Vincenzo Crunelli* and Giuseppe Di Giovanni*

Monoamine modulation of tonic $GABA_A$ inhibition

Abstract: In recent years, it has become evident that many neurotransmitters and endogenous ligands differentially modulate synaptic γ-aminobutyric acid type A receptors ($sGABA_ARs$) and extrasynaptic $GABA_AR$ ($eGABA_ARs$). In this mini-review, we will summarize the available evidence on the ability of the monoamines serotonin (5-HT), noradrenaline (NA), and, in particular, dopamine (DA) to alter the functional response of $eGABA_ARs$, thus either increasing or decreasing tonic $GABA_A$ inhibition. Although this field of research is still in its infancy, it has already been demonstrated that $eGABA_ARs$ show a nucleus-selective and neuronal-type-selective regulation by monoamines in a way that differs from that of $sGABA_ARs$. Further work will undoubtedly advance our knowledge of the intricate talk between monoamines and $eGABA_AR$ and may ultimately provide new leads for the treatment of neurological and neuropsychiatric disorders, where alteration in $GABA_AR$ function is one of the underlying causes.

Keywords: epilepsy; extrasynaptic $GABA_A$ receptors; G-protein-coupled receptors; Parkinson's disease; phosphorylation.

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Introduction

γ-Aminobutyric acid type A receptors ($GABA_ARs$) are expressed throughout the central nervous system (CNS) and represent the principal inhibitory receptors in the adult mammalian brain (Schwartz, 1988). Two main $GABA_AR$ populations have now been identified that mediate two distinct forms of inhibition: 'phasic' inhibition that is brought about by activation of synaptic $GABA_ARs$ ($sGABA_ARs$) and 'tonic' inhibition that is mediated by perisynaptic/extrasynaptic $GABA_ARs$ ($eGABA_ARs$) (Figure 1) (Farrant and Nusser, 2005; Belelli et al., 2009).

The different functional properties of these two classes of $GABA_ARs$ derive from their different subunit composition. Thus, in the dentate gyrus and cerebellar granule cells, thalamocortical (TC) neurons, and some cortical neurons (Nusser et al., 1998; Pirker et al., 2000; Nusser and Mody, 2002; Belelli et al., 2005; Cope et al., 2005; Jia et al., 2005), $eGABA_ARs$ contain a δ subunit, while the α5 subunit is present in $eGABA_ARs$ in CA1 and CA3 hippocampal pyramidal cells (Caraiscos et al., 2004; Hortnagl et al., 2013). The δ subunit containing $eGABA_ARs$ coassemble with two α (α4 or α6) and two β subunits. The α5 subunit containing $eGABA_AR$ usually coassemble with α, β, and γ2 subunits. α1 and α2 subunits as well as β3 subunits are also found in $eGABA_ARs$ on the soma of hippocampus CA1 pyramidal neurons (Kasugai et al., 2010).

The very low GABA concentration that is present in the extracellular space can activate $eGABA_AR$-mediated tonic inhibition, which thus occurs in a much more spatially and temporally diffuse manner than phasic inhibition (Farrant and Nusser, 2005). Tonic inhibition has been observed in the cerebellum (Brickley et al., 1996), hippocampus (Stell and Mody, 2002), striatum (Ade et al., 2008), and thalamus (Cope et al., 2005). Interestingly, tonic inhibition may also be involved in a number of neurological and neuropsychiatric disorders (Belelli et al., 2009; Hines et al., 2012; Egawa and Fukuda, 2013), including stroke (Clarkson et al., 2011), epilepsy (Cope et al., 2009; Di Giovanni et al., 2011a), anxiety (Lydiard, 2003), depression (Maguire et al., 2005; Luscher et al., 2011), schizophrenia (Guidotti et al., 2005), and autism (Pizzarelli and Cherubini, 2011).

In this article, we will summarize the data supporting the existence of a modulation of $eGABA_ARs$ by dopamine (DA), serotonin (5-HT), and noradrenaline (NA) receptors in different brain areas. Since the vast majority of these receptors are G-protein-coupled receptors (GPCRs), the emerging picture is one where both $sGABA_ARs$ and $eGABA_AR$ are under the influence of GPCRs (see Connelly et al., 2013a).

DA modulation of the tonic $GABA_A$ current

DA receptors (DARs) are members of the GPCR super-gene family (Kebabian and Calne, 1979), and dysfunction of the DA system has been implicated in many neurological

