INVITED REVIEW

The adjustment of γ-aminobutyric acid$_A$ tonic subunits in Huntington's disease: from transcription to translation to synaptic levels into the neostriatum

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Funding: *We are indebted with the programs for the postdoctoral fellowships - Chilean CONICYT-FONDECYT #3140218, Mexican CONACYT #164978 and DID-UACh S-2015-81, Sistema Nacional de Investigadores #58512 to Abraham Rosas-Arellano. Carola A. Mantellero was supported by USACH PhD fellowship. Carlos Tejeda-Guzmán is supported with a PhD fellowship from CONACYT (#299627). FONDECYT grants 1151206 and 1110571 to Maite A. Castro.*

Abstract

γ-Aminobutyric acid (GABA), plays a key role in all stages of life, also is considered the main inhibitory neurotransmitter. GABA activates two kind of membrane receptors known as $GABA_A$ and $GABA_B$, the first one is responsible to render tonic inhibition by pentameric receptors containing α4–6, β3, δ, or ρ1–3 subunits, they are located at perisynaptic and/or in extrasynaptic regions. The biophysical properties of $GABA_A$ tonic inhibition have been related with cellular protection against excitotoxic injury and cell death in presence of excessive excitation. On this basis, $GABA_A$ tonic inhibition has been proposed as a potential target for therapeutic intervention of Huntington's disease. Huntington's disease is a neurodegenerative disorder caused by a genetic mutation of the huntingtin protein. For experimental studies of Huntington's disease mouse models have been developed, such as R6/1, R6/2, HdhQ92, HdhQ150, as well as YAC128. In all of them, some key experimental reports are focused on neostriatum. The neostriatum is considered as the most important connection between cerebral cortex and basal ganglia structures, its cytology display two pathways called direct and indirect constituted by medium sized spiny neurons expressing dopamine D1 and D2 receptors respectively, they display strong expression of many types of $GABA_A$ receptors, including tonic subunits. The studies about of $GABA_A$ tonic subunits and Huntington's disease into the neostriatum are rising in recent years, suggesting interesting changes in their expression and localization which can be used as a strategy to delay the cellular damage caused by the imbalance between excitation and inhibition, a hallmark of Huntington's disease.

Key Words: *$GABA_A$; extrasynaptic and perisynaptic γ-aminobutyric acid$_A$ receptors; striatum; R6/1, R6/2, HdhQ92, HdhQ111, HdhQ150, N171-82Q and YAC128 HD transgenics mice models; chorea; mutant huntingtin; inhibitory neurotransmission; D1 medium sized spiny neurons; D2 medium sized spiny neurons*

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doi: *10.4103/1673-5374.230270*

Accepted: *2018-02-23*

The γ-Aminobutyric Acid

Described for the first time in the brain halfway through the 20th century as a free amino acid by Roberts and Frankel, it is found in plants, invertebrates and vertebrates where it has multiple functions: γ-aminobutyric acid (also known as GABA) is a non-protein amino acid which plays a key role in all stages of life, both in health and disease, as a molecule for guidance (Zhu et al., 1999), cell differentiation (Procacci et al., 2012; Ramírez et al., 2012), neurogenesis as well as synaptic plasticity (Duveau et al., 2011; Dieni et al., 2012; Kim et al., 2012). It is also considered the main inhibitory transmitter for neural transmission, certainly (Krnjevic and Phillis, 1963).

The enzyme glutamate decarboxylase (GAD) catalyses the decarboxylation of the amino acid glutamate to sinthesize GABA and CO_2 formation, it exists in two isoforms of different molecular weight, 65 and 67 kDa (GAD65 and GAD67). Both isoforms are expressed in the brain. GAD67 is constitutively active and has the function of basal GABA production. On the other hand, GAD65, is transiently activated in response to the demand for extra GABA in neurotransmition (Kaufman et al., 1991; Fenalti et al., 2007).

The GABA Receptors

The systemic release of GABA and its subsequent binding activates two membrane receptors with distinctive pharmacological profiles (Bowery et al., 1979); one of them is a heterodimer G-protein-coupled receptor, known as $GABA_B$ (Hill and Bowery, 1981), composed by two subunits ($GABA_B$R1 and $GABA_B$R2) (Jones et al., 1998). The interaction between the GABA neurotransmitter and the $GABA_B$ receptor induces cationic conductance towards the extracellular regions, presynaptically as autoreceptor suppress transmitter release by two ways: activation of potassium channels and inhibition of voltage dependent calcium channels, N-type or P/Q-type. Postsynaptically the activation of $GABA_B$ receptors produces hyperpolarization increasing potassium conductance given by GIRK or Kir3 potassium channels (Bettler et al., 2004).

