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Review

Symmetric and Asymmetric Synapses Driving Neurodegenerative Disorders

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Abstract: In 1959, E. G. Gray described two different types of synapses in the brain for the first time: symmetric and asymmetric. Later on, symmetric synapses were associated with inhibitory terminals, and asymmetric synapses to excitatory signaling. The balance between these two systems is critical to maintain a correct brain function. Likewise, the modulation of both types of synapses is also important to maintain a healthy equilibrium. Cerebral circuitry responds differently depending on the type of damage and the timeline of the injury. For example, promoting symmetric signaling following ischemic damage is beneficial only during the acute phase; afterwards, it further increases the initial damage. Synapses can be also altered by players not directly related to them; the chronic and long-term neurodegeneration mediated by tau proteins primarily targets asymmetric synapses by decreasing neuronal plasticity and functionality. Dopamine represents the main modulating system within the central nervous system. Indeed, the death of midbrain dopaminergic neurons impairs locomotion, underlying the devastating Parkinson's disease. Herein, we will review studies on symmetric and asymmetric synapses plasticity after three different stressors: symmetric signaling under acute damage—ischemic stroke; asymmetric signaling under chronic and long-term neurodegeneration—Alzheimer's disease; symmetric and asymmetric synapses without modulation—Parkinson's disease.

Keywords: Alzheimer's disease; asymmetric synapses; dopamine; GABAergic transmission; glutamatergic transmission; Parkinson's disease; stroke; symmetric synapses; tau

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1. Introduction

At the end of the 1950's, E. G. Gray used electron microscopy to define two different types of synapses in the central nervous system (CNS): asymmetric and symmetric synapses [1]. Based on his achievements, asymmetric (or type I) synapses are defined by a postsynaptic density (PSD), thicker than the presynaptic fraction, whereas symmetric (or type II) synapses present a PSD similar in width to the presynaptic membrane. Subsequently, asymmetric and symmetric synapses were correlated to excitatory or inhibitory signaling, respectively [2]. Although controversial [3], nowadays this terminology is still being used to identify excitatory and inhibitory synapses along CNS.

As mentioned, the PSD is a high-density fraction in the postsynaptic membrane with different roles such as mediating the apposition of pre- and post-synaptic membranes, clustering postsynaptic receptors or coupling the activation of these receptors to cellular signaling [4–6]. The PSD in asymmetric synapses is composed of membrane proteins (e.g., α-amino-3-hidroxi-5-metilo-4-isoxazolpropionic receptor [AMPAR], N-methyl-D-aspartate

receptor [NMDAR], metabotropic receptors, ion channels and adhesion molecules), scaffold proteins (such as the postsynaptic density protein 95 [PSD-95]), and signaling proteins [6,7]. PSD-95 is the most abundant scaffold protein in postsynapses, where it plays a crucial role in organization by interacting with adhesion molecules, glutamate receptors and signaling proteins through its PDZ domain [8,9]. Accordingly, high levels of PSD-95 are correlated with larger PSDs and enhanced synaptic strength [10]. In contrast, symmetric synapses display a different composition in their PSD, where gamma-aminobutyric acid (GABA) A ($GABA_A$, ionotropic) and GABA B ($GABA_B$, metabotropic) receptors are responsible for mediating inhibitory responses. Interestingly, the number of $GABA_A$ receptors at the membrane usually determines the strength of the inhibitory synaptic signaling [11]. Similarly to PSD-95, gephyrin plays an important role in the structure of the inhibitory PSD by clustering GABA receptors and acting as a scaffold protein [12,13]. Both asymmetric and symmetric PSDs are not fixed but constantly changing, reflecting the high plasticity presents in this network. The strength of these synapses can be modified in a bidirectional way by mechanisms such as long-term potentiation (LTP) or long-term depression (LTD), among others [14]. Likewise, modulatory neurotransmitters can also influence and regulate synaptic transmission [15].

LTP and LTD are well-known forms of synaptic plasticity. Most of our knowledge about LTP/LTD came from reports of asymmetric synapses, where NMDA-mediated LTP/LTD is the most studied [14]. In excitatory synapses, LTP is induced only when both pre- and post-synaptic neurons are active, and it is mandatory that the postsynaptic neuron is already depolarized at the moment glutamate binds to NMDARs. This is important because it is needed to reach the highest calcium influx to activate intracellular signaling pathways underlying these synaptic modifications [16]. Contrary to LTP, LTD is generally induced by repeated activation of the presynaptic neuron without postsynaptic activity, that leads to a smaller NMDA-mediated calcium influx and synaptic endocytosis of AMPARs [16,17]. Regarding inhibitory transmission, LTP/LTD mechanisms are also present in inhibitory synapses throughout the brain [18]. Inhibitory LTP or LTD needs the presence of glutamatergic synapses, and therefore, the activation of corresponding glutamate receptors to trigger the underlying cellular mechanisms [19].

Neuromodulators are compounds that modify synaptic transmission by regulating the excitability of both pre- and post-synaptic neurons and the response of receptors to neurotransmitters [20]. Within neuromodulators, dopamine (DA) is one of the most studied because its functions are of such importance that deficits in dopaminergic (DAergic) signaling lead to neurological disorders [15]. Midbrain DAergic neurons represent the main source of DA in the CNS, the *substantia nigra* pars compacta (SNc) and the ventral tegmental area being two important centers providing significant amount of DA to the basal ganglia (BG) and forebrain [21]. Through the activation of metabotropic receptors (D1-D5), DA can modify the excitability of neurons by regulating the voltage- or ligand-gated channels [15], as well as regulating the function and trafficking of GABA receptors, NMDARs, and AMPARs [22]. In this way, DA is able to affect different synaptic dynamics [23].

Both asymmetric and symmetric synapses have important roles in shaping the structural and functional outcomes of the brain. Therefore, the balance between excitation and inhibition is capital for a normal cerebral function. Here, we take advantage of Gray's definitions to review recent advances in the understanding of synaptic alterations at asymmetric and/or symmetric signaling under three different conditions: symmetric signaling following acute damage—stroke; asymmetric signaling in long-term neuronal degeneration—Alzheimer's disease; both signaling with no modulation—Parkinson's disease.

2. Ischemic Stroke

Stroke is becoming one of the most common causes of death in developed countries, representing the main cause of long-term disability due to the limited capacity of human brain to repair. Ischemic stroke, the occlusion of a blood vessel leading to a lack of blood flux, has fatal consequences even in short-term blockages and it represents the 85% of total

cases in Europe [24,25]. Following the insult, two large areas can be distinguished: the ischemic core, necrotic tissue with irreparable damage; and the peri-infarct, or penumbra, an area containing hypoperfused tissue that is still viable for several hours and can be salvaged by restoration of the blood flow. Over the next few hours to days, this peri-infarct tissue undergoes secondary damage by the activation of the ischemic cascade which eventually leads to neuronal death. The response to the damage varies depending on which cerebral area is affected, the cortex and hippocampus arising as two of the most susceptible areas [26,27]. The timeline of neuronal death differs among these two areas, with cortical neurons displaying a quick death in comparison with hippocampal neurons that show a delayed death occurring 3–5 days following the insult [26]. This exposes the complexity of neuronal connections since every cortical microcircuit responds differently after damage, and the outcome following treatment may not be the same throughout the different cortical layers [28,29].

