Mechanisms that regulate inhibitory neurotransmission

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$GABA_B$ receptors are heterodimeric G protein coupled receptors composed of R1 and R2 subunits that mediate slow inhibitory signalling in the brain. Postsynaptic $GABA_B$ receptors are predominantly found on dendritic spines adjacent to excitatory synapses and regulate neuronal activity. We have previously reported that $GABA_B$ receptors are intimately associated with protein phosphatase 2A and directly dephosphorylate S783 in the R2 subunit to enhance $GABA_B$ receptor endocytosis (Terunuma et al., *PNAS*, 2010).

To test the role that phospho-dependent modulation of $GABA_B$ receptors play in synaptic transmission and memory formation *in vivo*, we generated a knock-in mouse in which S783 was mutated to alanine (S783A) to prevent S783 dephosphorylation and degradation. Using these knock-in mice, we identified that S783A mice express stable $GABA_B$ receptors on the plasma membrane by reducing its endocytosis (Terunuma et al., *J Neurosci*, 2014). $GABA_B$ receptor stability on the plasma membrane led to decreased activation of cAMP-dependent protein kinase (PKA), CREB phosphorylation and immediate early gene Arc/Arg3.1 expression, proteins necessary for hippocampus-dependent spatial memory consolidation. In parallel to these observations, these mice were altered in hippocampus-dependent memory and long-term spatial memory.

In addition to their role in neurons, $GABA_B$ receptors are expressed in glial cells. We therefore have begun to assess the roles that $GABA_B$ receptors play in communication between neurons and astrocytes. To address this issue we have characterised the structure and functional properties of astrocytic $GABA_B$ receptors. Using imaging with Fluo-4 derivatives we show that astrocytic $GABA_B$ receptors are able to enhance intracellular accumulation of Ca^{2+}, but only after the pre-activation of purinergic receptors (Terunuma et al., *Neuropharmacology*, 2015). In addition P2Y receptors enhance the phosphorylation of astrocytic $GABA_B$ receptors on Serine 783 (S783) in the R2 subunit dependent upon the activity of AMP-dependent protein kinase (AMPK). Critically we have previously illustrated that S783 is important in regulating the effector coupling of neuronal $GABA_B$ receptors (Terunuma et al., *PNAS*, 2010). Therefore our studies suggest that $GABA_B$ receptor effector coupling in astrocytes is dependent upon prior activation of P2Y receptors in a mechanism dependent upon the activation of AMPK, and the subsequent phosphorylation of the R2 subunit. To further study the role of astrocytic $GABA_B$ receptors, we have generated astrocytic $GABA_B$ receptor R1 subunit conditional knockout mice. We are currently analysing the significance of this functional cross talk in regulating gliotransmission and animal behavior in these mice.

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