The other receptor is the widely distributed and member of the Cys-loop family of neurotransmitter-gated ion channels (Barnard, 1992). These hetero-pentameric channels are composed from a possible choice of nineteen subunits (α1–6, β1–3, γ1–3, δ, ε, θ, π and ρ1–3), generating a plethora of receptor combinations

to coordinate differential neural inhibition depending on the stoichiometry of each channel (Olsen and Sieghart, 2008). This kind of receptor has been named $GABA_A$, their activation opens an inward membrane chloride conductance, and therefore, also generates hyperpolarization and it is responsible for ionotropic phasic and tonic currents (Glykys and Mody, 2007).

$GABA_A$ Phasic and Tonic Subunits

The broad family of $GABA_A$ phasic heteropentameric receptors, composed by α1–3, β1 and 2, γ1–3, ε, π and θ, are located into the synaptic cleft, whereas the limited family of $GABA_A$ subunits that render tonic inhibition are strategically located outside the synaptic cleft, specifically at perisynaptic and/or in extrasynaptic regions, tonic inhibition is given by α4–6, β3, δ, or ρ1–3 subunits. Phasic inhibition consists of fast inhibitory postsynaptic potentials, pentameric receptors faces to presynaptic release sites, and are activated by a brief time of exposure to high GABA concentrations released from presynaptic terminals and producing high amplitude currents (Carver and Reddy, 2013); whereas the hallmark of the $GABA_A$ tonic resource involves high neurotransmitter sensitivity, long-lasting events where the electrical membrane potential slowly rises and falls, it is the cell response given by the spillover of neurotransmitter release outside of the synaptic cleft *per se*, pentameric receptors are not commonly faced to the presynaptic active sites (Polenzani et al., 1991; Ade et al., 2008). This provides a strategic function for efficiently sensing low local GABA levels, and then restore the balance between excitation and inhibition from extrasynaptic and or perisynaptic locations (Ade et al., 2008; Santhakumar et al., 2010; Janssen et al., 2011).

All $GABA_A$ receptors reach the plasma membrane by means of different scaffold proteins, the phasic receptors anchors to synaptic sites by gephyrin, a 93-kDa protein that forms a hexagonal network below the plasma membrane (González et al., 2013). Some other scaffolding proteins, common for phasic and tonic $GABA_A$ receptors include the GABA receptor associated protein (GABARAP) (Wang et al., 1999), and the Phox homology-Rho GTPase-activating protein (PX-RICS) (Nakamura et al., 2016). These complex form a sophisticated assembling interacting directly with the cytoskeleton. Although tonic receptors have lower distribution compared to the phasic subunits, their multiple assembly alternatives makes a wide stoichiometry range of these chloride channels possible at the cell membrane level.

The biophysical properties of long-lasting $GABA_A$ tonic mediated-currents have been related with cellular protection resource against excitotoxic injury and cell death through persistent inhibition in presence of an excessive excitation (Ade et al., 2008; Santhakumar et al., 2010; Janssen et al., 2011). Therefore, $GABA_A$ tonic activity is an essential cellular resource when unequilibrated predominance of excitation over inhibition exists. Examples of excitatory/inhibitory disequilibrium are some neural disorders as Epilepsy, affective disorders, schizophrenia, autism, and Huntington's disease, in which $GABA_A$ tonic inhibition has been proposed as an important target for therapeutic intervention (Santhakumar et al., 2010; Rudolph and Möhler, 2014; Schipper et al., 2016; Du et al., 2017; Kumar et al., 2017; Rosas-Arellano et al., 2018).

Huntington's Disease (HD) and Some Transgenic Mice Models

HD (also known as Huntington's chorea) is a progressive, autosomal dominant and neurodegenerative disorder with cognitive, physchiatric and motor dysfunctions (Bates et al., 2015; Colpo et al., 2017). As was described 25 years ago, this is caused by a genetic mutation that results in a polyglutamine expansion of the huntingtin (Htt) protein, producing a dominant toxic property that results in major cell damage or cell death due to the accumulation of this mutant Htt (mHtt) (No authors listed, 1993). At the motor system level, disequilibrium of excitatory-inhibitory pathways is characterized by clonic spasms of the voluntary muscles as was first reported by George Huntington (Huntington, 1872).