Two different phases can be distinguished from the onset of an ischemic insult, and each one shows how the imbalance between excitatory and inhibitory signaling can negatively affect neuronal/functional outcome [30]. During the acute phase, under a hypoxic environment, there is a massive presynaptic release of glutamate that overactivates postsynaptic NMDARs. This leads to the entry of large amounts of Ca^{2+} during the first minutes to hours, which stimulates a variety of cellular processes that ultimately produce irreparable neuronal damage and cell death (Figure 1) [25,30]. Recently, Tanaka et al. [31] reported increased levels of glutamate by using MALDI mass spectrometry imaging in the peri-infarct area of a mouse model. In addition to this, the astrogial-mediated reuptake of glutamate is reduced following injury, further increasing extracellular levels of glutamate [26]. In such a situation, the enhancement of GABA signaling counterbalances the excitatory inputs promoting neuroprotection (Figure 1) [32]. Conversely, during the post-acute/chronic phase, GABA signaling is highly increased and limits neural repair by decreasing neuronal excitability and impairing LTP [33,34]. This occurs simultaneously with a rearrangement of cortical networks underlying neuronal plasticity by enhancing the ability to induce LTP throughout prolonged excitatory signaling during the first week post stroke [33,35,36]. Therefore, treatments blocking GABA signaling during this phase may represent promising therapies to help in the recovery of patients following stroke [28,34,37,38].

Overall, avoiding the transformation of the penumbra into infarcted tissue is a key target to overcome neuronal damage, and it may improve the outcome of patients after stroke. Besides, it seems pivotal to understand how and when the switch from acute to post-acute/chronic phase occurs in humans in order to tackle the distinct cellular mechanisms underlying neuronal damage over time. Achievements in this field will allow the translation from animal models to human.

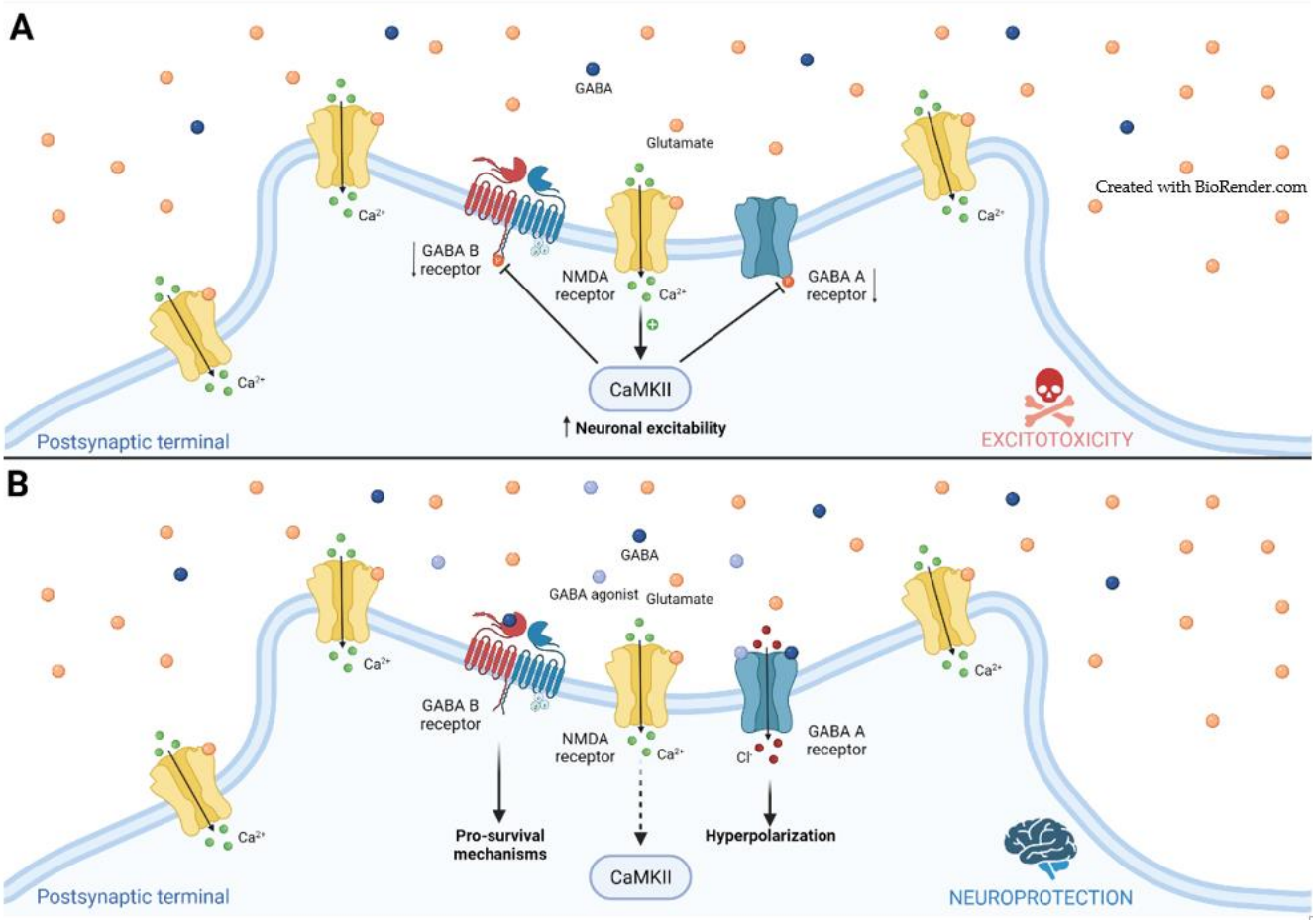

Figure 1. Glutamate-mediated excitotoxicity in ischemic stroke. (**A**) Following ischemic injury, the massive release of glutamate (orange spheres) leads to the entry of large amount of Ca^{2+}, increasing neuronal excitability and activating the Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII). CaMKII phosphorylates both $GABA_A$ and $GABA_B$ receptors, decreasing their availability; (**B**) The potentiation of symmetric signaling through agonists (light-blue spheres) of either $GABA_A$ or $GABA_B$ receptor, or GABA itself (dark-blue spheres), counteracts the glutamate-mediated excitotoxicity by hyperpolarizing the neuron and activating pro-survival second messengers that altogether leads to neuroprotection.

2.1. GABA Receptors

GABA signaling through the $GABA_A$ receptor is more relevant than the same mediated by $GABA_B$ receptors in the pathophysiology of stroke. Therefore, we will focus primarily on $GABA_A$ receptors, only citing the most relevant information regarding $GABA_B$ receptors.

The different subunits forming ionotropic $GABA_A$ receptors determine the properties and location of receptors. These changes in subunit composition are responsible for the synaptic and extrasynaptic location of $GABA_A$ receptors, which mediate phasic (synaptic) and tonic (extrasynaptic) inhibition, respectively [32]. During phasic inhibition, GABA released from presynaptic terminals reaches the postsynaptic membrane where it binds to $GABA_A$ receptors and triggers an inward chloride current, leading to the hyperpolarization of the neuron. This cellular mechanism represents a transient response defined by a rapid desensitization of the synaptic $GABA_A$ receptors and the removal of extrasynaptic GABA by GABA transporters (GATs). On the other hand, tonic inhibition mediates a continuously inhibitory current controlling the neuronal membrane potential and thus its fire potential. Such GABAergic signaling is triggered when extrasynaptic $GABA_A$ receptors with high affinity and slow desensitization for GABA respond to either ambient GABA levels outside the synapse or synaptic spillover of GABA. Regarding metabotropic $GABA_B$ receptors, they are the mainly regulators of presynaptic glutamate release in excitatory neurons; they also control the activity of postsynaptic glutamate receptors [39].