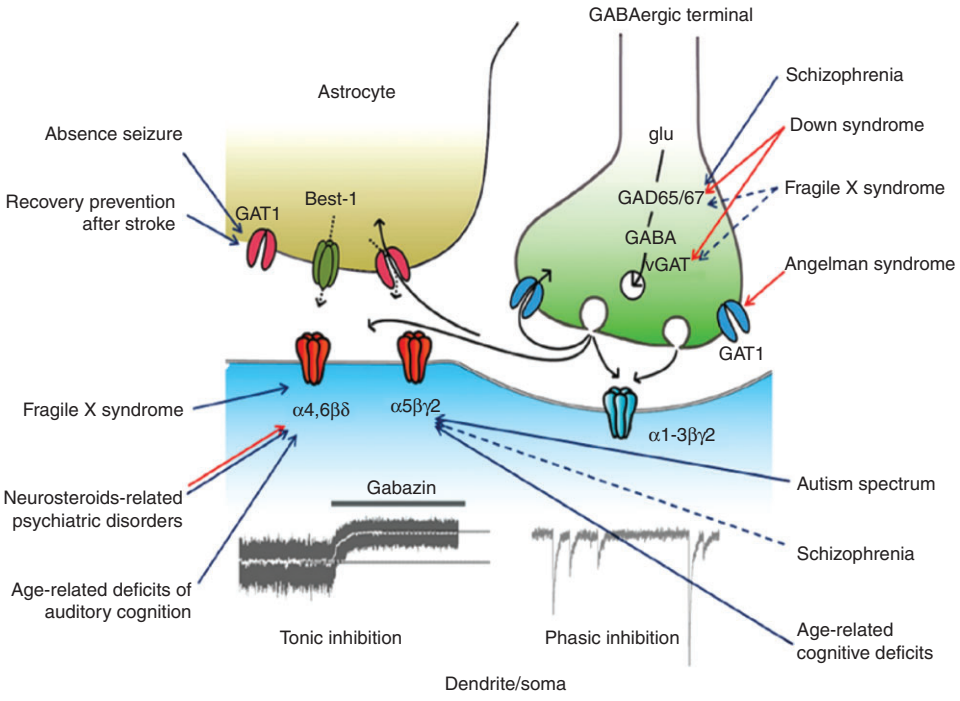

Figure 1 Regulation of tonic inhibition and CNS disorders.
Aberrant tonic inhibition is suspected to be a mechanism underlying the neuronal dysfunctions in the listed disorders based on at least one of the following: (1) a direct measurement of tonic inhibition in model animals, (2) the use of $eGABA_AR$-selective modulators in model animals, and (3) evaluation of α5 subunit expression in living human subjects (via positron emission tomography). Colored arrows indicate the proposed protein/subunit responsible for aberrant tonic inhibition (blue, down-regulation; red, up-regulation; black, GABA signaling during synaptic transmission). Dashed arrows indicate pathways still under debate. vGAT, vesicular GABA transporter; Best-1, bestrophin-1; glu, glutamate. Modified from Egawa and Fukuda (2013).

and neuropsychiatric disorders, including depression, schizophrenia, attention-deficit hyperactivity disorders, drug abuse, Gilles de la Tourette's syndrome, Alzheimer's disease, Parkinson's disease (PD), and epilepsy (Di Giovanni, 2008, 2010). Two subclasses of DARs have been identified, that is, D1-like (D1 and D5) and D2-like (D2-D4) (Missale et al., 1998). D1-like receptors are positively coupled to AC, while D2-like receptors generally inhibit this enzyme. Importantly, D1R agonists activate and D2R agonists block protein kinase A (PKA) (Chen et al., 2006) via different second-messenger cascade systems, that is, through Gs/Golf and Gi/o, respectively (Stoof and Kebabian, 1984).

Increasing evidence indicates that the interaction between the DA and GABA systems in the brain can be mostly attributed to the functional interactions between their receptors (Liu et al., 2000; Lee et al., 2005), which are mostly mediated by classic second-messenger systems (see below). However, a direct protein-protein interaction between these two receptors has also been reported, which is mediated by the carboxyl terminus of the D5R and the second intracellular loop of the $GABA_AR$ γ2 subunit (Liu et al., 2000). This direct D5R-$GABA_AR$ coupling mutually inhibits the activity of both receptors: thus, $GABA_AR$ stimulation inhibits the ability of D5Rs to activate AC, whereas D5R activation decreases $sGABA_AR$-mediated inhibition (Liu et al., 2000; Lee et al., 2005). Whether similar or different protein-protein interactions exist between DARs and $eGABA_ARs$ remains to be investigated.

Striatum

The striatum, the main input of the basal ganglia circuitry (DeLong, 1990), receives a robust dopaminergic innervation from the substantia nigra pars compacta (SNc) but also from the ventral tegmental area (VTA). In the striatum, DA binds to D1-like and D2-like receptors, modulating their intrinsic excitability and synaptic plasticity. The medium spiny neurons (MSNs) are the GABAergic principal projecting striatal neurons and selectively express D1Rs on those of the direct pathway (to the SN) and D2Rs on those of the indirect pathway (to the external part of pallidum) (Gerfen et al., 1990; Di Giovanni et al., 2009).

Contrasting results have been reported on the subunit composition of $GABA_A$Rs expressed in the striatum (Liste et al., 1997; Flores-Hernandez et al., 2000; Schwarzer et al., 2001; Ade et al., 2008; Santhakumar et al., 2010). The striatum stains positively for α1 to α5 subunits (although weakly for α3 and α5), all β subunits, as well as γ2 and δ subunits (Pirker et al., 2000). Others, however, have reported that MSNs do not express α3 and α6 subunits (Liste et al., 1997; Rodriguez-Pallares et al., 2000; Schwarzer et al., 2001) but do express α2 and β2/β3 subunits (Liste et al., 1997). Moreover, single-cell polymerase chain reaction (PCR) suggests that β1 and β3 subunits are expressed in MSNs (Flores-Hernandez et al., 2000), while β2 subunits appear to be solely present in striatal interneurons (Schwarzer et al., 2001).

