

### **Agonist-induced mu-opioid receptor desensitization in peripheral neurones**

Simon Andrews, Linnea Teintang, Janet Lowe, Chris Bailey. University of Bath, Department of Pharmacy & Pharmacology, Bath, BA2 7AY, United Kingdom.

The mechanism underlying tolerance to opioid drugs such as morphine is not fully understood, although one hypothesis is that it is caused by agonist-induced desensitization of the receptors on which they act, the mu-opioid receptor (MOPr; Christie, 2008). In the rat vas deferens and guinea-pig ileum, nerve-evoked smooth muscle contraction is inhibited by activation of MOPrs. In vas deferens preparations, only receptors at nerve terminals are responsible for this inhibition, whereas in the ileum, cell body as well as nerve terminal MOPrs may contribute to twitch inhibition. We examined rapid agonist-induced desensitization of MOPr mediated inhibition of twitch response in these two preparations to examine differences between the regulation of nerve terminal and cell body receptors, as well as examining possible agonist-selective MOPr desensitization (Kelly et al., 2008).

Rats (male 6-8 week-old Wistar strain) were killed by cervical dislocation and vasa deferentia were excised. The first 20% of each vas deferens from the prostatic end was removed and the remainder was suspended in a tissue bath (4ml volume) under 0.5 g tension in standard Krebs-bicarbonate buffer at 37°C. Guinea pigs (female 350-550 g, Dunkin-Hartley strain) were killed by CO<sub>2</sub> inhalation and ileum was removed. Intact ileal preparations (approx. 10mm in length) were suspended longitudinally in a tissue bath (4ml volume) under 1 g tension in standard Krebs-bicarbonate buffer at 37°C. Nerve-evoked muscle contractions were induced with single square pulses (0.1ms duration, 0.1 Hz).

In rat vas deferens, DAMGO dose dependently inhibited muscle twitch (max. inhibition: 73±5%; n=8). To eliminate receptor reserve, the irreversible MOPr antagonist β-FNA (120 nM) was applied for 30 minutes and significantly decreased the peak inhibition produced by 30 μM DAMGO to 49±3% (n=7; t-test p=0.002). This response remained stable over a 25 minute drug application (51±8% inhibition at 25 minutes) indicating that agonist-induced MOPr desensitization did not occur. Similarly, inhibition of twitch by normorphine (30 μM) did not desensitize (38±4% initial peak inhibition, 45±4% inhibition after 25 minutes, n=3). In contrast, agonist-induced MOPr desensitization occurs readily in the guinea-pig ileum. Application of β-FNA for 30 minutes was used to eliminate the receptor reserve (120nM for DAMGO responses and 60nM for morphine responses). DAMGO (30 μM) mediated inhibition decreased from 90±4% to 25±6 % after 20 minutes application (n=5; t-test p<0.001) and morphine (30 μM) mediated inhibition decreased from 46±6% to 20±4% (n=5; t-test p=0.007).

In the guinea-pig ileum, where both nerve terminal and cell body MOPrs are present, rapid agonist-induced receptor desensitization can be readily induced, whereas there is no desensitization in the rat vas deferens where only nerve terminal MOPrs are present. These data show that morphine can induce rapid MOPr desensitization under the right conditions and suggest that nerve terminal MOPrs do not readily desensitize.

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Kelly E et al (2008) *Br J Pharmacol* 153 Suppl 1:S379-88.

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