In the $GABA_A$ receptors, trafficking to and from the plasma membrane only occurs at the extrasynaptic space, lateral diffusion being the main mechanism controlling their synaptic pool, and therefore the strength of symmetric signaling [32]. Based on their location, the clustering of $GABA_A$ receptors is modulated by gephyrin (synaptic site) or radixin (extrasynaptic site), and both scaffold proteins are positively regulated by phosphorylation, strengthen the clustering at the membrane [32,40,41]. Mele and colleagues [40] suggested that the dephosphorylation of α1 subunit-containing $GABA_A$ receptors is directly involved in their internalization, likely by losing the link with gephyrin, following in vitro ischemic damage. Likewise, it has been proposed that the calcium-mediated activation of calpain leads to the cleavage of the gephyrin lattice and subsequent reduction in the synaptic clustering of $GABA_A$ receptors in hippocampal neurons from rats under in vitro excitotoxic conditions [42]. Hence, ischemic conditions lead to decreased levels of phosphorylated $GABA_A$ receptors, as well as $GABA_B$ receptors, suggesting that this is the reason underlying the ischemia-induced endocytosis of receptors. Moreover, this decrease could also explain why $GABA_B$ receptors cannot counteract the glutamate-mediated overexcitation [43,44].

Immediately after an ischemic event, large amounts of glutamate contribute to a strong activation of NMDARs that downregulates the expression of both $GABA_A$ and $GABA_B$ receptors through a phosphorylation process activated by high levels of Ca^{2+} (Figure 1) [32,43–46]. Accordingly, phasic GABA signaling is reduced in the first weeks after stroke [28,40]. This situation further increases neuronal depolarization and subsequent cellular damage. Recently, two proteomic studies have revealed increased levels of the GABA aminotransferase GABT, as well as reduced levels of GABA receptors and the excitatory amino acid transporter EAA2, in the infarct core area from postmortem tissue samples of stroke patients [47,48]. These results validate results from animal models by showing overall decreased GABAergic signaling (elevated catabolism of GABA and reduced GABA receptors) and increased glutamatergic signaling (reduced removal from synaptic cleft by EAA2). That is why the enhancement of GABA signaling at this point can exert a neuroprotective role by decreasing the cellular excitability (Figure 1). Indeed, an early study by Costa and coworkers [49] revealed that the coactivation of both $GABA_A$ and $GABA_B$ receptors promoted neuroprotection in an in vitro model of ischemic stroke. Similarly, the activation of either $GABA_A$ or $GABA_B$ receptors separately also has pro-survival outcomes. Several studies have reported that the remaining $GABA_B$ receptors can be activated between days 1–3 post stroke and this promotes neuroprotection [42,50]. Since the 1990′s, the neuroprotective role of enhancing phasic GABA signaling at the acute phase has been studied throughout pharmacological treatments in both in vitro and in vivo models [39,51]. Likewise, some studies suggest the benefits of enhancing phasic GABA signaling during the chronic phase of stroke in humans [52,53]. It has been reported that the phasic GABA signaling is increased in cortical pyramidal neurons during the chronic phase of stroke [29]. Pharmacological boost of α1 subunit-mediated currents at 3 days post stroke promotes functional recovery by targeting cortical plasticity [29].

Although glutamate is excitotoxic during the acute phase following stroke, it plays a beneficial role during the recovery phase by inducing LTP [33,34]. Indeed, studies in humans have suggested that the stimulation of the penumbra cortex by boosting local excitability as soon as 7 days post stroke improves functional outcome [54]. However, there is an increase in extrasynaptic levels of GABA due to the reduction in the amount of astrogial GABA transporters on day 7 post stroke in mice [28]. This event hyperpolarizes neurons at the penumbra area and negatively modulates the induction of LTP [32,34,55]. Indeed, a recent study using magnetic resonance spectroscopy showed that patients with a low excitatory–inhibitory ratio post stroke had a worse motor outcome [56]. The application of pharmacological treatments negatively targeting either all α subunits or only α5 subunit-mediated tonic GABA currents at 3 days post stroke has shown significant behavioral recovery in mouse models [28,34,37]. Interestingly, it has been reported that there is a possible role of extrasynaptic $GABA_C$ receptors, a well-known subclass of $GABA_A$ receptors, in these increased tonic currents during post-acute and chronic phases. The

application of antagonists targeting $GABA_C$ receptors from day 3 post stroke improved the motor function of injured mice [38]. These results together suggest that the time window for the administration of an extrasynaptic $GABA_A$ receptor blocker without affecting its initial neuroprotective role is around 3 days after the infarct, at least in mice.

Overall, the potentiation of symmetric signaling immediately after ischemic stroke counteracts the prominent excitatory cellular state promoting neuronal survival. Based on murine models, the acute phase lasts 3 days, and one of the most important questions to be solved is the exact duration of this phase in humans in order to replicate the results from animal models to patients. In contrast, during the postacute and chronic phase, the rise in tonic GABAergic signaling has to be blocked in order to achieve a better functional outcome. Curiously, the potentiation of phasic inhibition is beneficial during the recovery state. It would be interesting to combine pro-GABA drugs during the acute phase and then change them progressively to both prophasic signaling and antitonic currents.

2.2. Cation–Chloride Cotransporters

Ionotropic GABAergic signaling is primarily supported by the chloride ion gradient across the plasmatic membrane [57]. In mature neurons, the regular $GABA_A$-mediated transmission leads to hyperpolarization by allowing the entry of Cl^- ions that increases the intracellular concentration of chloride ($[Cl^-]_i$) (Figure 2) [26,57]. The maintenance of $[Cl^-]_i$ mainly depends on cation–chloride cotransporters, where Na^+-K^+-$2Cl^-$ cotransporters (NKCCs) and K^+-Cl^- cotransporters (KCCs) are the most important in the CNS [26,58]. The isoform NKCC1 is the only one expressed in the CNS, and its function is to increase the $[Cl^-]_i$. In contrast, the isoform KCC2 is the main one responsible for decreasing $[Cl^-]_i$ in mature neurons [26,58].