Many groups (Ade et al., 2008; Kirmse et al., 2008; Janssen et al., 2009, 2011; Santhakumar et al., 2010; Luo et al., 2013) have shown the presence of a tonic $GABA_A$ current in MSNs, although one study (Gertler et al., 2008) did not report a tonic $GABA_A$ current in either $D2^+$ or $D1^+$ MSNs. $D2^+$ MSNs have a greater tonic $GABA_A$ current (Zheng and Johnson, 2001) and are more sensitive to low doses of GABA than $D1^+$ MSNs (Ade et al., 2008). In young mice (P16-25), application of the $GABA_A$R antagonist bicuculline blocks spontaneous inhibitory postsynaptic currents (IPSCs) and consistently reduces the holding current in $D2^+$ MSNs, suggestive of an endogenous tonic $GABA_A$ current. This effect can also be observed in $D1^+$ MSNs, although its magnitude is significantly smaller, and in some neurons, it can be absent altogether (Ade et al., 2008). As it is the case in other brain areas (Bright et al., 2007), the strong TTX sensitivity of the tonic $GABA_A$ current in MSN indicates that synaptic spillover is the main origin of the ambient GABA that in the striatum is responsible for the tonic current (Ade et al., 2008).

The larger tonic current in $D2^+$ cells of young mice is likely to be mediated by α5β3γ2 receptors. This is based on the evidence that there is (i) a differential expression of α5- and β3-containing receptors in $D2^+$ compared to $D1^+$ neurons; (ii) the similar expression and effect of δ-subunit-containing e$GABA_A$Rs between the two MSN populations, with a minimal contribution to tonic $GABA_A$ currents; and (iii) a lack of effect of α1-containing $GABA_A$R receptor activation on both $D2^+$ and $D1^+$ MSNs (Ade et al., 2008; Janssen et al., 2009, 2011; Santhakumar et al., 2010). Since $GABA_A$R subunits are developmentally regulated (Laurie et al., 1992), it is not surprising that there is a developmental reversal in the tonic $GABA_A$ current profile of adult (p>30) MSNs: thus, a larger tonic current is present in $D1^+$ MSNs, due to an increase of δ-containing $GABA_A$Rs, and a smaller current in $D2^+$ MSNs, as a result of a reduced α5 subunit expression (Santhakumar et al., 2010). This developmental switch in the tonic inhibitory control of the MSNs from those of the indirect to those of the direct pathway will undoubtedly affect the input-output curve of the striatal circuit.

DA1Rs and DA2Rs modulate the tonic $GABA_A$ current in both young and adult MSNs (Janssen et al., 2009). Although DA is present in such low concentrations that it does not activate D1Rs and D2Rs in striatal slices, DA2R stimulation with quinpirole decreases the tonic current in $D2^+$ MSNs, whereas D1R activation with SKF-81297 induces a tonic $GABA_A$ currents in $D1^+$ MSNs (Janssen et al., 2009). This dopaminergic modulation of the tonic current is likely due to changes in the phosphorylation state of e$GABA_A$Rs in both young and adult mice, and β1 and β3 subunits are substrates for PKA-mediated phosphorylation (Moss et al., 1992; Poisbeau et al., 1999; Flores-Hernandez et al., 2000; Vithlani and Moss, 2009; Kang et al., 2011). Importantly, DA agonists and intracellular PKA application fail to significantly alter s$GABA_A$ currents in the striatum (Janssen et al., 2009), although it is well known that, in other brain areas, s$GABA_A$ responses are phosphorylation dependent (McDonald et al., 1998; Nusser et al., 1999; Flores-Hernandez et al., 2000). In conclusion, DA exclusively modulates tonic $GABA_A$ currents and not IPSCs in the striatum.

Thalamus

Differently from humans, the thalamus of rodents only shows a sparse dopaminergic innervation (Groenewegen, 1988; Papadopoulos and Parnavelas, 1990; Garcia-Cabezas et al., 2007, 2009) and moderate levels of DARs (Wamsley et al., 1989; Weiner et al., 1991; Khan et al., 1998). In addition, the precise cellular localization of DARs in the thalamus is mostly unknown. On the contrary, compelling experimental evidence shows an important DA modulation of thalamic cell excitability. For instance, the nucleus reticularis thalami (NRT) is rich in DA4Rs (Khan et al., 1998), which are located presynaptically on globus pallidus (GP) terminals and, once activated, lead to a reduced inhibitory input of these afferents to the NRT neurons (Floran et al., 2004; Gasca-Martinez et al., 2010). Moreover, strong *in vitro* electrophysiological evidence shows that DAR1 and DAR2 can modify the excitability of thalamic neurons with both cellular and nucleus specificity. For example, D2Rs but not D1Rs are involved in DA-mediated excitation of mediodorsal (MD) thalamic neurons (Lavin and Grace, 1998), while DA acting via D1Rs leads to a membrane depolarization in dorsal lateral geniculate nucleus (dLGN) TC neurons (Govindaiah and Cox, 2005).

On the contrary, DA has also been shown to indirectly inhibit these neurons via D2R-mediated excitation of local GABAergic interneurons, producing an increase of phasic $GABA_A$ inhibition (Munsch et al., 2005). In agreement with this, DA is capable of increasing the tonic $GABA_A$ current in rat dLGN TC neurons (Di Giovanni et al., 2008).