For experimental studies of HD mouse models provided us reliable information to understand in different ways this neural disorder and to develop new therapeutic strategies. Some available transgenic mouse models include R6/1 and R6/2 (both are the first transgenic mouse models designed for HD), HdhQ92 and HdhQ150 (are knock-in lines), as well as YAC128 (that carries the full-length human mHtt gene with 128 CAG repeats) (Mangiarini et al., 1996; Wheeler et al., 1999; Lin et al., 2001; Slow et al., 2003; Van Raamsdonk et al., 2005).

The transgenic mice R6/1 and R6/2, these mice have 116 to 150 repeats of CAG at the 5' end of the HD gene; R6/2 model has been the most studied because it shows a neuropathological and behavioral phenotype very similar to HD (Mangiarini et al., 1996). Behavioral analysis reveal alterations related to age in dystonic movements, motor performance and grip strength which progressively get worse until death. Their life span is 3–7 months, with no sex differences in the pathological phenotype (Hannan, 2004).

The R6/1 model shows a slower progression of the disease than the R6/2 model (Mangiarini et al., 1996). In these mice, motor performance problems occur after 4 or 5 months of age as abnormalities in gait and grip of the hind limbs in a similar way to that described in R6/2 mice. A poor performance in motor tests is clear at 3 months of age. Their life span is greater than 12 months (Naver et al., 2003).

In test of YAC128 for activity parameters, for example at the 3-month-old YAC128 have significant elevation in distance traveled, resting time, and time spent in ambulatory movements when it is compare with the littermates controls; however, both parameters remains without differences between 3- and 9-month-age between YAC128 animals. Interestingly, the YAC128 begin to manifest a hypokinetic phenotype at 6 months, age also known as early stage of progressive motor impairment (Jackson Laboratory, DATASHEET-004938; Brooks et al., 2012), hypokinetic compared with wild-type littermates, and this hypokinetic phenotype is progressive with age, becoming significant only until 12 months of age (Slow et al., 2003).

HdhQ150 mice models start to exhibit weight loss at week 70th, it is significant at week 100, when exhibit significantly motor impairment and reduced motor activity, this reduction is also observed at 70 weeks, although is not robust, compared with wild type. Limb coordination and balance was measured with the balance beam task, at 70 weeks, trend toward greater time to traverse and become significant at 100 weeks. Significant differences were found in stride lengths and base lengths, was a sensitive indicator of gait abnormalities at week 100, and at 40 weeks, mice exhibited a "hindlimb drag" behavior (Heng et al., 2007). The HdhQ-111 transgenic model displayed decreased levels of locomotor activity as they aged, significant differences are in the automated locomotor activity, at any age tested. There was a trend to have a decreased latency to fall from the rotarod at 12 months. HdhQ-111 were significantly impaired in all measures of balance beam. Latency to turn on the balance beam was progressively slower as animals aged, from 9 months of age (Yhnell et al., 2016). N171-82Q model displayed significantly higher clasping scores and general locomotor activity than wild type mice during the early (8–11 weeks) and late stages (15–18 weeks) (Chen et al., 2013).

Neostriatum, GABAergic Transmission and HD

The neostriatum is formed by caudate and putamen and is considered as the most important connection between cerebral cortex (glutamatergic input) and the rest of basal ganglia structures (receiving dopaminergic input from the substantia nigra pars compacta), functionally two pathways have been described known as direct and indirect, these two parallel basal ganglia circuits that are critical for motor function and procedural learning express dopamine receptors D1 and D2 preferentially and respectively (Gerfen et al., 1990; Ehrlich, 2012). The cytology of the neostriatum display two kinds of neurons: a) interneurons or aspiny neostriatal neurons and b) projection neurons or medium sized spiny neurons (MSSNs) (Kawaguchi, 1997). The direct pathway involves activation of inhibitory GABA and substance P MSSNs, whereas the indirect pathway involves activation of inhibitory GABA and encephalin MSSNs, these two pathways have opposite effects on the output of the basal ganglia: the direct pathway has a net positive effect on the basal ganglia output, while the indirect pathway has a negative effect (Alexander and Crutcher, 1990).

