Antinociception by Spinal and Systemic Oxycodone: Why Does the Route Make a Difference?

In Vitro and In Vivo Studies in Rats


Background: The pharmacology of oxycodone is poorly understood despite its growing clinical use. The discrepancy between its good clinical effectiveness after systemic administration and the loss of potency after spinal administration led the authors to study the pharmacodynamic effects of oxycodone and its metabolites using in vivo and in vitro models in rats.

Methods: Male Sprague-Dawley rats were used in hot-plate, tail-flick, and paw-pressure tests to study the antinociceptive properties of morphine, oxycodone, and its metabolites oxymorphone and noroxycodone. μ-Opioid receptor agonist–stimulated GTPγS autoradiography was used to study G-protein activation induced by morphine, oxycodone, and oxymorphone in the rat brain and spinal cord. Spontaneous locomotor activity was measured to assess possible sedation or motor dysfunction. Naloxone and the selective κ-opioid receptor antagonist nor-binaltorphimine were used to study the opioid receptor selectivity of the drugs.

Results: Oxycodone showed lower efficacy and potency to stimulate GTPγS binding in the spinal cord and periaqueductal gray compared with morphine and oxymorphone. This could relate to the fact that oxycodone produced only weak naloxone-reversible antinociception after intrathecal administration. It also suggested that the metabolites may have a role in oxycodone-induced analgesia in rats. Intrathecal oxymorphone produced strong long-lasting antinociception, whereas noroxycodone produced antinociception with very high doses only.

Conclusions: The low intrathecal potency of oxycodone in rats seems to be related to its low efficacy and potency to stimulate μ-opioid receptor activation in the spinal cord.

OXYCODONE is an opioid analgesic with high oral bioavailability in humans (> 60%)¹ compared with morphine (19–30%),² whereas its physicochemical properties are similar to those of morphine.³ Oxycodone is increasingly used worldwide to treat acute and chronic pain.

Opioids bind to specific G protein–coupled μ, δ, and κ-opioid and nociceptin/orphanin FQ receptors.⁴⁻¹⁰ Oxycodone shows μ-opioid receptor selectivity,¹¹ but it has a lower binding affinity to the μ-opioid receptor compared with morphine in the rat brain homogenates.¹² Oxycodone has also been shown to act as a μ-opioid receptor agonist in the mouse paraphenylquinone writhing, hot-plate, and tail-flick assays.¹³

In humans, intravenous, intramuscular, and oral administration of oxycodone produces pain relief similar to that produced by other μ-opioid receptor agonists.¹¹,¹⁴ In postoperative pain, the equianalgesic parenteral dose ratio of oxycodone to morphine has previously been reported as 2:3.¹ Intravenous oxycodone was found to be more potent than intravenous morphine in postoperative pain.¹⁵ Interestingly, Backlund et al.¹⁶ found that the epidural dose ratio between morphine and oxycodone was 1:9.8 in humans after abdominal surgery. Another study indicated that twice the dose of oxycodone compared with morphine was needed to achieve comparable analgesia after epidural administration following gynecologic surgery.¹⁷ In rats, both intrathecal¹⁸,¹⁹ and intracerebroventricular²⁰ administered morphine has been shown to induce significantly greater antinociception compared with oxycodone. After subcutaneous and intraperitoneal administration, oxycodone was found to be two to four times more potent than morphine in rats.¹⁹ These results suggest an active role for the metabolites of oxycodone.

Oxycodone is metabolized in humans by hepatic cytochrome P450 (CYP) isoenzymes. The main pathways of metabolism include oxidation to oxymorphone and noroxycodone, conjugation to α-D-glucuronic acid, and conversion to 6-oxycodol.²¹⁻²⁵ O-demethylation by CYP2D6 leads to the formation of the main active metabolite oxymorphone. Oxymorphone induces antinociception in rodents²⁶,²⁷ and humans.²⁸ Noroxycodone is formed through N-demethylation by CYP3A4. It has a poor antinociceptive effect after intracerebroventricular injection in rats.²⁰ It has been suggested that at least part of the analgesia after oxycodone administration is mediated by active metabolites such as oxymorphone.²⁹

The aim of the current project was to study the antino-
nuclear magnetic resonance spectroscopy ($^1$H NMR) data identical to those reported before.31