DA also modulates the activity of ventrobasal (VB) TC neurons: it increases firing (via an action on postsynaptic D2Rs) and induces membrane depolarization (via D1Rs) (Govindaiah et al., 2010). As far as inhibition is concerned, DA has no effect on miniature IPSCs (mIPSCs) (Yague et al., 2013) but strongly reduces $eGABA_AR$-mediated tonic inhibition in VB TC neurons of Wistar rats (Figure 2) (Yague et al., 2013). Quinpirole and PD-168,077 (D2R and D4R agonists, respectively) also reduced the tonic current without altering phasic inhibition (Figure 2). These DA effects might be mediated by D4Rs, since (i) quinpirole binds with higher affinity at D3/4Rs than at D2Rs (Sokoloff et al., 1990) and mimics the DA effects, (ii) D3Rs are not considerably expressed in the thalamus (Gurevich and Joyce, 1999), and (iii) PD-168,077 is a selective and potent D4 agonist (Glase et al., 1997). Finally, the action of DA,

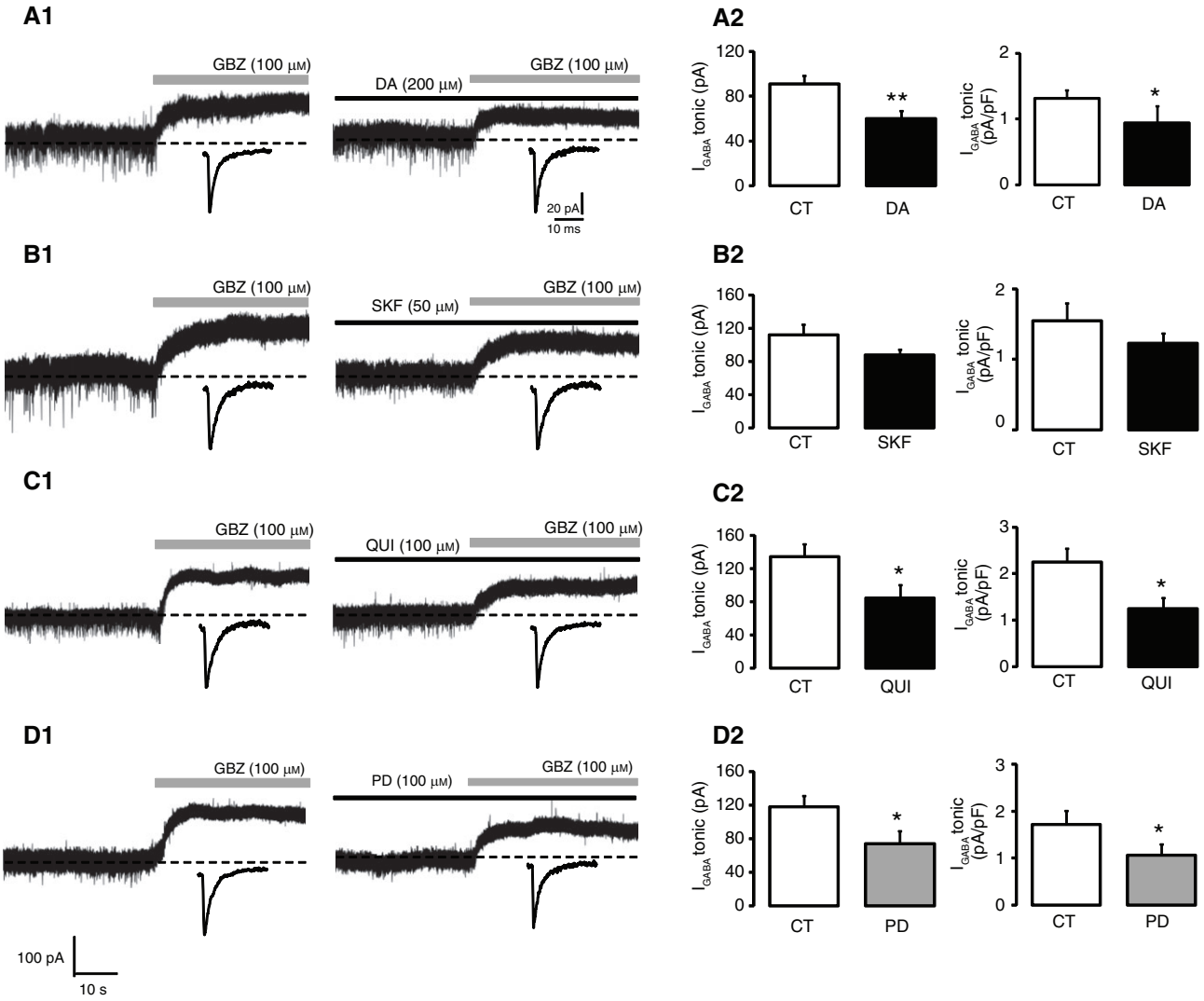

Figure 2 Dopaminergic modulation of the $eGABA_A$ tonic current in the VB thalamus.
(A1) Representative current traces (top) and averaged IPSCs (bottom) from different TC neurons in VB slices from Wistar rats, under control conditions [100 μM ascorbic added to artificial cerebrospinal fluid (aCSF)] and in the continuing presence of DA (200 μM; right). Focal application of gabazine (GBZ; 100 μM; gray bar) reveals different magnitude of tonic $GABA_A$ tonic current. (A2) Summary of the effects of DA on the tonic current (right) and normalized I_{GABA} tonic. (B1, C1, and D1) Representative current traces (top) and averaged IPSCs (bottom) from different TC neurons of the VB thalamus of Wistar rats under control conditions (left) and in the continuing presence of SKF-39383 (50 μM), quinpirole (50 μM), and PD-16,8077 (100 μM; right). (B2, C2, and D2) Summary of the effects of SKF-39383, quinpirole, and PD-16,8077 on $GABA_A$ tonic current (left) and normalized $GABA_A$ tonic current (right) (*p<0.05, **p<0.01, unpaired t-test). Adapted from Yague et al. (2013).

