PERSPECTIVES

$GABA_A$ receptor subunit specificity: a tonic for the excited brain

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γ-Aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the brain, where it mediates fast inhibition by activating synaptic ionotropic $GABA_A$ receptors. $GABA_A$ receptors are pentamers constructed from a possible 16 subunits (α1–6, β1–3, γ1–3, δ, θ, π and ϵ (Mohler, 2006). The subunit composition (two α, two β and another) determines the pharmacological and kinetic characteristics of the receptor. Certain combinations, such as $\alpha6\beta\delta$, $\alpha4\beta\delta$ and $\alpha5\beta\gamma2$, are expressed extrasynaptically, have a high affinity for GABA and incompletely desensitize (Semyanov *et al.* 2004; Mohler, 2006). These receptors are able to detect low ambient concentrations of extracellular GABA and so mediate a tonic current. Such tonic currents are developmentally regulated, depend on synaptic and non-synaptic GABA release and are modulated by GABA uptake (Semyanov *et al.* 2004). Tonic currents play critical roles in regulating neuronal excitability, information processing, cognition and memory. These currents are modified in conditions such as epilepsy, where up-regulation of tonic currents may act as an adaptive mechanism protecting the brain from seizure activity (Scimemi *et al.* 2005; Zhang *et al.* 2007).

There has been much work in elucidating the α subunit subtypes involved in mediating tonic currents. The drive for this research has derived from the specific pharmacologies of the different α subunits, in particular their sensitivity to modulators such as neurosteroids and benzodiazepines (Mohler, 2006). On the other hand, the β subunit subtypes expressed in synaptic and extrasynaptic receptors have largely been overlooked.

This omission has now been addressed in an excellent study from Herd *et al.* (2008) in this issue of *The Journal of Physiology*. Using a combination of physiological, pharmacological and molecular methods, they determined the subunit composition of synaptic and extrasynaptic $GABA_A$ receptors in dentate gyrus granule cells (Fig. 1). Dentate granule cells express a large tonic current that is modulated by neurosteroids (Stell *et al.* 2003). Previous work has established the involvement of $GABA_A$ receptors containing $\alpha4$ and δ subunits, which confer high affinity for GABA and neurosteroid sensitivity (Stell *et al.* 2003). Herd *et al.* have demonstrated that there are, in fact, a heterogeneous population of receptors that can mediate a tonic current in dentate granule cells. This is consistent with other studies in these neurons and hippocampal pyramidal cells, in which more than one $GABA_A$ receptor subtype contributes to the tonic current (Scimemi *et al.* 2005; Prenosil *et al.* 2006; Zhang *et al.* 2007). Such hetereogeneity increases the number of potential modulators (e.g. in this study, the tonic current in dentate granule cells is sensitive to both benzodiazepines and 4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridin-3-ol (THIP) acting at different receptors) and also may increase the range of extracellular GABA concentrations that can be detected by the neuron (Scimemi *et al.* 2005).

Second, in some elegant experiments which take advantage of etomidate, a drug that acts on $GABA_A$ receptors containing $\beta2$ or $\beta3$ subunits, and mice in which the $\beta2$ subunit has been made etomidate-insensitive, Herd *et al.* were able to demonstrate that tonic currents are predominantly mediated by $\beta2$ containing receptors, while synaptic currents are mediated by receptors that do not contain the $\beta2$ subunit but contain predominantly the $\beta3$ subunit.

What is the importance of this finding? There has been an increasing recognition of the role of the β subunit in $GABA_A$ receptor trafficking, surface expression, interactions with intracellular proteins and phosphorylation (Kittler & Moss, 2003; Chen & Olsen, 2007). Importantly, many of these processes, such as phosphorylation, demonstrate β subunit specificity. This may partly explain a number of observations such as the different effects of seizure activity on synaptic and extrasynaptic $GABA_A$ receptor expression (Naylor *et al.* 2005). It may also mean that it is possible to modify selectively tonic currents; this is important since tonic currents may serve different physiological and pharmacological roles from synaptic $GABA_A$ receptor inhibition (Orser, 2006). An additional intriguing finding in this study is that knocking out the δ subunit, which is expressed exclusively extrasynaptically, enhances the response of synaptic currents to etomidate. This suggests that reducing the tonic

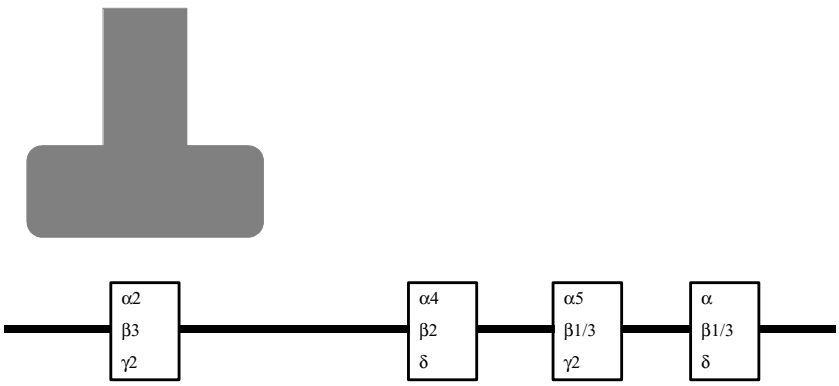

Figure 1. Putative $GABA_A$ receptor subtypes expressed synaptically and extrasynaptically in dentate granule cells, demonstrating the lack of $\beta2$ containing $GABA_A$ receptors synaptically and heterogeneous extrasynaptic $GABA_A$ receptors

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current modifies the receptors expressed synaptically.

These findings present a number of future challenges such as determining the role of the subcellular distribution of β subunit subtypes in differentially regulating phasic and tonic inhibition, and the development of more specific compounds to tease apart the roles of receptors containing different β subunit subtypes and perhaps to develop drugs with more specific and more potent actions.

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