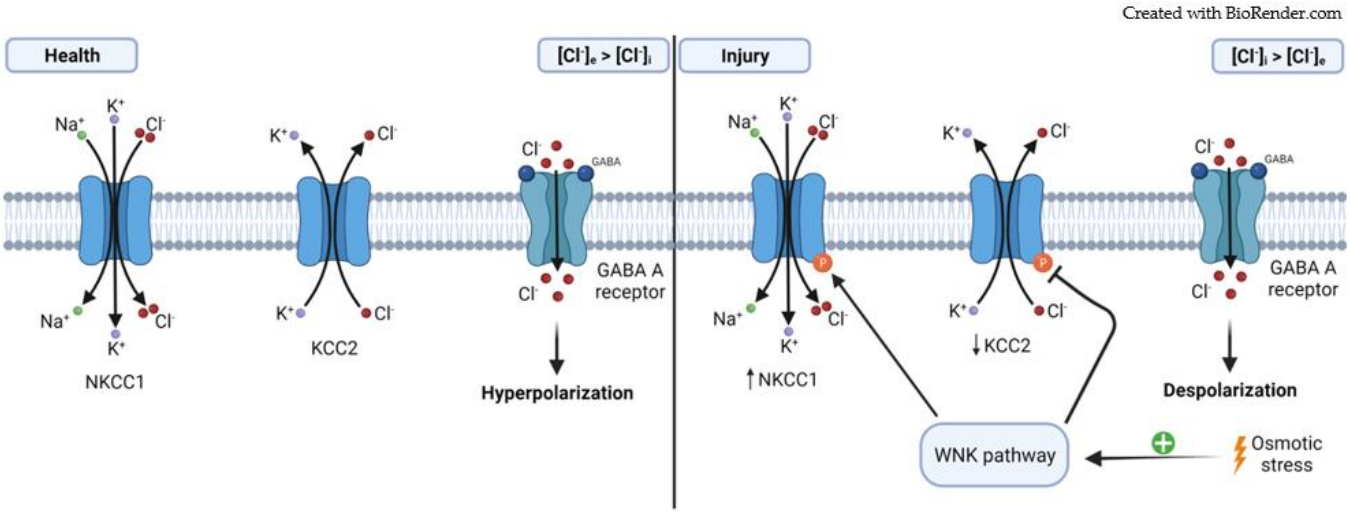

Figure 2. Role of NKCC1 and KCC2 cotransporters in the effect of Cl^- flow through $GABA_A$ receptor. (**Health**). In a normal situation, the expression of both cotransporters leads to a higher $[Cl^-]_e$ compared to the $[Cl^-]_i$. This results in neuronal hyperpolarization when GABAA receptors are activated; (**Injury**) After damage, there is an osmotic stress that activates the WNK pathway. This ultimately ends in the phosphorylation of both cotransporters with different outcomes, the expression of KCC2 decreases, whereas the expression of NKCC1 increases; leading to a higher $[Cl^-]_i$ compared to the $[Cl^-]_e$, which results in depolarizing $GABA_A$ receptor-mediated responses.

It has been well-documented that under some pathological conditions, $[Cl^-]_i$ can be dysregulated, leading to a depolarizating effect mediated by $GABA_A$ receptors (Figure 2) [59]. This is primarily motivated by a high expression of NKCC1 and a low expression of KCC2, leading to a higher $[Cl^-]_i$ compared to the extracellular concentration of chloride ($[Cl^-]_e$) [57,58,60]. The main cellular cascade involved in the regulation of NKCC1 and KCC2 following osmotic stress (low $[Cl^-]_i$) is the With-No-Lysine (K) (WNK) pathway,

which ultimately phosphorylates both NKCC1 and KCC2 with opposite outcomes: NKCC1 is activated whereas KCC2 is inhibited (Figure 2) [61,62].

There is compelling evidence showing an increase in neuronal NKCC1 expression immediately after ischemic stroke, an event that contributes to cellular hyperexcitability and cell death [45,60,63–66]. Wang and colleagues [60] have shown that NKCC1 is significantly upregulated in cortical neurons from 3 h to 48 h following focal cerebral ischemia in a rat model. Acute pharmacological treatment using bumetanide, an NKCC1 inhibitor drug, revealed a neuroprotective effect by increasing neuronal survival in an in vitro model of stroke [45]. This is concordance with previous in vivo results showing a reduction in the infarction volume as well as in the ischemic necrotic cell death, especially remarkable when bumetanide was applied preinjury [60,63,67,68]. A recent study has shown that the inhibition of NKCC1 from day 7 post stroke enhanced axonal sprouting from uninjured neurons, resulting in a significant behavioral improvement [66].

As previously shown, stroke triggers the WNK signaling pathway leading to both the activation of NKCC1 and the inhibition of KCC2 via phosphorylation (Figure 2) [62,69]. Indeed, the activation of the WNK signaling pathway significantly increased the activity of NKCC1 in cortical and striatal neurons at 6 and 24 h after ischemic stroke in mice [65]. These findings suggest that blocking the activation of the WNK cascade offers a new therapeutic target to improve the outcome following stroke by targeting NKCC1 activation [62,69–72].

Contrary to what it was seen for NKCC1, the amount of KCC2 at both mRNA and protein levels was downregulated in both rat and mouse models of ischemic stroke [45,64,66,73,74]. Curiously, whereas the KCC2 levels in the plasma membrane are notably reduced 3 h post ischemia [74], there is a progressive decrease in the levels of total KCC2 given that it is significant on days 1 and 7 post stroke, but not at 2 h after injury [64]. Therefore, a relationship between a maintained expression of KCC2 overtime and the long-term survival rate of neurons has been proposed [64], which was recently supported [26,74]. In this study, hippocampal pyramidal neurons had regular levels of KCC2 and did not display damage signals at 6 h post stroke, but they started to degenerate when KCC2 levels decreased at 48 h after stroke [26]. In a similar way, an acute blockage of upstream pathways inhibiting KCC2 showed an increased neuronal survival following an ischemic incident in mice [74]. Therefore, all these evidences seem to point at the upregulation of KCC2 as a therapeutic target to provide protection against stroke-induced cell death. However, similar to the manipulation of GABA signaling, it is a challenge to decipher the timing between acute and recovery phase in humans, and hence, to find the correct point at which to change KCC2 expression/activity from increased to decreased in order to achieve further functional outcome after ischemic stroke [26].

In summary, blocking NKCC1 during the first hours post stroke has a remarkable effect on neuronal outcome by reducing necrotic death. Likewise, increasing KCC2 levels displays a beneficial role at least during the acute phase, which raises the interesting question of what would happen if KCC2 was manipulated during the post-acute/chronic phase, since higher levels of KCC2 would induce GABA-mediated hyperpolarization leading to a tonic currents-like effect.

3. Alzheimer's Disease

Alzheimer's disease (AD) is clinically characterized as a progressive impairment of memory and cognitive disabilities, and is the most common neurodegenerative disorder of the elderly in developed countries. The two classical hallmarks of AD are amyloid plaques (extracellular deposits of amyloid-β peptide [Aβ]) and neurofibrillary tangles (NFTs, intracellular filamentous aggregates of tau) [75], the tau pathology being more correlated with neurodegeneration and cognitive impairments than the plaque pathology [76].

Although tau has been considered an axonal microtubule-associated protein for many years [77], recent advances have demonstrated that tau plays important roles as a synaptic protein, since changes in its structure or expression affect synaptic plasticity [78–82].

One of the most characteristic symptoms of AD is memory loss [83]. The hippocampus is the main area responsible for the storage, maintenance and processing of memory, where synaptic plasticity, both LTP and LTD, play an essential role [84]. Herein, we will review the most recent advances in the role of tau at asymmetric synapses in both health and pathological conditions.

3.1. Physiological Tau in Synapses

Although the presence of tau in dendrites and synapses was firstly thought to occur only during neuronal development or under pathological conditions [85], accumulating evidence is reporting physiological tau at dendrites and postsynapses [78,79,83,86,87], including human brains [88]. This location of tau at the somatodendritic domain can be attributed to a local translation [89] or diffusion from the axonal domain [90]. Curiously, there is also a natural translocation of tau from dendrites to the postsynaptic area of asymmetric synapses following LTP [91]. Tau can also be transported from pre- to post-synaptic terminals during neuronal activity in both physiological and pathological conditions [92–94]. As previously mentioned, synaptic tau plays different roles besides microtubule dynamics and axonal transport, and it is implicated in the formation, maintenance and plasticity of synapses as well as in neuronal signaling [86,95–97]. Indeed, tau is a key mediator in the increased spine density driven by brain-derived neurotrophic factor (BDNF) [95]. Of relevant physiological importance is the complex that tau forms with both the kinase Fyn and PSD-95, since it can interact with NMDA or AMPA receptors, connecting tau with glutamatergic receptors [86,87,98–100]. In fact, non-phosphorylated tau contributes to the induction of LTP [79,91,101].