At 0°C, 1-chloroethyl chloroformate (2.50 g, 17.5 mmol) was slowly added to a mixture of 1-acetyloxycodone (1.26 g, 3.53 mmol) and KHCO$_3$ (3.50 g, 35.0 mmol) in 1,2-dichloroethane (20 ml). The reaction mixture was refluxed for 25 h, allowed to cool, and filtered through a pad of Celite 545 (Aldrich, Steinheim, Germany). The filtrate was evaporated to give a brownish oil. Methanol (30 ml) was added, and the reaction mixture was refluxed for 1 h. The solvent was evaporated, and the resulting solids were dissolved in 6 m aqueous HCl (20 ml). The reaction mixture was stirred at 85°C for 42 h. Water was evaporated in vacuo, and saturated aqueous NaHCO$_3$ was added. The resulting mixture was extracted with CH$_2$Cl$_2$ (4 × 50 ml). The combined organic layers were washed with water (30 ml) and brine (30 ml), dried over MgSO$_4$, and evaporated. The crude product was dissolved in methanol, and HCl (5 ml, 1.25 m in 2-propanol) was added. The solvents were evaporated, and the resulting crude hydrochloride was recrystallized from MeOH/Et$_2$O to afford noroxycodone hydrochloride as a white solid. The yield was 350 mg (30% from oxycodone). The product had $^1$H NMR data identical to those reported.31

**Synthesis of Oxymorphone Hydrochloride**

Boron tribromide (12 ml, 1 m in CH$_2$Cl$_2$) was added drop-wise under argon at 0°C to a solution of oxycodone (650 mg, 2.00 mmol) in CH$_2$Cl$_2$ (10 ml). The reaction mixture was stirred for 1 h and poured into a mixture of ice and water (approximately 20 ml). The resulting mixture was made alkaline with concentrated aqueous NH$_4$OH, and the layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (8 × 20 ml). The combined organic layers were dried over MgSO$_4$, and evaporated. The resulting yellowish solid was dissolved in aqueous HCl (approximately 1 m) and stirred for 1 h, and the solvent was evaporated. The resulting hydrochloride was recrystallized from ethanol/ethyl acetate to afford oxymorphone hydrochloride as a brownish solid (138 mg, 23%). The product had $^1$H NMR data identical to those reported.32,33

**Intrathecal Cannulation**

Intrathecal cannulation was performed during anesthesia with 5.0 mg/kg subcutaneous midazolam (Midazolam Alpharma; Alpharma, Oslo, Norway) and 1.0 ml/kg Hypnorm® (0.2 mg/ml fentanyl and 10 mg/ml fluanisone; Janssen Pharmaceutica, Beerse, Belgium). A thin polyethylene cannula (Portex Ltd., Hythe, Kent, United Kingdom) was inserted through the cisterna magna to the lumbar subarachnoid space with the tip of the cannula at 8 cm from the insertion. The cannula was fixed with a suture to the paravertebral muscles.34 The condition of the animals was checked after surgery, and the animals were housed indi-
vidually in clear plastic cages. Animals with any neurologic disturbances were immediately killed. Proper placement of the polyethene cannula was verified with an intrathecal injection of 10 μl lidocaine, 10 mg/ml (Lidocain®; Orion Pharma, Espoo, Finland), 5 days after cannulation. Only rats with reversible symmetrical paralysis of both hind limbs after injection were used in the experiments, which started 10 days after the cannulation.

Nociceptive Tests

For the paw-pressure test, performed with a paw-pressure apparatus (Ugo Basile, Milan, Italy), the rats were gently wrapped in a towel. The left hind paw of the rat was placed under the weight of the apparatus, and the test was started. A brisk foot withdrawal of the hind leg after constantly increasing pressure terminated the measurement, and the pressure was recorded.

Hot-plate latencies were tested with a Harvard Apparatus Ltd. hot plate (Edenbridge, Kent, United Kingdom). In the test, the rats were kept inside a transparent plastic cage on a hot plate (52°C ± 0.5°C). Licking or shaking the hind paw or jumping were considered as signs of thermal nociception. To avoid tissue damage, 60 s was set as the cutoff time. Tail-flick latencies were tested with a Ugo Basile (Comerio, Italy) apparatus. In the test, the rats were placed in transparent hard plastic tubes. The tests were repeated three times (with a 15-s interval) at every time point. The cutoff was set at 8 s to avoid tissue damage.

The results of the nociceptive tests where a cutoff value was used (tail-flick, hot-plate, and paw-pressure tests) are shown as mean of the maximum percentage effect (MPE%), calculated as [(post value − pre value)/(cutoff − pre value)] × 100%.

