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REVIEW ARTICLE

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Alteration of GABAergic neurotransmission in Huntington's disease

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Summary

Hereditary Huntington's disease (HD) is characterized by cell dysfunction and death in the brain, leading to progressive cognitive, psychiatric, and motor impairments. Despite molecular and cellular descriptions of the effects of the HD mutation, no effective pharmacological treatment is yet available. In addition to well-established alterations of glutamatergic and dopaminergic neurotransmitter systems, it is becoming clear that the GABAergic systems are also impaired in HD. GABA is the major inhibitory neurotransmitter in the brain, and GABAergic neurotransmission has been postulated to be modified in many neurological and psychiatric diseases. In addition, GABAergic neurotransmission is the target of many drugs that are in wide clinical use. Here, we summarize data demonstrating the occurrence of alterations of GABAergic markers in the brain of HD carriers as well as in rodent models of the disease. In particular, we pinpoint HD-related changes in the expression of $GABA_A$ receptors ($GABA_A$Rs). On the basis that a novel GABA pharmacology of $GABA_A$Rs established with more selective drugs is emerging, we argue that clinical treatments acting specifically on GABAergic neurotransmission may be an appropriate strategy for improving symptoms linked to the HD mutation.

KEYWORDS

basal ganglia, disease progression, inhibitory postsynaptic currents, inhibitory tonic currents, rest/activity fragmentation, synapse

1 | INTRODUCTION

Huntington's disease (HD) is a hereditary neurodegenerative disease, caused by a mutation of the huntingtin protein that impairs cell functions and produces cell death. HD is associated with cognitive and psychiatric disturbances that precede chorea and other motor impairments. Several postmortem studies in humans have shown only limited signs of cell loss in the brain, despite overt clinical symptoms and the genetic confirmation of HD,[1-3] suggesting that neuronal and synaptic dysfunction, rather than cell death, may underlie the early behavioral manifestations of the HD mutation.[4,5] In addition, cognitive, psychiatric, motor, electrophysiological, and neuroimaging assessments in humans also suggest that early cognitive deficits occur years prior to cell death or predicted clinical diagnosis in HD carriers, and are probably due to synaptic and cellular dysfunction.[6-8]

The expression of the huntingtin protein is ubiquitous, and the mutation for HD affects virtually all brain structures. However, alterations are most obvious in the striatum. This structure is the main input nucleus of the basal ganglia, a group of subcortical nuclei that are closely connected with several brain areas, including the cerebral cortex and the thalamus.[9] The basal ganglia are considered to be involved in voluntary movement, memory, and cognitive functions. Medium spiny neurons (MSNs) are major constituents of the striatum and are comprised of 2, anatomically nonsegregated, subpopulations: 1 expressing mainly dopamine D1 receptors and the other expressing dopamine D2 receptors.[10] The 2 subpopulations are at the

origin of the direct striatonigral and indirect striatopallidal pathways, respectively. These projection neurons are also regulated by different classes of local interneurons.[11,12] Being tightly connected to the striatum via the indirect pathway, the external globus pallidus (GPe) is considered as a hub within the basal ganglia.[13-15] It is important to note, furthermore, that an alteration in GPe function is linked to HD symptoms.[16-20] The GPe also receives GABAergic collaterals from the direct pathway,[21] glutamatergic projections from the subthalamic nucleus, and some dopaminergic inputs from the substantia nigra pars compacta.[14] The GPe projects to virtually all basal ganglia components, including the striatum.[22] Interestingly, direct connections with the cortex have been recently described.[23,24] Therefore, the GPe may play an important integrative role in coordinating neuronal activity throughout the basal ganglia with direct links to the cortex.