quinpirole, and PD-168,077 on the tonic current does not result from a decreased vesicular GABA release, since $GABA_A$ sIPSC frequency, a measure of action potential-dependent vesicular GABA release, is unaffected by both DA and these two agonists.

It is difficult to speculate on the localization of the DARs that mediate the above effects on the tonic current. It is conceivable that DA might decrease eGABAR activity by reducing glial GABA release and its ambient concentration, since DARs have been reported to be present in astrocytes in some brain areas (Khan et al., 2001; Miyazaki et al., 2004) and because astrocyte-neuron GABA signaling in the VB specifically targets $eGABA_ARs$ (Jimenez-Gonzalez et al., 2011). As mentioned earlier, the only clear evidence regarding DAR localization in the thalamus is the high expression of D4Rs in GP terminals in the NRT (Ariano et al., 1997), where they negatively control this inhibitory input to the NRT (Gasca-Martinez et al., 2010). D4R activation, therefore, may decrease intra-NRT GABA release (Floran et al., 2004), leading, in turn, to an increase firing of GABAergic NRT neurons (Gasca-Martinez et al., 2010). However, selective D4R activation does not affect $sGABA_AR$ activity, indicating no change in the phasic NRT input to the VB. Thus, the effect of D4R activation on $eGABA_AR$-mediated tonic current (Yague et al., 2013) might be due to the presence of D4Rs expressed in VB TC neurons, in agreement with other recent electrophysiological evidence (Govindaiah et al., 2010).

In view of the increased $eGABA_AR$ function in experimental absence epilepsy (Cope et al., 2009), it is interesting that, in one of these models [the Genetic Absence Epilepsy Rats from Strasbourg (GAERS)], D4R activation decreases the tonic but not the phasic $GABA_A$ current (Yague et al., 2013). Since a selective reduction of the tonic current in the VB has been shown to drastically reduce absence seizures (Cope et al., 2009), it is possible that the known anti-absence effects of some dopaminergic drugs (Marescaux et al., 1992) may occur in part by their ability to decrease thalamic $eGABA_AR$ function.

In summary, DA can excite VB neurons through different actions, one of which involves a reduction in the tonic $GABA_A$ current. Strikingly, DA selectively modulates tonic vs. phasic inhibition similarly to its action in the striatum.

NA modulation of the tonic $GABA_A$ current

NA excites GABAergic interneurons (McCormick, 1992a; Kawaguchi and Shindou, 1998) and indirectly inhibits the principal neuron in different CNS areas (Segal et al., 1991). Moreover, NA can increase $GABA_A$ IPSCs in cerebellar stellate (Kondo and Marty, 1997), frontal cortex (Kawaguchi and Shindou, 1998), and cerebellum neurons and has opposite effects on GABAergic neurons of different cortical layers depending on the type of NAR involved (Salgado et al., 2011). NA slowly depolarizes dLGN TC neurons through a decrease in a K^+ conductance (McCormick and Prince, 1988) and strongly increases I_h via stimulation of β-adrenergic receptors (McCormick and Pape, 1990). Surprisingly, the effect of NA on GABAergic transmission in the thalamus has not been investigated, and our preliminary data show that NA does increase both the frequency of sIPSC and the amplitude of the tonic $GABA_A$ current in rat dLGN TC neurons (Di Giovanni et al., 2008). The effect of NA (50 μM; n=6) was even larger (107.2±14.8 pA; n=5; $p<0.005$) compared to the DA (50 μM; n=6) effect (90.7±5.6 pA; n=6; $p<0.005$) (Figure 3).

5-HT modulation of the tonic $GABA_A$ current

Almost all brain regions are innervated by serotonergic fibers arising from the midbrain dorsal (DR) and median raphe (MR) nuclei (Dahlstrom and Fuxe, 1964; Hillegaart, 1991; Abrams et al., 2004; Di Giovanni et al., 2010; Hale and Lowry, 2010). 5-HT receptors are presently divided into seven classes ($5\text{-}HT_1$-$5\text{-}HT_7$), which are then subdivided into subclasses with a total of at least 14 different receptors (Barnes and Sharp, 1999; Hoyer et al., 2002; Di Giovanni et al., 2011b). With the exception of the ionotropic $5\text{-}HT_3R$, all other 5-HTRs are GPCRs (Di Giovanni et al., 2011b).

5-HTR modulation of GABA inhibition has been extensively studied because of the involvement of these receptors in many neurological diseases that affect GABAergic systems, including schizophrenia, depression, drug abuse, sleep disorders, and epilepsy (Di Giovanni et al., 2001; Bankson and Yamamoto, 2004; Invernizzi et al., 2007; Nikolaus et al., 2010).