In GABAergic neurotransmition in neostriatum the cortex sends projections to the neostriatum through pyramidal glutamatergic neurons (Kreitzer and Malenka, 2007), they connect with MSSNs, which make up 95% of the total neuronal population in the striatum (Kemp and Powell, 1971; Parent and Hazrati, 1995). The glutamate released by the pyramidal glutamatergic neurons produces the activation of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) and N-Methyl-D-aspartate receptor (NMDA), activating the MSSNs and producing GABA neurotransmitter release, MSSNs also receive domamigergic afferents from the mid brain (Kreitzer and Malenka, 2007). MSSNs have two projection patterns on the nuclei of the basal ganglia, responsible for the planning of motor control: 1) those that project towards the internal globus pallidus (GPi) and towards the substance nigra pars reticulata (SNr), and 2) those that send afferences to the external globus pallidus (GPe). Both pathways converge on the thalamus, which in turn send glutamatergic inputs to the neostriatum (Kreitzer and Malenka, 2007), and have opposite functions on it. The first (D1 or direct pathway) produces its activation, while the second (D2 or indirect pathway) its inhibition. The control of motor behavior depends on the inhibition/excitation balance in these pathways (Yager et al., 2015).

The importance of the neostriatum for basal ganglia function is highlighted by neurological disorders where its function is compromised, as it occurs in HD. In early HD in neostriatum as fast as the mHtt accumulates in the MSSNs of the neostriatum, some other mHtt affected cells, as the fast spiking (FS) interneurons, accumulate cyclic AMP (cAMP) by a dysregulation of the protein kinase A (PKA) pathway (Ariano et al., 2002, 2005). PKA activity increases significantly, and PKA substrates as the NMDA receptor subunit GluN1 gets hyper-phosphorylated (Tingley et al., 1997; Torres-Peraza et al., 2008). GluN1S897 residue, which is specifically phosphorylated by cAMP/PKA pathway modifies the biophysical properties of NMDA receptor (Tingley et al., 1997), increasing the Ca^{2+} conductivity, and leading to a cytosolic Ca^{2+} rise, synergizing the cAMP/PKA signals to activate the transcription factor Ca^{2+}/cAMP response element binding protein (CREB) to accelerate gene expression (Dudman et al., 2003; Aman et al., 2014). CREB binds to cAMP response elements (CRE) in the nucleus, decreasing the transcription of the downstream genes like parvalbumin (PV) and glutamate decarboxylase (GAD67), a couple of crucial proteins related to the inhibitory neurotransmission in interneurons (Hashimoto et al., 2003; Belforte et al., 2010; Nakazawa et al., 2012). The decrease in the levels of these two proteins reduces the GABA synthesis and release (Belforte et al., 2010) (**Figure 1**). At the date it remains unclear if in first instance D1- or D2-pathway degenerates initially, increasing vulnerability and cell death of MSSNs. However, some studies conclude that D2 MSSNs (indirect pathway) are relatively more vulnerable than D1 (direct pathway), leading to an imbalance favoring the over-functionality of D1 over the D2, since early to late stages of HD in postmortem human brains and murine models (Augood et al., 1997; Glass et al., 2000; Deng et al., 2004; Crook and Housman, 2012). Despite of that other data indicates that the D1 pathway becomes to be dysfunctional earlier than D2 (Ehrlich, 2012), controversy will remains as long as it continues extremely difficult to isolate D1 of D2 pathway.

In general, in early stage of HD an imbalance of the neostriatal circuit occurs. This may be due to three different mechanisms related to the loss of dopaminergic neurons in the substance nigra pars compacta (SNc): 1) Loss of inhibitory afferences mediated by GABA release from the dopaminergic neurons of the SNc (Tritsch et al., 2012); 2) Loss of MSSNs in the neostriatum, responsible for maintaining the inhibitory pathway (D2 neurons), producing the over-activation of the excitatory pathway (D1 neurons); 3) Loss of dopaminergic modulation on the GPe, which would cause an imbalance of the GABA regulation in the afferents of this nucleus towards the neostriatum and the subthalamic nucleus (STN) (Mallet et al., 2012). In summary, loss of the enkephalin containing MSSNs of the indirect pathway especially early in the disease lead to less inhibition of the GPe and subsequent increased inhibition of the STN, decreased excitation of GPi, and subsequent decreased inhibition of the thalamus resulting in thalamic over excitation of the cerebral cortex leading to choreic movements (Waldvogel and Faull, 2015).