Studies in animal models have established that glutamate neurotransmission, including glutamate release, clearance and receptor trafficking, is altered in HD (reviewed in[4,5,25]). An early alteration of glutamatergic neurotransmission has been recently described in the subthalamic nucleus neurons of BAC transgenic and Q175 knock-in mouse models of HD, leading to the loss of autonomous pacemaking.[26] Because the striatum receives extensive excitatory glutamatergic innervation from the cerebral cortex and thalamus and is primarily affected in HD, changes in glutamatergic neurotransmission resulting in excitotoxicity and neuronal damage have been considered as a key event in HD pathogenesis. Besides the impairment of the predominant excitatory glutamate neurotransmission, inhibitory GABAergic neurotransmission, although largely neglected, is also altered in the HD-affected brain.[27-30] This review focuses mainly on our current knowledge of the alteration in inhibitory neurotransmission through changes in $GABA_A$ receptor ($GABA_AR$) subtype expression (Figure 1A). We will also consider whether current pharmacological tools targeting GABAergic transmission could be of relevance for future treatment of HD symptoms.

2 | GABAergic NEUROTRANSMISSION

GABA exerts inhibitory control on many neurons in the central nervous system. The diversity in GABAergic signaling is due to several peri-, pre-, and postsynaptic factors (Figure 1B) that are the target of many drugs that are currently in wide clinical use.[31,32] It is also well documented that an alteration in any aspect of this system is linked to several neurological and neurodevelopmental disorders.[33-40] $GABA_AR$s are the main inhibitory receptors in the brain, and their heteromeric structure contributes in several ways to the physiological properties of brain GABAergic neurotransmission. GABA also acts on $GABA_BR$s which have different molecular and functional properties to those of $GABA_AR$s (eg, see [41]). As data on alterations of $GABA_B$ neurotransmission in HD are sparse, they are not considered further in this review.

3 | STRUCTURE AND FUNCTION OF $GABA_AR$s

Ionotropic $GABA_A$ receptors are responsible for fast and flexible postsynaptic transmission. GABA binding results in the opening of anion-selective intrinsic channels through which primarily chloride anions flow. This in turn changes neuron excitability. Many studies have demonstrated that the subunit composition determines both the functional properties and subcellular localization of $GABA_AR$s. These receptors are heteromeric structures composed of a combination of