Spontaneous Motor Activity

Possible sedative effects of the drugs were tested by measuring spontaneous motor activity. The rats were placed one at a time in a measurement box (70 × 70 × 35 cm) that was covered and isolated from sounds and light. Photocells were located at two different levels inside the box (2 and 12 cm) above its bottom. They automatically detected horizontal and vertical movements of the rat inside. A 30-min period of testing was undertaken 30 min after subcutaneous drug injection. Because there is usually very little motor activity 15-30 min after the animal has been placed in the box, the mean percentage of inhibition at 0–15 min after the drug administration was used for the dose–response analysis and calculated as

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\%\text{inhibition} = \frac{\text{mean} \{\text{AUC}_{\text{sal}0−15}\} - \text{mean} \{\text{AUC}_{\text{drug}0−15}\}}{\text{mean} \{\text{AUC}_{\text{sal}0−15}\}} \times 100\%,
\]

where (AUCdrug0−15) is the area under the curve from 0 to 15 min after the drug administration, and mean (AUCsal0−15) is the average of the same AUC:s measured after the saline injections.

GTPγ[35S] Autoradiography

After decapitation, the brains and the lumbar spinal cords of the opioid-naive rats were carefully dissected. Tissues were rinsed in ice-cold saline, frozen on dry ice, and stored at −80°C. Brain and lumbar spinal cord sections (14 μm thick) were cut in a cryostat (Leica CM3050 S; Leica Microsystems, Nussloch, Germany). After this, they were mounted on poly-L-lysine-coated slides that were kept desiccated at −80°C until used. The GTPγ[35S] autoradiography was conducted essentially as described before. Briefly, sections were first preincubated with 0.95 ml of 50 mM Tris-HCl, 100 mM NaCl, 5 mM MgCl2, and 1 mM EDTA (pH 7.4) per slide for 20 min at 20°C, followed by a second preincubation (0.95 ml per slide for 60 min at 20°C) with the same buffer with presence of 48 mM GDP and 24 mM DPCPX (Tocris). The final incubation (90 min at 20°C) was performed using the buffer supplemented with 20 mM DTT, 48 mM GDP, 24 mM DPCPX, and 42 μM GTPγ[35S] (PerkinElmer Inc., Boston, MA) supplemented with various concentrations of the ligands studied. Nonspecific binding was determined in the presence of 10 μM unlabeled GTPγS. DAMGO, 10 μM, represented as maximal binding, and non-μ-opioid receptor-mediated binding of the ligands studied were determined in the presence of 10 μM naltraloxone. Slides were washed twice for 5 min in ice-cold washing buffer (50 mM Tris-HCl, pH 7.4, 5 mM MgCl2), followed by one 30-s rinse in distilled water at 0°C and drying under cool air. Slides were exposed to Kodak Bio Max MR film (Eastman Kodak, Rochester, NY). After 5 days of exposure together with [14C]-plastic standards (GE Healthcare, Buckinghamshire, United Kingdom), the films were developed using a Kodak GBX developer (Eastman Kodak) for 5 min, H2O rinse for 5 s, then fixed with a Kodak GBX fixer (Eastman Kodak) for 4 min at 20°C, and finally rinsed under cold running tap water. Films were further analyzed and quantified with Dage MTI-apparatus (DAGE-MTI Inc., Michigan City, IN) combined with MCID Elite M5+ version 4.0 (Imaging Research Inc., St. Catharines, Ontario, Canada). The binding densities in the studied central nervous system (CNS) regions were converted to nCi/g values with the help of the simultaneously exposed standards. Nonspecific binding was subtracted from all values. Finally, all values for the various ligands were expressed as percentages of the 10 μM DAMGO-stimulated maximal values. All chemicals were purchased from Sigma-Aldrich (St. Louis, MO), if not otherwise stated.

Statistical Analysis

Paired t test and nonparametric analyses of variance (the Kruskal–Wallis and Mann–Whitney tests), of StatView 5.5 (SAS Institute Inc., Cary, NC), with Bonferroni
correction for multiple comparisons, when appropriate, were used for the statistical analysis.

**Results**

**Antinociception and the Route of Drug Administration**

Saline injections had no significant effects on the pain thresholds in any of the tests. In the tail-flick test, subcutaneous oxycodone (fig. 1A) and oxymorphone (fig. 1B) produced dose-related antinociception (significantly different from the saline group) with a maximum effect 30 min after the injection. A 100% MPE was achieved with 2.5 mg/kg oxycodone and 0.15 mg/kg oxymorphone. Subcutaneous administration of 25 mg/kg noroxycodone (fig. 1C) caused a 60% MPE 60 min after the injection.

