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Calcium channel $\alpha_2\delta$ subunits: GPI-anchoring, trafficking and mechanism of action of gabapentinoid drugs

Ivan Kadurin, Anita Alvarez-Laviada, Anthony Davies, Alexandra Tran-van-Minh, Manuela Nieto-Rostro, Claudia S Bauer and Annette C Dolphin

Department of Neuroscience, Physiology and Pharmacology, UCL, London, UK

The $\alpha_2\delta$ auxiliary subunits of voltage-gated calcium channels enhance calcium currents and affect their properties, but their mechanism of action is not well understood. We have recently shown that $\alpha_2\delta$ subunits are glycosyl phophatidyl inositol (GPI)-achored proteins (Davies et al., 2010, PNAS 107:), and this is essential for their function, and explains their localization in lipid raft fractions (Davies et al, 2006 J. Neurosci. 26: 8748-8757). The anti-epileptic and anti-nociceptive drugs gabapentin (GBP) and pregabalin (PGB) are known to bind to $\alpha_2\delta$-1 and $\alpha_2\delta$-2, and the $\alpha_2\delta$-1 target is essential for the antihyperalgesic action of this drug (Field et al., 2006 PNAS 103: 17537-17542). We have found that acute application of GBP does not affect calcium currents in several different systems. However, chronic application of GBP to cultured cells reduces both calcium currents and cell-surface expression of heterologously expressed $\alpha_2\delta$ and α1 subunits (Hendrich et al., 2008, PNAS 105: 3628–3633), and PGB also affects $\alpha_2\delta$ trafficking in *vivo* (Bauer et al., 2009, J. Neurosci. 29:4076–4088). This process involves an inhibition of trafficking through the recycling endosomes (Tran-Van-Minh and Dolphin, submitted). Our evidence indicates that gabapentinoid drugs act chronically to impair the trafficking function of $\alpha_2\delta$ subunits.