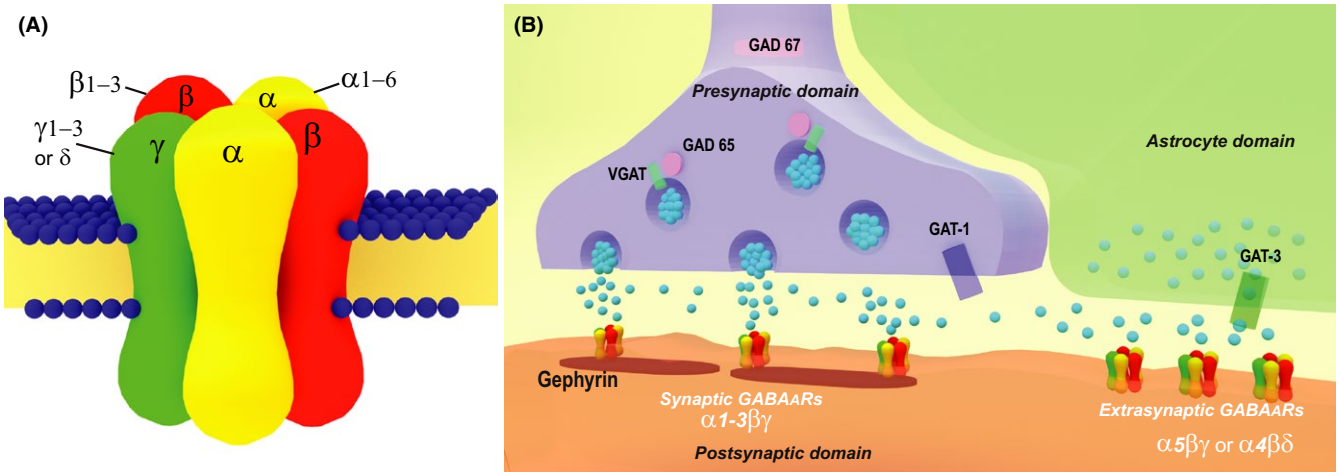

FIGURE 1 Schematic drawing of $GABA_A$ receptors ($GABA_AR$s, A) and a GABAergic synaptic terminal (B). Native $GABA_AR$s, which are heteropentameric structures containing α1, α2, or α3 with β and γ subunits, are located at the synapse and mediate a phasic inhibitory effect correlated with presynaptic action potentials. The aggregation of receptors on the postsynaptic domain depends on scaffolding proteins, including gephyrin. $GABA_AR$s containing the α5 or δ subunits are extrasynaptic with a high sensitivity to GABA and mediate tonic activity as a function of ambient transmitter level in the extracellular space. GABA levels depend on the expression of 2 isoforms of glutamate decarboxylase (GAD 67 and 65), the vesicular transporter VGAT, and the transporters GAT-1 and GAT-3. These GABAergic components are all subject to alteration in Huntington's disease

5 of 19 different subunits, grouped in several classes.[42-44] Different subtypes of $GABA_A$Rs are generated by a coassembly of the α1-6, β1-3, γ1-3, δ, ε, θ, π, and ρ1-3 subunits.[45] Strong evidence supports a model in which subunit composition confers a distinctive cellular distribution, functional properties, and the specific effect of allosteric modulators like benzodiazepines or neurosteroids.[36,45,46] In brain regions, including the striatum, synaptic neurotransmission mediating phasic inhibition is linked to $GABA_A$Rs composed of α1, α2, or α3 in combination with β and γ2 subunits (Figure 1A). The substitution of an α5 by an α1-3 or a δ by a γ2 subunit has been shown to form extrasynaptic receptors (Figure 1B) mediating tonic inhibition.[47,48] Indeed, it is now established that receptor subtypes are associated with significant physiological outcomes and specific cognitive functions.[37,49,50] These findings have in turn led to the search for selective drugs with enhanced efficacy and fewer side effects.[51]

4 | ALTERATION OF THE GABA SYSTEM IN THE HD BRAIN

Over the last decades, benzodiazepine or muscimol binding on $GABA_A$Rs has been widely used. Postmortem analyses in the human HD brain have shown a decrease in benzodiazepine binding in the caudate nucleus or the putamen.[52-54] In contrast, binding is increased in the cerebellum, frontal cortex, and the GPe.[53-56] Other studies have measured concentrations of GABA and found a decrease in the caudate putamen and the GPe.[57,58] More recently, positron emission tomographic (PET) imaging using [^{11}C]flumazenil as a marker of $GABA_A$Rs has been performed (reviewed in[59]). In patients with early HD, benzodiazepine binding levels were found to be reduced in the caudate nucleus, while no changes were observed in the putamen, thalamus, frontal cortex, or cerebellum.[60,61] Transcranial magnetic stimulation investigations have revealed significant GABA-mediated cortical inhibitory deficits in premanifest and early symptomatic HD patients.[62]

The most thorough and recent investigations on GABAergic neurotransmission, including molecular and functional analyses, have been conducted on transgenic rodent models. Interestingly, quantitative autoradiography has been used to assess neurotransmitter receptor densities in several brain regions in a rat model for the HD mutation.[63] These analyses showed that the expression levels of receptors of the cholinergic, dopaminergic, serotoninergic, noradrenergic, glutamatergic, and GABAergic systems are either increased, decreased, or remain unchanged. These findings in turn suggest that receptor alterations in HD are subtype selective and regionally differential. Moreover, the most recent studies on GABAergic neurotransmission in the striatum have analyzed receptor subtype alterations in identified neurons.