5-HT enhances the frequency of $GABA_A$ mIPSCs in a population of VTA and SNc dopaminergic neurons (Pessia et al., 1994; Theile et al., 2009), nucleus raphe magnus serotonergic neurons (Inyushkin et al., 2010), dorsal horn neurons (Inyushkin et al., 2010), and suprachiasmatic nucleus neurons (Bramley et al., 2005) but reduces evoked IPSCs in the rat dorsolateral septal nucleus (Matsuoka et al., 2004). Since the amplitude of mIPSCs is not affected by 5-HT or its ligands, it is highly likely that 5-HT

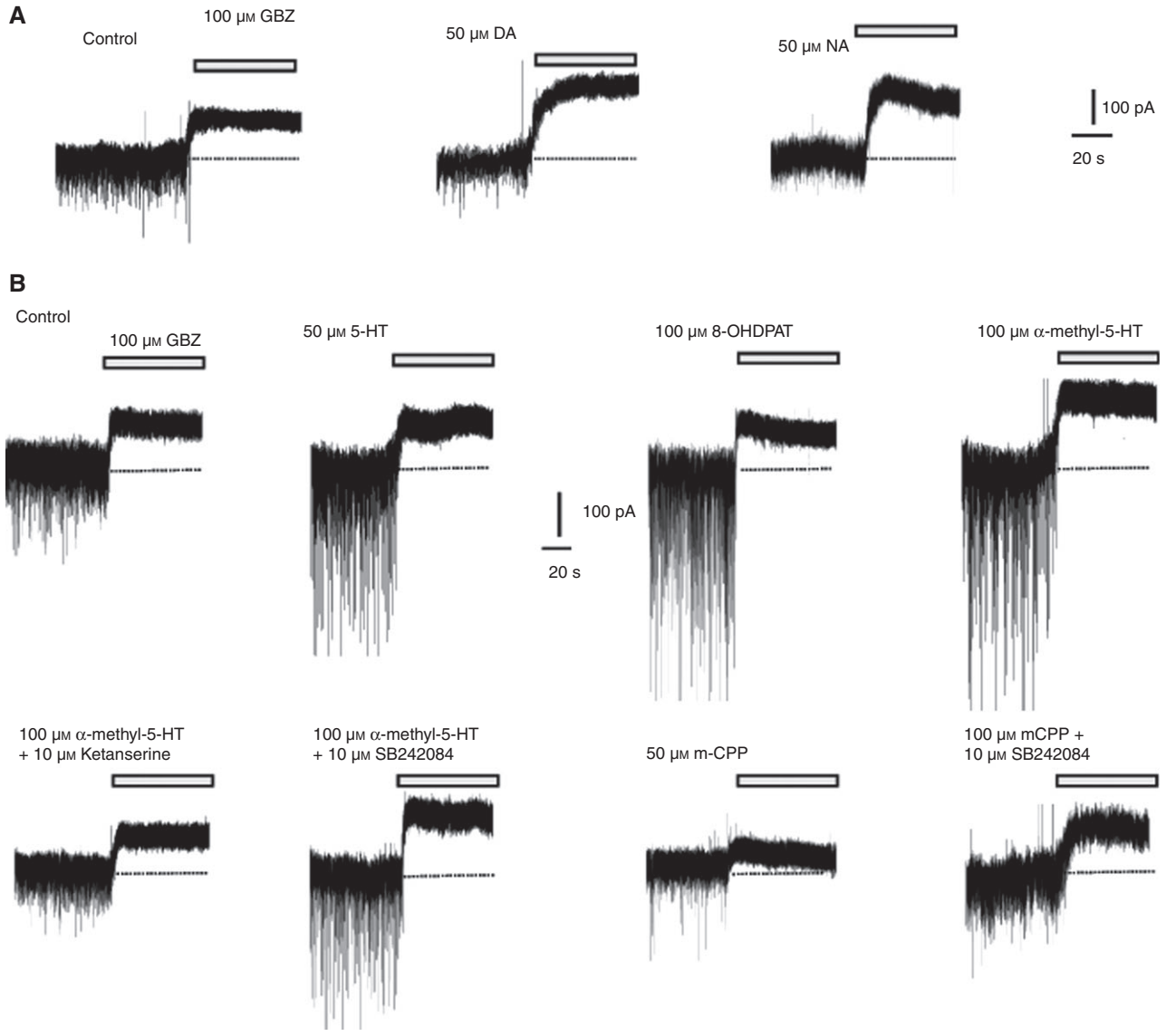

Figure 3 Monaminergic modulation of tonic $GABA_A$ current in the dLGN.
(A) Focal application of gabazine (GBZ; 100 μM; gray bar) reveals different magnitude of tonic current. Representative current traces from different TC neurons of the dLGN of Wistar rats under control conditions (top left) and in the continuing presence of DA (50 μM; middle) and NA (50 μM; right). (B) Representative current traces from different TC neurons in dLGN slices from Wistar rats under control conditions (left) and in the continuing presence of 5-HT (50 μM), 8-OH-DPAT (100 μM), and α-m-5-HT (100 μM; top traces) and α-m-5-HT (100 μM)+Ketanserine (50 μM), α-m-5-HT (100 μM)+SB242084 (10 μM), and mCPP (50 μM) and mCPP (100 μM)+SB242084 (10 μM; bottom traces).

augments GABAergic synaptic transmission via presynaptic mechanisms. Indeed, an enhanced Ca^{2+} release from intracellular stores by $5\text{-}HT_{2C}R$ activation is believed to be involved in the ethanol-induced enhancement of GABA release onto dopaminergic VTA neurons (Theile et al., 2009).