$GABA_A$ Tonic Subunits and HD

The simple fact that the inhibitory system fails to stop involuntary and sudden jerking movements in HD increased our curiosity about of the fate of neostriatal $GABA_A$ tonic subunits and their inherent functional characteristics in this motor disorder. The neostriatum shows strong expression of many types of ionotropic $GABA_A$ receptors including tonic subunits as: α4–5, β3, δ and ρ1–3 (Fritschy and Mohler, 1995; Albrecht et al., 1997; López-Chávez et al., 2005; Rosas-Arellano et al., 2007, 2012, 2018; Bhandage et al., 2014; Waldvogel and Faull, 2015; Du et al., 2017; Kumar et al., 2017; Reyes-Haro et al., 2017).

In a study of Cepeda and colleagues in 2013 that include $GABA_A$ tonic subunits by the using R6/2 mice crossed with D1-EGFP or D2-EGFP, there were compared potential differences in tonic $GABA_A$ current by application of lower concentrations of bicuculline (20 μM), an antagonist of $GABA_A$ receptor (that no exert effect on $GABA_A$ ρ subunits). Tonic $GABA_A$ current amplitudes were significantly reduced only in D2 receptor expressing MSSNs from R6/2 mice. There was showed that tonic currents were reduced in HD mice but only in MSSNs of the indirect pathway (Cepeda et al., 2013). On the other hand, Hsu and colleagues in 2017 by means of qRT-PCR described down regulation of $GABA_A$ δ subunits at 12, 16 and 15-months-old in neostriatum of R6/2, N171-82Q and Hdh150Q respectively. A similar down regulation was also found and validated in postmortem caudate nucleus of 5 HD human brains. Likewise, lower expression was found for $GABA_A$ α4 subunit, this down regulation of both tonic subunits

occur at the premanifest stage. Additionally, HD mice models displayed impaired responses to gaboxadol, a behavior related with tonic inhibition, all together suggesting that the number of α4βδ pentameric receptors required for tonic inhibition might be significantly reduced in HD (Hsu et al., 2017).

Another study showed an over alteration in HD of GABAergic neurotransmission in the neostriatum, performed in R6/1 and HdhQ111 HD transgenic mice models of HD. There R6/1 was used at 3-month-age, that means tracking starting with slow disease progression in the cognitive deficits, where symptoms are not evident and in late stages (6-month-age) and motor deficits are fully evident. Using Western blot, quantitative real time polymerase chain reaction (qRT-PCR), and immunohistochemistry, they reported variations in the expression of $GABA_A$ receptor subunits even at a young age when motor alterations are not yet observed. The main alterations in R6/1 mouse model for phasic and tonic $GABA_A$ subunits were evidenced, and were including α5 and δ, both of them responsible for generating tonic currents; α5 display significant over expression at 6-month-old at RNA and proteins levels, whereas δ subunit decreases significantly at the age of 6 months, also in RNA and protein levels of this HD model. It is suggested that the δ decrease has greater contribution determining whether specific antagonist of δ subunit could improve HD disease progression (Du et al., 2017). The $GABA_A$ β3 and α4 subunits have been recognized to render tonic inhibition (Chandra et al., 2006; Janssen et al., 2011), Du and cols do not found major changes for β3 in the expression at 3- and 6-month-old-age compared with wild type animals; whereas α4 display RNA differences at 6-month-old with wild type. On the other hand, no significant variations were observed in the expression of GAD67, GAD65, NL2 or gephyrin proteins, which are involved in the synthesis of GABA or postsynaptic scaffolding, except GAD67, which only is modified before the onset of motor deficits, so they would not be contributing to the development of the pathology.

To date, several studies of HD suggest changes in the expression of: α4–5, β3, δ subunits, commonly. However, Kumar and colleagues in 2017 conducted a pioneer work about of neostriatal distribution of $GABA_A$ ρ3 subunit in HD in R6/2 mice at the age of 11 weeks. $GABA_A$ ρ3 subunit exhibited a significant loss of immunoreactivity and was observed to be expressed in neuronal cells with displayed distorted morphology. This downexpression suggest that $GABA_A$ ρ3 subunit may possibly perturb normal GABAergic transmission and proposes the use of agonist along with blockade of NMDA receptors as potential therapeutic resource for the treatment of HD.