5 | ALTERATION OF GABA NEUROTRANSMISSION IN MSNs

In the striatum of transgenic mouse or rat models of HD, no changes in benzodiazepine or GABA binding [63,64] or a slight, albeit significant increase[65] have been reported. Functional and molecular analyses of GABAergic neurotransmission in the striatum have revealed complex changes in this brain structure (Figure 2). The kinetics of evoked GABAergic currents are altered in MSNs of animal models of HD,[66] associated with a reduction both in rise and in decay times leading to faster currents. Because it is well established that α1 is responsible for fast inhibitory currents,[67] this kinetic alteration is probably linked to the global increase in α1 subunit expression in the MSN neuropil of HD mice.[68,69] In addition to the increased expression of α1, immunohistochemical labeling analyses of MSN cell body membranes showed an increased number of clusters containing the α2 subunit at postnatal 2 months followed by a decreased expression at 6 months in presymptomatic and symptomatic R6/1 mice, respectively.[69] Among α subunits, α2 is the major component of $GABA_A$Rs in MSNs. Thus, a decreased expression of the α2 subunit on MSN cell bodies of 6-month-old R6/1 mice[69] is consistent with a decreased number of GABAergic terminals in contact with MSN somata in the zQ175 KI mouse model of HD.[29] In vitro analyses have shown that cell surface receptor expression, as well as the expression of α1 and α2 subunits in MSNs, is regulated by dopamine and $GABA_A$R activity.[70,71] Thus, changes in $GABA_A$R subtypes might be directly linked to alterations of both dopaminergic and GABAergic neurotransmission in HD.[66,72] An alteration of $GABA_A$R trafficking resulting in reduced mIPSCS has also been shown in striatal MSNs of the N171-82Q mouse model.[73]

It is also interesting to note that the α1 subunit is present in postsynaptic structures facing dopaminergic striatal synapses [74] which are believed to corelease dopamine and GABA onto MSNs.[75-77] Although the functional role of this GABAergic inhibition remains elusive, it would be of interest to analyze the impact of the HD mutation on nigrostriatal synaptic transmission.

6 | ALTERATION OF GABA NEUROTRANSMISSION IN STRIATAL INTERNEURONS

Other than the predominant MSN projection neurons in the striatum, several local interneurons (INs) are also GABAergic (Figure 2). It is well established that the GABAergic control of MSNs originates from different classes of INs[78]: fast-spiking INs (FSI) expressing parvalbumin, persistent low-threshold spiking INs (PLTS) expressing somatostatin or nNOS, INs expressing calretinin, as well as collaterals from MSNs themselves (Figure 2). In addition to these GABAergic neurons, the striatum also contains cholinergic INs that regulate local inhibitory circuits.[79] Striatal INs are relatively spared from degeneration in HD, although there is evidence for dysfunctions.[66,80-84]

In the brain, GABAergic INs are involved in the coordination and regulation of network functions, and many pathological conditions are linked to their alteration.[47,78,85,86] In the striatum, it has been suggested that the functional role of inhibition from fast-spiking PV cells might be in shaping striatal output conveyed in