There is also evidence for a postsynaptic interaction between 5-HTRs and $GABA_AR$s. $5\text{-}HT_{2C}R$ inhibit $GABA_A$ currents in *Xenopus* oocytes coexpressing both receptors via an action that requires elevated intracellular Ca^{2+} levels (Huidobro-Toro et al., 1996) but does not involve changes in $GABA_AR$s phosphorylation (Huidobro-Toro et al., 1996). On the contrary, some evidence shows that PKA and protein kinase C (PKC) are involved in mediating the effects of 5-HT on $GABA_AR$ function. Thus, activation of postsynaptic $5\text{-}HT_2R$s in prefrontal cortex pyramidal neurons can inhibit $GABA_A$ currents via a PKC-induced phosphorylation of the $GABA_A$ γ2 subunit, which in turn is dependent on RACK1-anchored PKC (Feng et al., 2001). Moreover, $5\text{-}HT_4R$ activation modulates $GABA_A$ currents bidirectionally: thus, elevated PKA levels due to increased neuronal activity have been shown to reverse the enhancing effect

of 5-HT_4R activation into depression of neuronal excitability (Cai et al., 2002).

dLGN of the thalamus

5-HT_{2A}Rs and 5-HT_{2C}Rs are present in TC neurons of the rodent dLGN (Li et al., 2004; Coulon et al., 2010). A recent study has shown a preferential immunohistochemical staining for 5-HT_{2C}Rs vs. 5-HT_{2A}Rs in mice dLGN TC neurons, although these receptors are not somatically expressed (Coulon et al., 2010). 5-HT_2R mRNA has also been detected in GABAergic interneurons of the dLGN, with similar pattern of expression for the 2A and 2C subtypes (Munsch et al., 2003).

As other brainstem neurotransmitters, 5-HT depolarizes TC neurons of the dLGN, eliciting a shift from rhythmic bursting to tonic firing activity (McCormick, 1992b). This depolarization is caused both by inhibition of a leak K^+ conductance (Meuth et al., 2006) and by modulation of the hyperpolarization-activated current I_h (Pape and McCormick, 1989; Chapin and Andrade, 2001). 5-HT and activation of 5-HT_{2C}Rs produce similar membrane depolarizations, which depend on Gq-coupled intracellular signaling cascades (Coulon et al., 2010). The intracellular pathways that couple 5-HT_2Rs to the Ca^{2+} influx mechanism seems to depend on the PLC system. This does not involve intracellular Ca^{2+} release or voltage-gated Ca^{2+} channels but is critically dependent on a transient receptor potential (TRP) protein, the transient receptor potential channel 4 (TRPC4) (Munsch et al., 2003).

5-HTR modulation has complex effects on phasic and tonic $GABA_A$ currents in dLGN TC neurons. Interestingly, 5-HT itself does not affect the tonic $GABA_A$ current in dLGN TC neurons but increases sIPSC frequency (Di Giovanni et al., 2008). Similarly, application of the 5-$HT_{1A/7}$R agonist 8-OH-DPAT does not change the tonic current but increases the weighted decay time constant and the frequency of mIPSCs. The 5-$HT_{2A/2C}$R agonist α-methyl-5-hydroxytryptamine (α-m-5-HT) strongly increases the tonic current as well as the amplitude and frequency of mIPSCs. These effects are mediated by 5-HT_{2A}Rs since they are blocked by ketanserin, an antagonist with higher selectivity for 5-HT_{2A}Rs than 5-HT_{2C}Rs, but not by SB 242084, a selective 5-HT_{2C}R antagonist. Moreover, concomitant application of 5-HT and ketanserin decreases the tonic $GABA_A$ current and increases the decay time constant and charge transfer of mIPSCs. Finally, the unselective 5-HT_{2C}R agonist *m*-chlorophenylpiperazine (mCPP) markedly reduces the tonic current, whereas all mIPSC properties are unchanged with the exception of a decrease in amplitude. These effects of mCPP are probably mediated by 5-HT_{2C}Rs since they are blocked by coapplication of SB 242084 (Figure 3) (Di Giovanni et al., 2008).

VB nucleus of the thalamus

5-HT is able to modulate the firing VB TC neurons directly (McCormick, 1992b), although early evidence indicated that it plays more of a modulatory role by facilitating the response of these neurons to excitatory amino acids (Eaton and Salt, 1989) or by inhibiting acetylcholine-induced excitation (Andersen and Curtis, 1964). Exogenous application of 5-HT in VB slices was reported to have no effect on sIPSC (Munsch et al., 2003). We recently have started evaluating the effects of 5-HT_{2A}R and 5-HT_{2C}R ligands on phasic $GABA_A$ inhibition in VB TC neurons of Wistar rats (Cavaccini et al., 2012). Similarly to the dLGN, 5-HT_{2A}R activation enhances while 5-HT_{2C}R ligands decrease the tonic $GABA_A$ current: this opposite effects may result from different signal transduction pathways. Alternatively, they could be due to a different receptor distribution, that is, a preferential postsynaptic location of 5-HT_{2C}Rs on VB TC neurons, while 5-HT_{2A}Rs might be expressed mostly presynaptically on GABAergic NRT neurons or their axon terminals, which are both preserved in our slices.

