Oxycodone Inhibits Electrical Field Stimulation-Induced Contractions of the Guinea-Pig Myenteric Plexus Longitudinal Muscle Via the mu-Opioid Receptor

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The opioid analgesic oxycodone is a commonly used drug to manage severe pain, yet its mechanism of action is still not clear. Oxycodone inhibits electrical field stimulation-induced contractions of the guinea pig myenteric plexus longitudinal muscle. This tissue is reported to contain mu (µ), delta (δ) and kappa (κ) opioid receptors (Holzer, 2009). The current study investigated the opioid receptor type underlying this effect of oxycodone.

Male Dunkin-Hartley guinea pigs were killed by CO₂ and the small intestine and brain removed. The myenteric plexus longitudinal muscle (MPLM) was gently stripped from the small intestine and 2 cm lengths mounted in Linton organ baths under a resting tension of 1g in Krebs physiological saline solution gassed with 95/5% O₂/CO₂ at 37°C and allowed to equilibrate for around 30min. Tissues were continuously contracted by electrical field stimulation (EFS; 0.1Hz, 0.5 msec pulse width, 60 - 100 mV). In vitro experiments were conducted to estimate the affinity of the antagonists naloxonazine (µ-opioid receptor selective), nor-BNI (κ-opioid receptor selective) and naloxone (non-selective) using inhibition of EFS-induce contraction by the agonists DAMGO (µ-opioid receptor selective), U69593 (κ-opioid receptor selective) and by oxycodone. Data (mean pEC₅₀ values ± SEM) were analysed using ANOVA. RNA and protein were extracted from brain and MPLM for analysis of µ-, δ- and κ-opioid receptor expression using PCR and Western blotting.

High levels of µ-, δ- and κ-opioid receptor mRNA were detected in brain and MPLM tissues; µ- and κ-opioid receptor proteins were also abundant in these tissue, while expression of δ-opioid receptor protein was lower. DAMGO, U69593 and oxycodone caused concentration-dependent inhibitions of EFS-induced contractions of MPLM. The concentration response curves (CRC) were shifted to the right by naloxonazine (pEC₅₀ values ± SEM and antagonist affinity (pKᵢ): DAMGO, 7.6 ± 0.03; DAMGO + naloxonazine, 6.5 ± 0.04, n = 16, p < 0.001, pKᵢ = 8.03; Oxycodone, 6.5 ± 0.04; Oxycodone + naloxonazine, 5.4 ± 0.04, n = 16, p < 0.001, pKᵢ = 8.09; U69593, 8.5 ± 0.04; U69593 + naloxonazine, 8.0 ± 0.07, n = 16, p < 0.001, pKᵢ = 7.32).

Nor-BNI did not affect the CRC for DAMGO or oxycodone but caused a rightward shift of the U69593 CRC (pEC₅₀ ± SEM: U69593, 8.3 ± 0.04; U69593 + nor-BNI, 6.3 ± 0.03, n = 12, p < 0.001, pKᵢ = 10.03). Naloxone (10, 30, 100, 300nM) produced concentration dependent rightward shifts of the CRC for DAMGO, oxycodone and U69593. Schild analysis produced pA₂ values of 8.8, 8.8 and 7.6, respectively.

The present study indicates that the effects of oxycodone on the guinea-pig MPLM are mediated via activation of the µ-opioid receptor.