberg, A.; Abela, L.; Plecko, B.; Kroell-Seger, J.; et al. Further corroboration of distinct functional features in SCN2A variants causing intellectual disability or epileptic phenotypes. Mol. Med. 2019, 25, 6.
63. Perucca, P.; Perucca, E. Identifying mutations in epilepsy genes: Impact on treatment selection. Epilepsy Res. 2019, 152, 18–30.
64. Wolff, M.; Johannesen, K.M.; Hedrich, U.B.S.; Masnada, S.; Rubboli, G.; Gardella, E.; Lesca, G.; Ville, D.; Milh, M.; Villard, L.; et al. Genetic and phenotypic heterogeneity suggest therapeutic implications in SCN2A-related disorders. Brain J. Neurol. 2017, 140, 1316–1336.
65. Schwarz, N.; Bast, T.; Gaily, E.; Golla, G.; Gorman, K.M.; Griffiths, L.R.; Hahn, A.; Hukin, J.; King, M.; Korff, C.; et al. Clinical and genetic spectrum of SCN2A-associated episodic ataxia. Eur. J. Paediatr. Neurol. EJPN Off. J. Eur. Paediatr. Neurol. Soc. 2019, 23, 438–447.
66. Zaman, T.; Helbig, K.L.; Clatot, J.; Thompson, C.H.; Kang, S.K.; Stouffs, K.; Jansen, A.E.; Verstraete, L.; Jacquinet, A.; Parrini, E.; et al. SCN3A-Related Neurodevelopmental Disorder: A Spectrum of Epilepsy and Brain Malformation. Ann. Neurol. 2020, 88, 348–362.
67. Corrochano, S.; Blanco, G.; Acevedo-Arozena, A. Skeletal Muscle Modulates Huntington's Disease Pathogenesis in Mice: Role of Physical Exercise. J. Exp. Neurosci. 2018, 12, 1179069518809059.
68. Wagnon, J.L.; Barker, B.S.; Ottolini, M.; Park, Y.; Volkheimer, A.; Valdez, P.; Swinkels, M.E.M.; Patel, M.K.; Meisler, M.H. Loss-of-function variants of SCN8A in intellectual disability without seizures. Neurology Genet. 2017, 3, e170.

69. Blanchard, M.G.; Willemsen, M.H.; Walker, J.B.; Dib-Hajj, S.D.; Waxman, S.G.; Jongmans, M.C.; Kleefstra, T.; van de Warrenburg, B.P.; Praamstra, P.; Nicolai, J.; et al. De novo gain-of-function and loss-of-function mutations of SCN8A in patients with intellectual disabilities and epilepsy. J. Med. Genet. 2015, 52, 330–337.