A similar scenario with an opposite role for 5-HT_{2A} and 5-HT_{2C}Rs in the modulation of this type of $GABA_A$ inhibition is also present in GAERS rats (Cavaccini et al., 2012). Our preliminary data are in agreement with previous results suggesting an impairment of the serotonergic system in absence epilepsy; indeed, 5-HT depletion has been shown in Long Evans rats, another strain that expresses spontaneous absence seizures (Bercovici et al., 2006).

Other thalamic nuclei

5-HT_{1A}Rs and 5-HT_{2A}Rs are relatively highly expressed in the GABAergic neurons of the NRT (Li et al., 2004; Bonnin et al., 2006; Rodriguez et al., 2011). 5-HT_{1A}Rs are mainly present on the soma and proximal dendrites of these neurons, whereas 5-HT_{2A}R are less abundant and moderately expressed on cell bodies and more abundant on fine and medium-sized dendrite (Rodriguez et al., 2011).

The highest expression of 5-HT_7Rs in the rat brain occurs in the intralaminar and midline thalamic nuclei, where they strongly modulates neuronal excitability by inhibiting the calcium-activated potassium conductance that is responsible for the slow after-hyperpolarization (Goaillard and Vincent, 2002). In contrast, 5-HT_7Rs

depolarize neurons of the anterodorsal thalamic nucleus primarily by increasing I_h through a cyclic AMP (cAMP)-dependent and PKA-independent mechanism (Chapin and Andrade, 2001).

Surprisingly, no study has investigated 5-HTR modulation of the GABAergic function in NRT neurons or cells in the intralaminar, midline, or anterior thalamic nuclei.

Conclusions

It is now well established that the amplitude of the $eGABA_AR$-mediated tonic current changes in relation to the ambient GABA concentration (Pavlov et al., 2009) is modulated by exogenous agents including neurosteroids, alcohol, and anesthetics (Belelli et al., 2009) and that $eGABA_ARs$ show plasticity in response to changes in $sGABA_ARs$ activity (Nani et al., 2013). As reviewed here, $eGABA_ARs$ are also subject to modulatory actions by the monoamines that can act presynaptically, modulating GABA release, or postsynaptically, directly altering $eGABA_AR$ activity (see also the recent findings of postsynaptic $GABA_BRs$ interaction with $eGABA_ARs$ (Connelly et al., 2013b; Tao et al., 2013). Since these modulations of $eGABA_AR$ are both nucleus selective and neuronal type selective, the functional interactions of GABA with other neurotransmitters are more complex than previously envisioned. Moreover, while activation of $GABA_B$, D2, and $5\text{-}HT_{2A/2C}Rs$ preferentially modulates $eGABA_AR$ over $sGABA_AR$-mediated conductance in the thalamic VB nucleus (Di Giovanni et al., 2008; Cavaccini et al., 2012; Connelly et al., 2013b; Yague et al., 2013), mGlu, D2, and different 5-HTRs do affect both phasic and tonic inhibition in the dLGN (Munsch et al., 2005; Di Giovanni et al., 2008; Errington et al., 2011b). The monoamine modulation of $eGABA_AR$ could be due to the different synaptic localization of the associated GPCRs between dLGN and VB or to different direct protein-protein interaction.

Nevertheless, it is clear that the diverse modulations of $eGABA_ARs$ by monoamines provide a powerful route for the fine-tuning of single neuron and network excitability in physiological conditions as well as in neurological diseases. Thus, since PD symptoms result from an imbalance in the two striatal pathways (Mallet et al., 2006; Esposito et al., 2007; Obeso et al., 2008) and Huntington's disease from a selective loss of $D2^+$ MSNs (Estrada Sanchez et al., 2008), the differential expression of the tonic $GABA_A$ currents in $D1^+$ and $D2^+$ MSNs does offer novel potential targets for the treatment of these diseases.

The ability of some monoamines to selectively modulate only one type of $GABA_AR$-mediated inhibition may also have important therapeutic relevance in pathologies such as absence epilepsy, where there is an aberrant increase in thalamic $eGABA_AR$ function but an unchanged phasic inhibition (Cope et al., 2009). Since this enhanced thalamic tonic $GABA_A$ current is a necessary and sufficient condition for the expression of typical absence epilepsy (Cope et al., 2005; Di Giovanni et al., 2011a; Errington et al., 2011c), it is conceivable that the anti-absence action of systemically injected 5-HT and DA ligands (Danober et al., 1998; Isaac, 2005; Bagdy et al., 2007) occur in part via a modulation of the thalamic tonic $GABA_A$ inhibition. Indeed, since there are no specific antagonists for δ-subunit-containing $eGABA_ARs$, the possibility of modulating the tonic $GABA_A$ current by the monoamine receptor activation/inhibition offers an interesting novel therapeutic target for this type of generalized epilepsy (Errington et al., 2011a) and other disorders for which an impairment of $eGABA_ARs$ has been reported. Indeed, the cross-talk between GPCRs and $eGABA_ARs$ might be the target underlying the pharmacological actions of some of the monoamine receptor ligands that are currently marketed for this and other neurological diseases.

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