Functional consequences of clustering $GABA_A$ receptors

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Inhibitory signals in mammalian brains are mediated primarily by γ-aminobutyric acid type A receptors ($GABA_AR$). Different subtypes of these receptors, distinguished by their subunit composition, are either concentrated at postsynaptic sites where they mediate phasic inhibition or found at non-synaptic (extrasynaptic) sites where they mediate tonic inhibition. Neurons, therefore, require discrete trafficking mechanisms to regulate the subcellular distribution of $GABA_AR$ subtypes. Although its precise role *in vivo* is yet to be clearly defined, the $GABA_A$ receptor-associated protein GABARAP has been shown to participate in trafficking and membrane fusion events that underlie organisational processes at GABAergic synapses (Kittler *et al.*, 2001; Kneussel, 2002). Co-expression of GABARAP has been shown to cluster recombinant $GABA_A$ receptors (Chen *et al.*, 2000; Everitt *et al.*, 2004) and, as a consequence of this ordered packing arrangement, the recombinant $GABA_A$ receptors function differently. At the single-channel level we have shown that $GABA_A$ receptors co-expressed with recombinant GABARAP in L929 cells may display high conductances (>40 pS) (Everitt *et al.*, 2004) which is in stark contrast to the conductance of αβγ receptors expressed without GABARAP (<40 pS) (Luu *et al.*, 2005). Single-channel amplitude distribution histograms and open probabilities were analysed to examine the effects of drugs such as GABA and diazepam. The presence of the soluble intracellular protein GABARAP influences recombinant $GABA_A$ channels such that they may open to multiple discrete states and the maximum single-channel conductance is dependent on the effective GABA concentration. It remains a fundamental issue as to what these multiple conductance states represent. Is it a single channel or multiple channels opening in concert? An important conclusion is that recombinantly expressed αβγ receptors behave more like native receptors when cotransfected with GABARAP.

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