In the hot-plate test, a subcutaneous injection of oxycodone (fig. 2A) did not induce a 100% MPE, and the effect of 76% MPE was reached 30 min after the administration of 2.5 mg/kg oxycodone (significantly different from the saline group). Subcutaneous injection of oxymorphone (fig. 2B) produced clear dose-related antinociception with a maximum effect 30 min after the injection (significantly different from the saline group). A 100% MPE was achieved with 0.63 mg/kg oxymorphone. Subcutaneous administration of 25 mg/kg noroxycodone (fig. 2C) caused a 13% MPE.

In the paw-pressure test, a subcutaneous injection of 2.5 mg/kg oxycodone (fig. 3A) induced statistically significant dose-related antinociception, and a 73% MPE was reached 30 min after the administration. Subcutaneous injection of oxymorphone (fig. 3B) produced clear dose-related antinociception (significantly different from the saline group) with a maximum effect 30 min after the injection. A 100% MPE was achieved with 0.63 mg/kg oxymorphone. Subcutaneous administration of 25 mg/kg noroxycodone (fig. 3C) caused a 22% MPE 60 min after the injection.
Intrathecal administration of oxycodone (fig. 4A), oxymorphone (fig. 4B), and noroxycodone (fig. 4C) produced dose-related antinociception that was significantly different from that of the saline group. The duration of oxycodone-induced antinociception was markedly shorter compared with that induced by oxymorphone and noroxycodone. A 100% MPE was achieved with an intrathecal injection of 1.25μg oxymorphone.

**Effects of μ- and κ-Opioid Receptor Antagonists**

In the hot-plate test, subcutaneous administration of the selective κ-opioid receptor antagonist nor-binaltorphimine (10 mg/kg) with oxycodone or oxymorphone 30 min before the testing did not significantly reduce hot-plate latencies (fig. 5). Antinociception by oxycodone or oxymorphone was completely antagonized with coadministration of 1 mg/kg subcutaneous naloxone 30 min before the testing.

The MPE% of the tail-flick latency after 200μg intrathecal oxycodone was significantly reduced from 96% to 15% after administration of 1 mg/kg subcutaneous naloxone 30 min before testing (fig. 6).

**Spontaneous Locomotor Activity**

The locomotor activity was dose-dependently decreased after subcutaneous injections of oxycodone and oxymorphone 30 min before the measurements (figs. 7A and B). A statistically significant reduction of spontaneous locomotor activity compared with the saline control group was observed during the first 10 min of the 30-min period of measurement, when most of the exploratory activity takes place. Subcutaneo
ous administration of 25 mg/kg noroxycodone had no statistically significant sedative effect compared with the saline control.

**Opioid Receptor Signaling**

μ-Opioid receptor–mediated G-protein activation was differentially observed in all studied rat brain regions and in the dorsal horn of the spinal cord with all study drugs, and it was absent in the presence of 10 μM naltrexone. There were also regional differences in the basal GTPγ[S] binding: The amygdala, periaqueductal gray (PAG), and dorsal horn of the spinal cord showed increased levels of basal GTPγ[S] binding compared with the frontal cortex, thalamus, and striatum (figs. 8–10).

DAMGO-stimulated (10 μM) GTPγ[S] binding was high in the striatum, amygdala, and dorsal horn of the spinal cord (fig. 8 and autoradiographs in figs. 10B, D, and F). Moderate stimulation of the GTPγ[S] binding was observed in the thalamus and PAG (fig. 8 and autoradiographs in figs. 10C and E). Low stimulation was found in the frontal cortex (fig. 8 and autoradiograph in fig. 10A). In the spinal cord, μ-opioid receptor–mediated G-protein activation was mainly located in the most superficial layers of the dorsal horn (fig. 10F). The maximal G-protein activation in the spinal cord induced by oxycodone was lower than that induced by oxymorphone and morphine (fig. 9F). The weakest effect of oxycodone compared with morphine and oxymorphone was observed in the PAG and the spinal cord (fig. 9E, F). Oxymorphone was the most potent of the drugs in all of the CNS regions studied. All drugs studied were apparently partial agonists. Oxymorphone was in all regions as efficacious as morphine, but it needed approximately 10- to 100-fold lower concentrations than oxycodone. The frontal cortex showed the lowest 10 μM...
DAMGO–stimulated GTP$_{\gamma}$[$^{35}$S] binding in the studied CNS regions (fig. 8), whereas oxymorphone caused the strongest G-protein activation compared with oxycodone and morphine in this region (fig. 9A). Morphine-stimulated maximal GTP$_{\gamma}$[$^{35}$S] binding was considerably higher in the striatum (fig. 9B) and in the amygdala (fig. 9D) compared with other studied CNS regions.