Tau undergoes different posttranslational modifications (e.g., phosphorylation or acetylation) at different regulatory sites that affect the function of the protein [102]. Glycogen synthase kinase-3 beta (GSK3β) represents one of the most prominent tau kinases, and its function is strongly influenced by patterns of neuronal activity that ultimately induce synaptic plasticity. There is a bidirectional pathway whereby physiological GSK3β-mediated phosphorylation of tau is needed to induce hippocampal LTD [79], but also LTD-inducing stimuli cause GSK3β-mediated phosphorylation of tau in an NMDA receptor-dependent manner [78,79,87]. Concretely, tau has a main influence in the NMDA-triggered trafficking of AMPA receptors from synapses by promoting their internalization through the GSK3β/protein interacting with C kinase-1 (PICK1) pathway, which is key for LTD induction [79,103–105]. This suggests that only the induction of LTD is associated with the phosphorylation of tau as a downstream target of the GSK3β activity, since tau loss-of-function experiments blocked the induction of LTD but not LTP [78], and GSK3β activity is inhibited during the induction of LTP [106].

3.2. Pathogenic Tau in Synapses

Although tau is necessary at the postsynaptic area, it also acts as a mediator of AD-related synaptic deficits [107]. In fact, a recent proteomic study performed in post-mortem tissue from AD patients has revealed that hyperphosphorylated tau directly interacts with proteins that regulate synaptic plasticity [108]. However, these tau-associated synaptic pathologies can be seen even before the formation of NFTs [109,110], and they may be caused by different mechanisms.

The hyperphosphorylation of tau causes most of the pathological synaptic features seen in AD by increasing the mislocalization of tau from the axonal compartment to the somatodendritic compartment, where it aggregates into oligomers [80,111]. Indeed, AD brains show decreased levels of protein phosphatase 2 (PP2A), a phosphatase implicated in the regulation of AMPARs in membrane. Accordingly, treatments increasing PP2A levels improve the functional outcome in animal models of AD [110]. The increase in hyperphosphorylated tau at dendrites triggers different pathways underlying pathological synapse weakening. For example, it has been reported that there is a specific pruning of asymmetric synapses that is carried out by microglia and induced by hyperphosphorylated

tau [80,82]. Besides, aberrant tau is critically involved in the turnover and trafficking of NMDA and AMPARs related to the blockade of asymmetric LTP. Tau mediates the lateral movement of NMDARs from synapses to extrasynaptic regions [112], and the hyperphosphorylation of tau at serine 396 has been suggested as an enhancer of this diffusion [79,113]. Likewise, different aberrant types of tau decrease the synaptic clustering of both NMDA and AMPA receptors [101,114–117]. Recently, the use of the mass spectrometry has allowed the detection of significant decreases in AMPARs and NMDARs located at the PSD fraction in a mouse model of AD [80]. Overall, the induction of LTP at asymmetric synapses is compromised, which ultimately ends in the loss of dendritic spines [118]. A new study from Mijalkov et al. [81] has revealed that the loss of dendritic spines in AD individuals occurs at clustered locations and not as a random loss. This fact, added to the reduction in the miniature excitatory postsynaptic currents (mEPSCs) by a postsynaptic decrease in AMPA clustering [114], results in a compromised asymmetric synaptic transmission. The main player underlying this hyperactive LTD is again GSK3β, leading to aberrant phosphorylation of tau at the somatodendritic compartment and not at the axon, as thought at first [87,119,120].

A recent and surprising achievement came from the study of Park and coworkers [100] where they described the link between NMDARs, tau/PSD-95 complex and the neuronal nitric oxide synthase by which hyperphosphorylated tau disrupts this association and leads to endothelial dysfunction. This study highlights the complexity behind tauopathies, including AD, where many proteins involved in synapse weakening can also be playing other roles underlying brain dysfunction. Currently, several epigenomic studies on human AD tissue have revealed that different brain regions affected by tau pathology undergo histone acetyl changes that dysregulate transcription [108,121,122]. Following these lines, another new and promising line of investigation points at the relationship between tau aggregates and different RNA molecules, due to the fact that they can be found together in the cytosol and the nucleus [123]. Large concentrations of tau oligomers have a direct effect on nuclear speckles by altering its composition, organization and dynamics [123], which opens a new window to study how these tau-driven alterations in RNA processing can impact neurotransmitter receptor dynamics [124].

Another mechanism that can cause the misfolding of tau and subsequent formation of its pathogenic version is the extracellular deposition of Aβ [125]. A striking study from Fani and colleagues [126] has shown that extracellular Aβ oligomers are able to principally activate extrasynaptic NMDARs, but also AMPARs to a lower extent. This is carried out by interacting with the lipid membrane that perturbs its mechanical properties, leading to alterations in the mechanosensitivity of receptors (Figure 3) [126]. Since GSK3β kinase can be activated by NMDARs [87], it would not be strange to speculate that this mechanosensitivity-mediated activation of NMDARs can increase GSK3β activity and promote tau hyperphosphorylation (Figure 3). In fact, GSK3β kinase is also the main factor connecting extracellular Aβ with intracellular tau since the inhibition of GSK3β blocks the increase in phosphorylated tau and therefore prevents the Aβ-induced impairment of LTP [101,127]. Similarly to what is described above, treatments with Aβ oligomers enlarge the dendritic/synaptic location of phosphorylated tau [91], but only when tau it is already phosphorylated [128]. Other kinases can be also implicated in the aberrant function of tau induced by Aβ. For example, Wu et al. [129] obtained proteomic data suggesting that Aβ activates cyclin-dependent kinase 5 (CDK5) which eventually phosphorylates tau at synaptic sites.

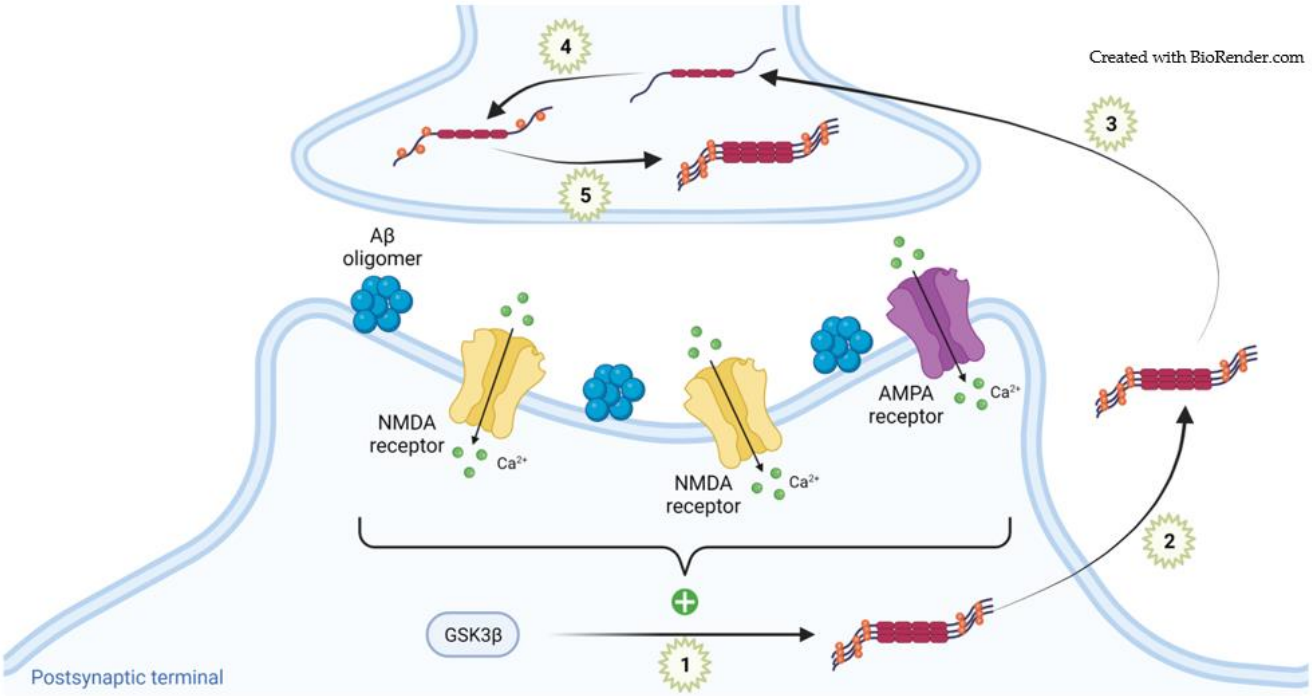

Figure 3. Aberrant tau phosphorylation mediated by Aβ oligomers and seeding. (**1**) The interaction of Aβ oligomers with the plasma membrane provokes the activation of NMDA receptors and subsequent entry of Ca^{2+}, and this activates the GSK3β hyperphosphorylating tau; (**2**, **3**) Aberrant tau can diffuse via plasma membrane to the extracellular space and corrupt healthy tau in another neuron, promoting its hyperphosphorylation (**4**, **5**).