Recently, together with our colleagues (Rosas-Arellano et al., 2018), we made an effort to describe changes in the expression and distribution of five $GABA_A$ tonic subunits reported previously in the neostriatum. In YAC128 transgenic mouse model we observed mRNA up- and down-regulation of tonic subunits, up-regulation of $GABA_A$ α5 in late HD. Nonetheless, up regulation of $GABA_A$ δ and β3 subunits were observed in 6- to 12-month-old YAC128. Moreover, we followed the relation between $GABA_A$ tonic subunits and the neostriatal inhibitory pathway (D2). As expected, D2 immunolabeling showed reduced expression as well labeling of $GABA_A$ tonic subunits associated to this pathway. Probably D2 pathway become dysfunctional and degenerate as previously reported, leading to a disconnection of the neostriatum from upstream cortical inputs and downstream basal ganglia nuclei and producing severe motor deficits associated to the cell damage and/or cell death. Curiously, there is an overexpression of $GABA_A$ tonic subunits in an unknown cellular entity within the YAC128 neostriatum; possibly in D1 neurons, since we assume that it is an attempt to stop overexcitation of the excitatory pathway by establishing the tonic inhibition; as an additional hypothesis, this change could be related to overexpression in interneurons, specifically those that exert inhibitory control over the function of the D2 neurons, allowing disinhibition of the remaining or survivor inhibitory pathway with the aim of reestablishing the equilibrium between excitation and inhibition. Perhaps both hypotheses are correct. For our previous $GABA_A$ receptor localization studies (Mejía et al., 2008; Rosas-Arellano et al., 2011, 2012), synaptic regions (pre and postsynaptic) have been subdivided into three main areas on the plasma membrane: 1) Extrasynaptic, are receptor locations unrelated with the synaptic density but close to one 2) Perisynaptic is a receptor flanking a defined synaptic density, on one or both sites of the synaptic cleft, and 3) Synaptic, it is when a receptor is clearly inside of the proper synaptic density. Under these parameters an unexpected adaptation was observed when we detected the distribution at electron microscopy level. A message was given by a "new" localization within the active zone (into synaptic density) of $GABA_A$ tonic subunits at the age of 6 through 12 months old in YAC128 compared with wild type animals, this localization was not exclusively nor replaceable between extra- and perisynaptic to synaptic regions. Furthermore, the synaptic relocalization of $GABA_A$ tonic receptors had good correlation with the augmented sensitivity to $GABA_A$ receptor antagonists during extracellular electrophysiological recordings in YAC128 neostriatal slices, suggesting that these subunits are positioned within the synaptic cleft, intentionally or not, to be functional.

GABA Neurotransmitter Release and HD

Early studies suggest low concentration of GABA neurotransmitter in human putamen with HD, suggesting correlation with the hypothesis that neostriatal GABA-containing neurons degenerate in HD (Spokes et al., 1979). In agreement low GABA environment in HD in the neostriatum significant reductions of this neurotransmitter were found, it was greater in late stages in human neostriatum with HD, and in a mouse model based on quinolinic acid treatment (Ellison et al., 1987).

Perspectives

HD produces selective damage on MSSNs of the neostriatum, and $GABA_A$ tonic inhibition protects the cell from a pharmacological insult, as it has been clearly demonstrated by Santhakumar and colleagues in 2010. Based on this assumption, motor studies can be performed with the aim to identify some improvement in the early damage caused by HD in mice transgenic models by early administration of a pharmacologic treatment using specific agonist/antagonist drugs, or by the use of knockout or knock-in mice for GABA alpha5, beta3, delta and rho subunits since early stages of HD. This measure will show if there is any protective effect due to the participation of these mentioned subunits. In non-pathological states the specific question about how $GABA_A$ tonic subunits are transported to the cell-surface into specific synaptic areas as membrane-anchored proteins, remains principally unanswered; now we must answer more questions in the cellular neurobiology field: whether the synaptic relocation of GABA-tonic subunits is a cellular strategy to reestablish the balance between excitation-inhibition as adaptations to the low GABA levels and the cellular and molecular mechanisms that underlie it, as well as its pentameric stoichiometry in early and late ages of YAC128 stoichiometry in early and late ages of YAC128.

