μ-Opioid receptor desensitization: homologous or heterologous?

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There is considerable controversy over whether μ-opioid receptor (MOPr) desensitization is homologous or heterologous and over the mechanisms underlying such desensitization (Raveh et al., 2010). In different cell types MOPr desensitization has been reported to involve receptor phosphorylation by various kinases, including G-protein-coupled receptor kinases (GRKs), second messenger and other kinases as well as perturbation of the MOPr effector pathway by GRK sequestration of G protein β/γ subunits or ion channel modulation.

Brainstem slices were prepared from young (<20 day old) and relatively mature (>150g) rats and whole cell voltage clamp recordings (Vh = -60mV) were made from individual locus ceruleus (LC) neurones as described previously (Bailey et al., 2009). MOPr activation evoked a transmembrane K^+ current the amplitude of which is a measure of MOPr function. LC neurones also express α_2-adrenoceptors which couple to the same K^+ channels and by measuring responses to α_2-adrenoceptor agonists following MOPr desensitization we can determine whether the desensitization is homologous or heterologous.

In neurones prepared from relatively mature rats rapid MOPr desensitization induced by the high efficacy opioid peptide DAMGO was largely homologous in that during a 15 min exposure to DAMGO (10 μM) the evoked current decreased by 57 ± 4 % (n = 5) whereas the amplitude of the response to a subsequent application of a submaximal concentration of noradrenaline (5 μM) was decreased by only 14 ± 6 % (n = 5) following DAMGO exposure. Given that MOPrs and α_2-adrenoceptors couple through G proteins to the same set of K^+ channels it is unlikely that in mature neurones MOPr desensitization involves G protein β/γ subunit sequestration or ion channel modulation. In contrast, in slices from immature animals, MOPr desensitization was observed to be heterologous in that the DAMGO (10 μM) evoked current decreased by 60± 4 % (n = 6) over 15 min and the response to a subsequent application of noradrenaline (5 μM) was decreased by 58 ± 6 % (n = 6).

Western blotting experiments on extracts from rat brain demonstrated that the level of GRK2 expression was higher in immature than mature rat cortex and striatum. GRK2 expression in mature animals was 14 ± 4 % n = 3 (cortex) and 70 ± 3 % n = 3 (striatum) of that in immature animals ($p<0.001$ in both cases).

These observations are compatible with the hypothesis that in LC neurones from immature animals heterologous desensitization could result from GRK2 sequestration of free G protein β/γ subunits but that in mature animals, with lower GRK2 levels, desensitization is largely homologous. Whether GPCR desensitization is observed as homologous or heterlogous could therefore be due simply to varied GRK expression levels. That the mechanisms underlying MOPr desensitization change with neuronal development is important when extrapolating to the mature brain results obtained from experiments on expression systems, cell lines and immature neuronal preparations.

Bailey CP, et al., (2009) Eur J Neurosci 29:307–318
Raveh H, et al., (2010) Cell 143 :750-760