Tau aggregates have the ability of recruiting and misfolding naïve monomeric tau, and so they corrupt healthy tau, spreading the neuronal damage in a process called seeding (Figure 3) [130]. This process has a major relevance since it has been recently discovered that the seeding of synaptic tau starts much before the pathology can be detected in human AD brains [94,131]. Interestingly, Dujardin et al. [132] have recently found that a higher seeding activity alarmingly correlates with the rate of clinical AD progression. Moreover, this seeding activity was significantly linked to the phosphorylation at several sites, as shown by mass spectrometry results [132]. Two major routes are involved in the dissemination of corrupted tau: (1) travelling between neurons through synapses, and (2) direct translocation to the extracellular space crossing the plasma membrane [94,125,133]. Similar to extracellular Aβ oligomers, extracellular tau oligomers trigger seeding and cause the aggregation of monomeric intracellular tau and its posterior mislocation to the somatodendritic compartment [134]. This mechanism is likely involved in the high inhibition of hippocampal LTP seen by Ondrejcak et al. [135]. Promisingly, a new pharmacological treatment promotes the microglial-mediated engulfment of extracellular tau oligomers and therefore blocks the spreading of tau pathology within neurons [82]. This achievement opens new lines of investigation addressing the blockage of aberrant tau dissemination once it is released to the extracellular space.

The upregulation of tau acetylation represents a novel mechanism promoting cognitive decline in AD patients [136]. The acetylation of different lysines may involve distinct pathological mechanisms, such as accumulation of toxic forms of tau and the enhancement of tau oligomerization, which can have a significant effect on the encoding of hippocampal-dependent memory, among other outcomes [119,136]. For example, the acetylation at specific residues, such as K280/K281, has dual and negative outcomes, the loss of microtubule-regulatory function and the gain of aberrant tau aggregation [137]. Related to the ability of tau for extracellular release and subsequent spreading, an interesting study from Caballero and coworkers [138] has revealed that acetylation reduces tau degradation and increases its extracellular location in AD brains.

4. Parkinson's Disease

Parkinson's disease (PD) is a chronic neurodegenerative disease involving the death of the nigral dopaminergic neurons by the combination of different factors, e.g., ambient, genetics, oxidative stress and/or aging [139–141]. The progressive disappearance of DA modulation in the basal ganglia (BG) leads to the characteristic motor symptoms of PD, i.e., akinesia, bradykinesia, resting tremor, and rigidity [141]. Adaptive changes at the synaptic level following DA depletion play a main role in the development of these symptoms.

The BG are composed of interconnected subcortical regions participating in a large variety of brain functions, such as motor programming and execution, and action selection, among others [142]. The mammalian BG comprise the striatum (STR), the external and internal segments of the globus pallidus (GPe and GPi, respectively), the subthalamic nucleus (STN), and the *substantia nigra pars compacta* and *pars reticulate* (SNc and SNr, respectively) (Figure 4) [142]. DAergic innervations provided by SNc neurons are essential for controlling BG functions, e.g., modulation of synaptic properties (Figure 4) [143]. Therefore, the degeneration of DA neurons leads to synaptic alterations underlying the appearance of PD motor symptoms [143,144].

Both symmetric and asymmetric synapses are present along the different BG nuclei, and they are modulated by DAergic terminals. Following DA denervation, both synapses suffer major changes that underlie motor symptoms of PD. Here, we will present the synaptic symmetry in the different BG nuclei and how it changes after the death of DA neurons.

4.1. Symmetric Synapses

The majority of the nuclei are inhibitory, so GABAergic innervations represent the main system to regulate the firing rate and the pattern of neuron responses within the BG, such as hyperpolarizing the membrane potential that resets the pacemaking activity of neurons [145–147].

4.1.1. The Striatum—STR

The STR comprises the largest integrating nucleus for cortical and thalamic inputs (see next subsection "*asymmetric synapses*" for more information). The main cell population in the STR is the GABAergic spiny projection neurons (SPNs), with several classes of other GABAergic and cholinergic interneurons [148,149]. SPNs process afferent information to BG in direct (d) or indirect (i) pathways, that are defined by two different types of SPNs: dSPNs and iSPNs, respectively (Figure 4) [150,151]. dSPNs expresses D1 receptors and project directly to SNr/GPi, whereas GPe and STN relay the information from iSPNs-expressing D2 receptors to SNr/GPi (Figure 4) [150,151]. Accordingly, these different pathways give rise to opposite motor outputs, the release of GABA and a subsequent decrease in the activity of SNr/GPi neurons through the activation of dSPNs that reduces tonic inhibitory outputs to downstream motor regions and promotes movement; and the activation of iSPNs that produces an excitatory effect on SNr/GPi neurons by disinhibiting mechanisms and results in inhibiting movement [152].

4.1.2. The External Segment of the Globus Pallidus—GPe

The GPe is composed of two main subtypes of neurons, the prototypic and arkypallidal neurons [153]. The first projects downstream to STN and SNr nuclei, and upstream to the STR; whereas the latter exclusively projects to the STR, being the most important source of GABA (Figure 4) [154]. Projections from GPe neurons to the cortex and thalamus have been also reported [155]. The inhibition provided by prototypic neurons is key to reset the autonomous activity of STN neurons [156]. Likewise, GPe neurons are the receivers of GABAergic extrinsic innervations from iSPNs (the majority of them) and dSPNs, intrinsic innervations from collaterals of prototypic neurons to other GPe neurons, and interconnections between prototypic neurons (Figure 4) [157,158]. Moreover, arkypallidal neurons integrate signals from dSPNs, iSPNs and STN [158]. Both short-term facilitation

(STF) and short-term depression (STD) can be found at extrinsic synapses, while intrinsic synapses present STD [159,160].

4.1.3. The Substantia Nigra Pars Reticulate—SNr

The SNr operates as an integrating nucleus, as each SNr neuron receives afferents from different origins such as dSPNs, the GP and the STN (Figure 4). Symmetric synapses from STR and GPe display opposite mechanisms as STR–SNr inhibitory postsynaptic currents (IPSCs) exhibit STF, whereas GP–SNr IPSCs are influenced by STD [161]. SNr neurons display a significant level of spontaneous firing rate that allows a tonic inhibition of downstream motor areas (Figure 4) [162,163]. They present a high collateralization and receive solid inhibitory inputs, acting through both ionotropic ($GABA_A$) and metabotropic ($GABA_B$) receptors, even during a strong activation [164–166]. Four types of GABAergic neurons projecting to different targets can be found in the SNr, the thalamus being the one that receives the majority of SNr innervations [167,168].