In the thalamus (fig. 9C), the study drugs caused comparable maximal GTP$_{\gamma}$[$^{35}$S] activation.

Discussion

The intrathecal as compared with systemic pharmacologic effects of oxycodone, oxymorphone, and morphine were studied, and GTP$_{\gamma}$[$^{35}$S] autoradiography$^{35–37}$ was used to visualize the agonist-stimulated G-protein activation in the rat brain and spinal cord sections. Previous pharmacologic studies have shown that $\mu$-opioid receptor agonists have differences in their ability to activate intracellular G proteins in the CNS.$^{38–40}$ The fact that the function of the $\mu$-opioid receptor system has regional specificity$^{41,42}$ offers new possibilities for the study of pharmacodynamic differences between various opioids.

In the current study, the regional differences in the basal GTP$_{\gamma}$[$^{35}$S] binding indicate high basal GTP$_{\gamma}$[$^{35}$S] binding in amygdala, which is in agreement with previous studies.$^{42}$ PAG and dorsal horn of the spinal cord also showed high levels of basal GTP$_{\gamma}$[$^{35}$S] binding compared with the frontal cortex, thalamus, and striatum.

In the GTP$_{\gamma}$[$^{35}$S] binding assay, oxycodone had reduced ability (lower efficacy and potency) to activate G proteins, particularly in the dorsal horn of the spinal cord and PAG, compared with other study drugs. PAG and the descending inhibitory tracts play a crucial role in the modulation of nociception in the spinal cord.

Fig. 4. Effect of intrathecal administration of the drugs studied in the tail-flick test. Time course of the antinociceptive effect of oxycodone (A), oxymorphone (B), and noroxycodone (C) after intrathecal administration in the tail-flick test. The mean of the maximum possible effect (MPE%) ± SEM is plotted over time (in minutes). * Statistically significant differences ($P < 0.05$) as compared with the saline control.
The in vivo findings of the current study and previous reports indicate that oxycodone is a potent antinociceptive agent after systemic administration, but it produces only weak antinociception when administered intrathecally or intracerebroventricularly. In the current study, intrathecal administration of oxycodone produced significantly weaker antinociception compared with oxymorphone and noroxycodone. Even the highest dose of 200 μg intrathecal oxycodone did not produce a 100% MPE in the tail-flick test, whereas this was achieved with only 2.5 μg intrathecal oxymorphone. The poor efficacy and potency of oxycodone after intrathecal administration is not sex or strain specific, as it has been shown in both female Wistar and male Sprague-Dawley rats.

Poor intrathecal efficacy of opioids has been explained by high lipophilicity. However, intrathecally administered morphine induces significantly greater antinociception than oxycodone, even though the lipophilicity of oxycodone is similar to that of morphine, indicating that lipophilicity may not be a major factor. Therefore, the most likely explanation to the weak antinociceptive effect of intrathecal oxycodone would be that oxymorphone or some other active metabolite is not formed in the CNS after direct administration of oxycodone into the CNS.

Oxymorphone induced potent antinociception after both systemic and intrathecal administration in both thermal and mechanical tests of noiception. Previously, oxymorphone-induced antinociception has been shown in both rodents and humans. The role of oxymorphone as an active metabolite in oxycodone-induced analgesia has been questioned because the serum concentrations of oxymorphone have been extremely low after oral, intravenous, or intramuscular administration of oxycodone in humans. In humans, blocking CYP 2D6, the isoenzyme catalyzing the conversion of oxycodone to oxymorphone, with quinidine (CYP 2D6 inhibitor) converted the metabolic pathway from O-demethylation (oxymorphone) to N-demethylation (noroxycodone). However, the pharmacodynamics of oxycodone were not altered. These findings support the idea that the analgesic effect of oxycodone in humans would mainly result from its own analgesic activity, or it could be a cooperative effect with some downstream active metabolite, e.g., noroxymorphone.

In rabbits, oxymorphone was found in the urine mainly...
in the conjugated forms after subcutaneous administration. It is not known whether the conjugated oxymorphone has antinociceptive effects.