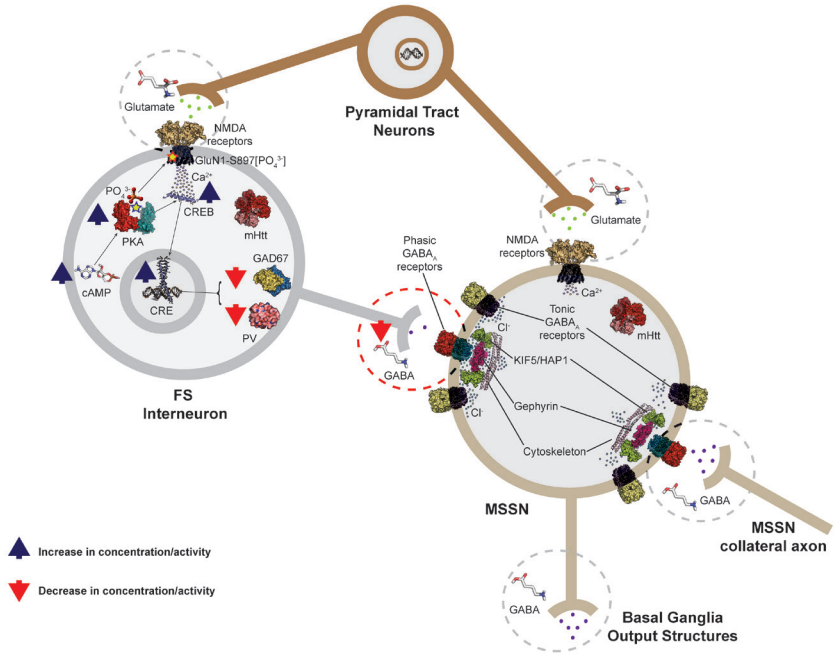

Figure 1 Early stages of Huntington's disease (HD) in the neostriatum.
Along HD, mutant huntingtin (mHtt) affects medium sized spiny neurons (MSSNs) and fast spiking (FS) interneurons. Cyclic AMP (cAMP) accumulates in interneurons because of a disequilibrium of the protein kinase A (PKA) pathway, this activates the PKA activity followed by their substrates, such as the N-methyl-D-aspartate receptor (NMDA) receptor. The GluN1S897-NMDA hyper phosphorylated increases the Ca^{2+} conductivity, synergizing cAMP/PKA activity to stimulate cAMP response element binding protein (CREB) at the nuclear level, decreasing the transcription of parvalbumin (PV) and glutamate decarboxylase (GAD67), and hence reducing γ-aminobutyric acid (GABA) synthesis and release. CRE: cAMP response elements.