4.1.4. Healthy and Pathological DA Modulation in Symmetric Synapses

STR is the main target of nigral DAergic innervation [144]. As previously mentioned, dSPNs and iSPNs express D1 and D2 receptors, respectively, which gives rise to opposite motor outputs following DA release. Upon DA release, dSPNs increase their activity through D1 receptor activation, whereas D2 receptors mediate the decreased activity of iSPNs (Figure 4) [169,170]. The resulting effect is the overactivation of the direct pathway compared to the indirect one, disinhibiting the thalamus and initiating movement. Therefore, DA modulates synaptic and intrinsic properties of STR neurons by activating distinct DA receptors (Figure 4). Recently, an interesting study has revealed that astrocytic GATs play a critical role in the regulation of striatal DA release by removing extrasynaptic GABA spillover, decreasing tonic inhibition, and therefore, promoting DA release [171]. Indeed, there is an inadequate reduction in GATs that further impairs DA output at early steps of the disease [171]. Following full DA depletion, the overall activity of dSPNs decreases and there is a loss of spine density [152]. Consequently, this disinhibits GABAergic projections from SNr/GPi neurons [172]. In contrast, the lack of DA increases the excitability of iSPNs by eliminating the inhibition through D2 receptors, even when there is also a reduction in spine density (Figure 4) [152,170]. Furthermore, the lack of DA has been also related to a higher GABA production, as shown by a nuclear magnetic resonance spectroscopy study in the striatum of a rat model [173]. Altogether, this disinhibits STN activity leading to a higher excitation of SNr/GPi [170,174]. The resulting outcome is the imbalance between direct and indirect pathways shown by the reduction in motor outputs (paucity and slowness of movements), exposing the capital need of having a coordinated striatal activity [175,176].

DA modulates the excitability of GPe neurons, the D2 receptor being the one that is present in all GPe neurons, although prototypical neurons show higher levels of D2 receptors than arkypallidal neurons [177]. Accordingly, activation of presynaptic D2 receptors reduces the GABAergic pallidosubthalamic innervations, decreasing the strength of this connection [178]. Under the parkinsonian state, the activity of prototypic cells is likely disrupted by the hyperactivity of iSPNs, as previously mentioned (Figure 4) [179,180]. However, this is not an obstacle to see an increased GPe–STN GABAergic transmission in a NMDA-mediated manner [181,182]. Similarly, the GABAergic inhibition from arkypallidal neurons to STR is increased under DA depletion, even when their excitability is reduced (Figure 4) [183,184]. As previously stated, both STF and STD can be seen in striato-pallidal and pallido-pallidal synapses, respectively [159,160]. Besides their opposite roles, STF and STD also have the difference that only the STF strength is modulated by presynaptic D2 receptors, resulting in a decreased GABA release [185]. Additionally, GABAergic transmission can be regulated by reducing the amplitude of $GABA_A$-mediated postsynaptic currents through the activation of D4 receptors. Similarly, intrinsic connections can also reduce the postsynaptic firing rate [186]. Only the study from Stefani and colleagues [187]

shed light on action mechanisms underlying the reduced excitability seen in GPe neurons. There, the authors showed that the activation of D2 receptors inhibits GPe excitability in a protein-kinase-C-dependent manner.

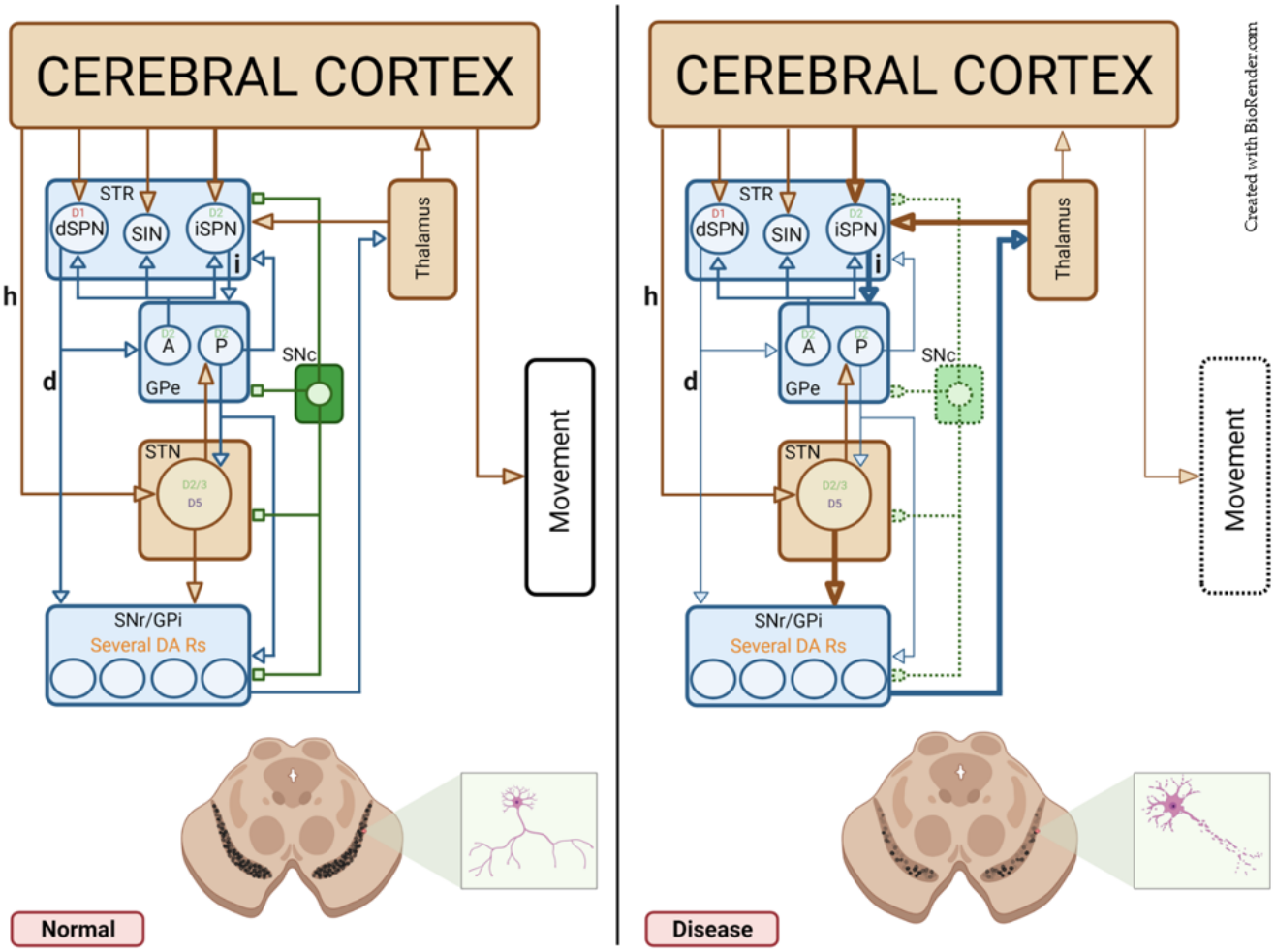

Figure 4. Basal ganglia network in normal condition and its changes during PD. (**Normal**) In the healthy brain, cortical asymmetric inputs activates both GABAergic (blue) and glutamatergic (brown) neurons in the STR and STN, respectively. The information from cortical efferents to the SNr/GPi can be transmitted through 3 different ways: the direct (d), indirect (i), and hyperdirect (h). Then, the SNr/GPi regulates the outcome of downstream motor control areas. Dopaminergic projections (green) from the SNc modulate cellular activity through distinct DA receptors (DA Rs). (**Disease**) Following the degeneration of DAergic neurons, there is an imbalance due to the hyperactivity of the indirect pathway and the hypoactivity of the direct pathway, leading to the disinhibition of both the STN and GPi/SNr (red), and resulting in an enhanced inhibition of downstream motor regions.