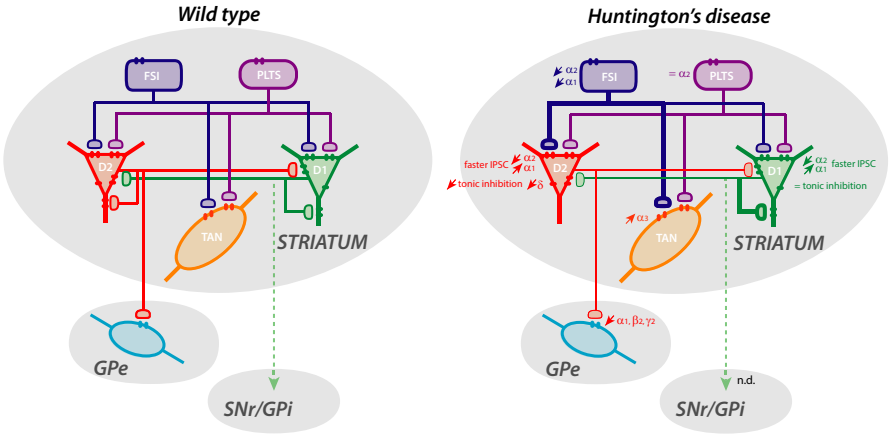

FIGURE 2 Schematic representation of striatal local circuits highlighting alterations of inhibitory currents and $GABA_AR$ subunit expression in identified neurons in mouse models of HD. The striatum includes medium-sized output neurons expressing dopamine D1 or D2 receptors, and fast-spiking, persistent low-threshold spiking, or tonically active interneurons. The 2 main projection pathways to the external globus pallidus and substantia nigra pars reticulata/internal globus pallidus are also indicated. Alteration of inhibitory currents in symptomatic HD mice is indicated by thicker (increase) or thinner (decrease) lines. Alteration in subunit expression or tonic inhibition is indicated by↑, increase; ↓, decrease; or =, no change. The figure was constructed using data from[30,66,69,80,101]

both direct and indirect pathways.[87] This feed-forward inhibition from fast-spiking PV INs to MSNs is altered in HD.[66] We found a decreased expression of the α1 subunit in striatal PV interneuron cell bodies at postnatal 2 and 6 months, while the expression of α2 is increased at 2 months and decreased at 6 months.[69] Although a comprehensive study of the molecular, pharmacological, and functional properties of GABAergic conductances in these cell types is still lacking, the increased expression of the α2 subunit and decreased expression of α1 in mutant mice predict that GABAergic currents in PV cells from 2-month-old R6/1 should have lower decay times compared to their WT counterparts.[67] Interestingly, following a striatal-dependent cognitive task, we found an alteration in activation of interneurons that express parvalbumin in the dorsomedial striatum at both presymptomatic and early symptomatic ages, thereby confirming a severe and early impairment of these INs in HD mice.[84]

Cholinergic INs also play a major role in striatal physiology.[83] It has been shown that in human and animal models, there is no, or a limited, loss of these INs, whereas the level of vesicular acetylcholine transporters and choline acetyltransferase is decreased.[81,88,89] In symptomatic R6/1 or R6/2 mice, a decrease in acetylcholinesterase expression and acetylcholine levels has also been reported.[69,90] With immunohistochemical labeling, we found an increased expression of the α3 $GABA_AR$ subunit in cholinergic INs.[69] The α3 subunit is the main α subunit expressed in cholinergic striatal INs,[91] which is likely to represent the major $GABA_AR$ subtype in these neurons. In R6/2 mice, striatal cholinergic INs receive more GABAergic inhibitory postsynaptic currents compared to their WT counterparts.[80] Together these data suggest that an increased number of α3-containing postsynaptic $GABA_ARs$ are involved in the increased inhibition of striatal cholinergic INs in HD (Figure 2) and underlie the decreased level of acetylcholine.

7 | ALTERATION OF TONIC INHIBITORY NEUROTRANSMISSION

Both δ- and α5-$GABA_ARs$ are responsible for generating tonic inhibitory conductances in the brain (Figure 1), which is recognized as a key factor in controlling local networks.[35,92] These 2 $GABA_AR$ subtypes are developmentally regulated in MSNs.[48] Tonic inhibition is decreased in MSNs in mouse models of HD.[66,93] In addition, a decrease in striatal δ subunit mRNA expression has been reported in different HD mouse models as well as in human patients,[69,94,95] suggesting that a reduction in δ subunit expression plays a major role in the tonic inhibition decrease. It is also of note that it has been shown[93] that an alteration in tonic GABA currents in HD might be also due to a reduced release of GABA from surrounding astrocyte processes (Figure 1B). However, the role played by astrocytes in the regulation of GABA homeostasis remains poorly understood, and further studies should be conducted to tackle this important question. A striking finding in a recent study from our laboratory was that α5 and δ subunit expression in the striatum is increased and decreased, respectively.[69] In addition to MSNs, the expression of both α5 and δ subunits has been identified in striatal INs.[48,66,93,96] Because tonic inhibition of interneurons may also be modified in many movement or psychiatric disorders,[47,78] it would be of interest to identify the neuron types whose specific α5 or δ subunit expression is modified in HD.