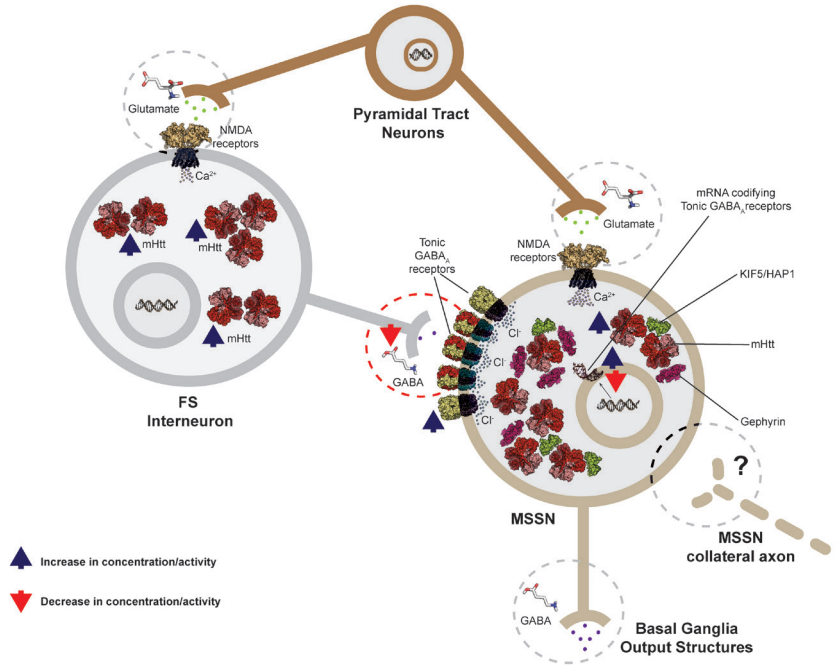

Figure 2 Advanced stages of Huntington's disease in the neostriatum.
When mutant huntingtin (mHtt) aggregates in medium sized spiny neurons (MSSNs), key protein factors, as the scaffolding proteins of phasic γ-aminobutyric acid $(GABA)_A$ receptors in the synaptic level, such as gephyrin and kinesin family motor protein 5 (KIF5) in complex with the cytoskeleton are disrupted since the adaptor-protein keeping this complex, Huntingtin-associated protein 1 (HAP1), is directly affected by mHtt. The reduction of phasic $GABA_A$ receptors in the postsynaptic density turns the N-methyl-D-aspartate receptor (NMDA)-permeated calcium ion to excitotoxic. MSSNs increase and decrease the expression of tonic $GABA_A$ subunits (for example α5, β3 and δ) some of them migrate into the postsynaptic density, as a temporary strategy to stop cell damage and avoid cell death. The doted line in collateral axon means that the fate of neighbor neurons is uncertain. FS: Fast spiking.

Conclusions

By way of conclusion in the **Figure 2** are represented a summary of HD changes and consequences mentioned throughout the text. mHtt protein aggregates accumulate and interfere with nerve cell function by disrupting key cell regulatory factors in the MSSNs (Noakes et al., 2015; Xu and Wu, 2015). Factors as the protein gephyrin, and the kinesin family motor protein 5 (KIF5) self-assembles into a scaffold interacting with the cytoskeleton (Twelvetrees et al., 2010), such factors are fundamental to phasic $GABA_A$ receptors being trafficked to synapses, and promotes the formation of gephyrin nanodomains, which potentiate the phasic $GABA_A$ amplitude of postsynaptic currents (van Rijnsoever et al., 2005; Pennacchietti et al., 2017). These proteins form a complex by an adaptor linking the receptors to KIF5, the adaptor is the Huntingtin-associated protein 1 (HAP1) (Kittler et al., 2004; Twelvetrees et al., 2010). When the aggregates of the mHtt protein increase because of the progress of HD, phasic $GABA_A$ receptor transport, and inhibitory synaptic currents are disrupted (Twelvetrees et al., 2010). This significant reduction of phasic $GABA_A$ receptors in the postsynaptic density, in addition to the decreased GABA release by FS Interneurons turns the glutamatergic input, from pyramidal tract neurons, to excitotoxic because of the over-exciting effect of calcium ion permeated by active NMDA receptors in the MSSNs (Zeron et al., 2002; Shehadeh et al., 2006; Santhakumar et al., 2010; Schipper et al., 2016; Rosas-Arellano et al., 2018). In order to stabilize this imbalance by attenuating the excitotoxic effects, the MSSNs increase the expression of $GABA_A$ tonic receptors, some of them which migrate into the postsynaptic density, in this way they counteract the harmful excitatory NMDA currents, generating larger inhibitory tonic $GABA_A$ currents, avoiding temporarily in this way the cell death (Du et al., 2017; Rosas-Arellano et al., 2018).

Acknowledgments: *In memoriam of Prof. Ricardo Miledi (1927–2017): the greatest Mexican neuroscientists, who studied the GABAergic system and precursor of the studies of the neurotransmitter release in the synapse. Thanks to Fanis Missirlis (Cinvestav, Mexico), Lourdes Palma-Tirado (INB-UNAM, Mexico), Patricio Rojas (USACh, Chile), Enrique Lorca-Ponce (USACh, Chile).*

Author contributions: *ARA designed and drafted the first version; MAC edited the first version of the manuscript. ARA designed second version; ARA, AEM, CAM and CTG wrote the second version of the manuscript. AEM designed all figures. ARA and AEM, both edited the final version of the mini-review.*

Conflicts of interest: *None declared.*

Financial support: *We are indebted with the programs for the postdoctoral fellowships - Chilean CONICYT-FONDECYT #3140218, Mexican CONACYT #164978 and DID-UACh S-2015-81, Sistema Nacional de Investigadores #58512 to Abraham Rosas-Arellano. Carola A. Mantellero was supported by USACH PhD fellowship. Carlos Tejeda-Guzmán is supported with a PhD fellowship from CONACYT (#299627). FONDECYT grants 1151206 and 1110571 to Maite A. Castro.*

Plagiarism check: *Checked twice by iThenticate.*

Peer review: *Externally peer reviewed.*

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