Functions of the SNr are also modulated by DA through the expression of different receptors in SNr neurons (Figure 4). Although D1 receptors are the ones more expressed, the presence of D4 and D5 receptors has been also reported [188–190]. The study by Zhou et al. [191] revealed that the activation of D1 receptors depolarizes SNr neurons, and therefore excites them. In contrast, the pharmacological blockade of D1 or D2 receptors leads to the hyperpolarization of SNr neurons, and this is similar to what was seen in recordings from rodents with DA depletion [192,193]. For STR–SNr synapses, there is an increase in IPSCs amplitude that is likely driven by both dysfunctional $GABA_B$ receptors and a presynaptic reduction in GABA release [194]. Regarding synaptic regulation, presynaptic D4 receptor activation reduces the transmission in GPe–SNr connections, whereas presynaptic D1 receptors mediate the increase in GABAergic signaling [195,196].

4.2. Asymmetric Synapses

4.2.1. The STR

The STR integrates cortical and thalamic excitatory information, making contact with the spine heads of GABAergic SPNs (Figure 4) [149,197]. Within the STR, cortical and thalamic terminals can be differentiated by the distinct expression of vesicular glutamate transporter 1 (vGLUT1) and vesicular glutamate transporter 2 (vGLUT2), respectively [198]. These excitatory inputs are key to hyperpolarizing SPN neurons, which subsequently allows the firing of their action potentials (APs) [199,200]. Both dSPNs and iSPNs express AMPA and NMDA receptors, as well as metabotropic glutamate receptors (mGluRs) that mediates synaptic transmission and LTP/LTD [201]. In dSPNs, the activation of NMDA and D1 receptors is responsible for the LTP induction, whereas LTD induction is mediated by muscarinic acetylcholine M4 and mGluR5 receptors [202,203]. On the other hand, LTP induction in iSPNs is mediated by the activation of NMDA and A2A receptors, whereas LTD is induced by postsynaptic D2 receptors and mGluR5 receptors [202].

4.2.2. The Subthalamic Nucleus—STN

Similarly to STR, the STN receives monosynaptic inputs from the cerebral cortex through the hyperdirect pathway (Figure 4) [197]. Subsequent AMPAR/NMDA-mediated postsynaptic excitatory currents (EPSC), along with GPe inhibition, regulate the ability of STN neurons to fire APs spontaneously [182]. These antagonistic inputs regulate the firing rate and pattern of STN transmission, and changes in the firing pattern are considered a hallmark of PD [204,205]. In contrast to the inhibitory STR, STN neurons are glutamatergic and project simultaneously to the GPe and SNr/GPi (Figure 4). Concretely, activation of STN provides two different outcomes: strong and sustained excitation of prototypic cells leading to the disinhibition of SPNs, and briefly, excitation of arkypallidal, implying a short time inhibition onto SPNs (Figure 4) [158,206]. Regarding SNr, STN innervations represent the main excitatory inputs, triggering monosynaptic EPSCs and increasing GABAergic signaling in downstream motor areas [162,207].

4.2.3. Healthy and Pathological DA Modulation in Asymmetric Synapses

DAergic innervation in the STR is involved in two capital aspects: regulating LTP of cortiostriatal synapses, and also regulating the functional specificity of STR neurons in response to cortical and thalamic afferents [208]. Accordingly, DAergic denervation promotes the loss of cortico- and thalamo-striatal terminals, leading to a dysregulation of activity between direct and indirect pathways as well as important changes in LTP and LTD (Figure 4) [151,208,209]. Indeed, the death of nigral DAergic neurons reverses the strength of thalamic inputs to dSPNs and iSPNs by enhancing thalamostriatal inputs only to iSPNs, therefore driving asymmetric activation of basal ganglia (Figure 4) [210]. As previously mentioned, LTP and LTD are present in striatal SPNs, and this bidirectional synaptic plasticity is altered in the parkinsonian state [209,211]. Without DA, dSPNs lose LTP due to the absence of D1 receptor activation, similar to the lack of LTD in iSPNs because of a lack of D2 receptor activation [202]. These PD-associated changes give rise to a scenario where dSPNs only exhibit LTD and iSPNs only exhibit LTP, leading to a disruption between dSPNs and iSPNs activity [211].

DA release has a main role in the function of STN neurons by regulating synaptic transmission as well as the strength of cortico-subthalamic inputs, therefore, lacking DA modulation has dramatic consequences in locomotion [204,212]. D2 and D5 receptors are the ones with high levels of expression on the STN neuron membrane, and the activation of each one has different outcomes for their firing rate (Figure 4) [15,213]. Previous results have revealed that D2 activation increases the firing discharge of STN neurons by depolarizing the membrane potential [214]. The activation of D5 receptors, however, triggers different conductance depending on the mode of discharge of STN neurons [215]. Hyperpolarized STN neurons fire bursts of APs, and D5 activation prolongs burst duration [216]. In depolarized STN neurons, D5 activation increases the firing rate of single and tonic

APs [217]. More recently, it has been shown that the activation of D5 receptors in STN neurons can modulate cortical inputs by depressing AMPAR-mediated EPSC [214].

Following DAergic denervation, STN neurons lose their autonomous pacemaking due to both increased inputs from iSPNs to GPe neurons that disinhibits STN neurons, and excessive activation of NMDARs [218] even when the cortical glutamatergic innervations is significantly reduced (Figure 4) [219–221]. This fact, and probably alterations in other channels such as the potassium/sodium hyperpolarization-activated cyclic nucleotide-gated ion channel 2 (HCN2) [222], allows a pathological hyperactive state for STN neurons with rhythmic and synchronous bursts of APs [223]. Under this state, there also is a strengthened connection between GPe and STN that is mediated by an excessive activation of NMDARs in the STN [176,181]. Although this can be contradictory, it can be explained since STN neurons activity is off-phase to GPe activity and in-phase to cortical activity [224] so it is expected that GPe–STN inhibitory inputs are less effective in suppressing cortical excitation [225].

Regarding SNr, dopamine receptors D1 and D2 have opposite roles modulating EPSC amplitude: the D1 receptor acts as an enhancer, while the D2 receptor decreases it [226]. The presence of LTD at STN–SNr synapses, induced by the activation of postsynaptic D1 receptors, has also been reported. During this LTD, endocytosis of AMPARs mediated by NMDARs depresses EPSC amplitude [214]. In the absence of dopamine, STN–SNr LTD is completely depleted leading to an increased synaptic transmission in the STN–SNr circuitry [227,228].

5. Conclusions

Both asymmetric and symmetric synapses have important roles in shaping the structural and functional outcomes of the brain. Therefore, the balance between excitation and inhibition is capital for a correct cerebral function. Besides, even after a particular damage, the progression of the disease defines the response of circuitries; something beneficial at the beginning becomes negative later. In this regard, it has been described that promoting symmetric signaling following cerebral ischemia is beneficial only during the acute phase; afterwards, it further increases the initial damage. Synapses can be also altered by players not directly related to them; in Alzheimer's Disease, the chronic and long-term neurodegeneration mediated by tau targets primary asymmetric synapses, decreasing neuronal plasticity and functionality. Indeed, the death of midbrain dopaminergic neurons impairs locomotion, underlying Parkinson's disease. Since symmetric and asymmetric synapses play an important role in the pathophysiology of several neurological disorders, such as stroke, Alzheimer's or Parkinson's Disease, further studies are needed to elucidate the underlying molecular mechanisms that could lead to the development of new therapeutic targets for these devastating diseases.

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