Taken together, analyses in the striatum of HD brains show that GABAergic neurotransmission undergoes complex changes leading to alterations in synaptic and extrasynaptic GABAergic functions. The change in $GABA_AR$ subunit composition would likely influence the pharmacological and gating properties of the $GABA_ARs$ of interneurons and MSNs and thus alter inhibitory neurotransmission in the striatum of the HD brain. Interestingly, the change in synaptic $GABA_A$ receptor subunit expression in HD follows the opposite

trend in experimental models of Parkinson's disease,[97] suggesting the occurrence of mirror alterations in GABAergic synaptic neurotransmission in hyperkinetic and hypokinetic disorders, respectively.

8 | ALTERATION OF GABA NEUROTRANSMISSION IN THE GPe

The GPe receives many sources of GABA. In addition to massive GABAergic input from the striatal indirect pathway,[98] local GPe collaterals[99] and bridging collaterals from the striatal direct pathway[21] control GPe neuronal excitability. In humans, the GPe is overactive in HD,[19] and GPe deep brain stimulation has been shown to alleviate motor and cognitive dysfunctions in both human patients and a rat model of HD.[16-18,20] Ex vivo, the firing pattern of GPe neurons is altered in R6/2 mice where blockade of $GABA_A$Rs facilitates bursting activity.[100] It is then reasonable to anticipate that the HD mutation has an impact on GABAergic neurotransmission in this brain structure.

In R6/1 mice, we showed a decreased expression of α1, β2, and γ2 subunits (Figure 2) in addition to a decreased expression of the vesicular GABA transporter (VGAT) involved in the synaptic release of GABA as well as gephyrin and neuroligin 2, both of which are involved in inhibitory synapse formation.[101] We also found a decrease in the frequency of mIPSCs (Figure 2) supported by a reduced number of synapses, whereas the amplitude of mIPSCs was not altered, suggesting that the number of receptors in individual synapses is not decreased. Interestingly, the modification of mIPSC kinetics in 2-month-old R6/1 mice in the absence of a change in the short-term facilitation of striatopallidal synapses suggested postsynaptic alterations in $GABA_A$R subunit composition.[102]

In addition to α1, β2, and γ2 subunits, α2, α3, and γ1 are also expressed in the GPe.[103,104] The GPe also contains a number of distinct neuronal subtypes and projections with different physiological functions.[13,14] It would thus be of interest to investigate the localization of the different subunits expressed in GPe neurons and correlate functional property alterations with specific $GABA_A$R subtypes. It is of note that data on the GPe from R6/1 and HdhQ111 mouse models [101] are at odds with immunohistolabeling from the postmortem human GPe.[105] This may highlight one limitation of rodent models where a limited neuronal death is observed.[106] It also suggests that rodent transgenic models display an alteration occurring in humans, before any dramatic cell damage occurs in the brain. The hyperactivity of the GPe in animal models and human HD [20,107] may be the consequence of a decrease in GABAergic neurotransmission and $GABA_A$R synapses. The development of PET analyses in the future should allow monitoring the evolution of GABA binding, well before the overt onset of the disease.

9 | POTENTIAL THERAPEUTIC AVENUES

Although $GABA_A$ neurotransmission is clearly altered in HD, drugs, whether already approved or under clinical trials, are currently being employed to target other neuromodulatory systems aiming to improve motor dysfunction in HD.[5] Only limited treatment evaluations have been conducted,[108-111] and to our knowledge, no drug therapies that target the alteration in GABAergic neurotransmission in HD are currently available (reviewed in[112]). A new benzodiazepine pharmacology acting on $GABA_A$Rs and comprising selective hypnotics, nonsedative anxiolytics, and cognition enhancement is emerging.[32] This suggests potential therapeutic avenues for nonmotor symptoms including anxiety, sleep alteration, cognitive dysfunctions, or psychiatric disorders linked to the HD mutation that are present long before the appearance of overt motor symptoms (reviewed in[113]). In addition, an altered tonic inhibitory conductance as found in HD (see above) is also the therapeutic target for the treatment of several other diseases.[114,115]