Noroxycodone has been found in relatively large amounts in human serum after intramuscular and oral administration of oxycodone. The antinociceptive activity of noroxycodone after intracerebroventricular administration has been reported to be low in rats. In the current study, in all tested models of nociception subcutaneous administration of noroxycodone produced antinociception only after a high dose of 25 mg/kg, indicating that it has no role in oxycodone-induced analgesia after systemic administration. Spinal administration of noroxycodone, however, produced a longer-lasting antinociceptive effect compared with oxycodone but only after relatively high doses (100 μg). Noroxycodone was previously studied in the GTPγS binding assay, and it was not significantly different in potency compared with oxycodone in rat thalamus. Noroxycodone was therefore not used in the GTPγS binding assay in the current study.

It has been suggested that oxycodone has δ-opioid receptor-mediated activity when administered intracerebroventricularly. In the current study, the antinociceptive effects of subcutaneous oxycodone and oxymorphone were antagonized by subcutaneous administration of naloxone, showing the opioid system-mediated analgesic effect. However, the antinociceptive effects were not antagonized by the selective δ-antagonist nor-binaltorphimine. This would indicate that antinociception by both oxycodone and oxymorphone is mediated by the δ-receptor.

The weak and short antinociceptive effect of intrathecal oxycodone was also reversed by subcutaneous naloxone. Our findings are in agreement with previous studies showing that oxycodone acts as a µ-opioid receptor agonist in mice and binds selectively to the µ-opioid receptor.

**Fig. 7.** Drug effects on spontaneous motor activity. The effects of oxycodone, oxymorphone, and noroxycodone on spontaneous locomotion are shown 30 min after subcutaneous drug administration. (A) Time courses of the locomotor activity with example doses. The activity counts (number of photocell crossings in 5-min periods) over time (± SEM) are shown. (B) The dose–response curves for oxycodone, oxymorphone, and noroxycodone plotting mean percentage of inhibition of activity, as compared with the locomotor activity in the saline control group (± SEM) of 0–15 min period. * Statistically significant difference (P < 0.05) compared with the saline control group.

**Fig. 8.** Regional comparison of the basal and 10 μM DAMGO-stimulated GTPγS binding in studied brain regions and in the dorsal horn of the spinal cord. Data are expressed as mean (± SEM) in nCi/g. * Statistically significant difference (P < 0.05) as compared with the basal GTPγS binding. Am = amygdala; DHSC = dorsal horn of the spinal cord; FC = frontal cortex; PAG = periaqueductal gray; Str = striatum; Th = thalamus.
There was a dose-related, statistically significant reduction in the spontaneous locomotor activity after subcutaneous injections of oxycodone and oxymorphone, whereas noroxycodone was ineffective even after a relatively high dose. Previously, we have demonstrated that measurement of spontaneous locomotion is very sensitive to the sedative effects of centrally acting drugs. Sedation is a major adverse effect of opioids, and it may interfere with the nociceptive tests, particularly when higher doses are used.

Conclusions

Oxycodone is a potent analgesic after subcutaneous administration, but its analgesic potency is poor after intrathecal administration. Our current results suggest that the poor spinal antinociceptive effect of intrathecal oxycodone relates to its low activity to induce intracellular G-protein activation in the spinal cord in rats.

Oxymorphone had the highest relative potency of the drugs studied after subcutaneous and intrathecal administrations. Noroxycodone was more potent than oxycodone after intrathecal administration but did not induce potent antinociception after subcutaneous administration, possibly indicating a high rate of metabolism after systemic administration or limited transport to the CNS.

The role of oxymorphone in oxycodone analgesia after systemic administration in man remains unclear. However, oxymorphone should be an interesting opioid for spinal administration.

It remains to be seen whether some of the discrepancies of the results regarding the antinociceptive actions of oxycodone and oxymorphone after systemic administration can be explained by differences in the rate of metabolism in the spinal cord.
of oxycodone in rats and human beings can be explained by differences of the metabolic pathways between rats and humans, and whether the key to understanding oxycodone-induced analgesia lies in the complex pharmacology of the G-protein receptors in the CNS.

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References


Fig. 10. Maximal agonist-stimulated GTPγ[S] binding by the opioid drugs. Representative autoradiograms illustrating the maximal basal and agonist-stimulated GTPγ[S] binding in the rat brain and spinal cord sections: frontal cortex (A), striatum (B), thalamus (C), amygdala (D), periaqueductal gray (E), and dorsal horn of the spinal cord (F).

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