Sleep disturbances are believed to contribute to HD symptoms,[116-118] and recent findings suggest that the GABA system may be a target for preventing sleep alteration and reduce the cognitive and psychiatric symptoms of this neurodegenerative disease.[119-121] In transgenic mouse models, it has been shown recently that treatment with zolpidem, an hypnotic benzodiazepine acting preferentially on α1-containing $GABA_A$Rs, corrects EEG abnormalities.[119] In addition, the regulation of sleep/wake activity with a benzodiazepine treatment has been found to improve cognitive function and apathy.[121] Interestingly, consistent with the well-established alteration of rest/activity in HD,[101,116,122-124] a role for the basal ganglia in sleep/wake regulation has been highlighted (reviewed in[125]), and lesions of the GPe in rats have a profound effect on sleep/wakefulness fragmentation.[126] A link between the striatopallidal pathway and the regulation of sleep/wake behavior has also been shown very recently.[127] Therefore, it is tempting to speculate that an early alteration in GABAergic neurotransmission in the striatum or GPe and an early modification in rest/activity are not independent phenomena.

Based on analyses with point-mutated mice of a benzodiazepine binding site, it was possible to attribute specific behavioral responses following benzodiazepine treatments to specific $GABA_A$Rs comprising either α1, α2, α3, or α5 subunits, thereby providing the opportunity to selectively modulate brain areas or neuronal networks (review in[128]). In HD, changes in $GABA_A$R subtype expression are specific not only to brain area[53,63,69,101,129] but also to neuronal cell type.[66,69] The fact that the expression of $GABA_A$R subunits in the different striatal neuron classes is differentially altered suggests that subtype-specific benzodiazepine drugs may act on particular symptoms linked to HD disorders.

Besides the altered expression of $GABA_A$Rs containing α1-3 subunits essentially present in the postsynaptic domain, the expression of extrasynaptically localized α5- and δ-containing $GABA_A$Rs is also altered in human HD carriers and animal models.[69,94,95,129] These extrasynaptic receptors are key factors in the control of local networks[35] and are potential therapeutic targets for synthetic compounds or endogenous neuroactive steroids.[34,130-132] On the basis of an increased expression of α5 in the striatum of R6/1 mice,[69] it would be relevant to test whether an α5-specific antagonist could slow disease progression or symptoms in HD, as is

the case in mouse models of Down syndrome.[32,115] Our preliminary data point to the validity of such a possibility because an alleviation of HD symptoms was observed following an acute treatment with an inverse α5 agonist (M. Garret, M.C. Potier, Y.H. Cho, unpublished observations). Although a clinical trial with 1 synthetic agonist of δ-containing $GABA_A$Rs failed to improve symptoms of HD patients,[111] it would be of interest to test the effect of several available compounds on animal models during the progression of HD.[114] Interestingly, striatal tonic $GABA_A$ currents mediated by δ-containing $GABA_A$Rs have neuroprotective effects against excitotoxicity[133] and might be a relevant target to slow disease evolution.

10 | CONCLUSION

GABAergic neurotransmission is altered early in HD and is likely to precede the appearance of overt symptoms. Significantly, studies on animal models suggest that such alterations depend on the particular brain structure, neuronal cell type, and the stage of the disease. It remains to study these changes during aging in HD carriers using new technologies such as PET imaging[59] with a view to determine whether the GABA system could be a therapeutic target for preventing sleep alteration and reducing the cognitive and psychiatric symptoms of this neurodegenerative disease.[32,118] Although HD-related changes have been mostly studied in the basal ganglia, it would be of further interest to assess whether GABAergic neurotransmission is also altered in other areas of the HD-affected brain. Because deficits in the ontogeny of GABAergic neurotransmission may impact on adult brain functions,[134] it would also be relevant to assess whether synapses involving $GABA_A$Rs are altered during development in HD carriers.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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