Analgesia by Dihydrocodeine Is Not Due to Formation of Dihydromorphine: Evidence from Nociceptive Activity in Rat Thalamus

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ABSTRACT
Dihydrocodeine is increasingly used in slow-release preparations for the treatment of chronic pain on step 2 of the "analgesic ladder" of the World Health Organization. Dihydrocodeine is suggested to act after O-demethylation to dihydromorphine. To test this possibility, experiments were carried out on rats under urethane anesthesia in which nociceptive activity was evoked by electrical stimulation of afferent C fibers in the sural nerve and recorded from neurons in the ventrobasal complex of the thalamus. Dihydrocodeine administered by intravenous injection reduced the evoked nociceptive activity in a dose-dependent manner. Like morphine, dihydrocodeine was capable of completely suppressing the evoked activity. Maximum depression was caused by 2 mg/kg, and the ED50 is 0.47 mg/kg. Naloxone (0.2 mg/kg) reversed the effect of dihydrocodeine (2 mg/kg). To inhibit O-demethylation of dihydrocodeine to dihydromorphine, metyrapone or cimetidine (50 mg/kg) was injected intraperitoneally 20 min before dihydrocodeine (1 and 2 mg/kg). This failed to markedly reduce the effect of dihydrocodeine. Dihydromorphine injected intravenously also reduced the evoked activity in a dose-dependent way. Maximum depression occurred at a dose of 4 mg/kg, and the ED50 is 0.97 mg/kg. Dihydrocodeine and dihydromorphine were equieffective when administered by intrathecal injection at a dose of 100 μg. It is concluded that dihydrocodeine causes analgesia independent of biotransformation to dihydromorphine.

Dihydrocodeine is gaining increasing importance as step 2 of the "analgesic ladder" originally proposed by the World Health Organization (1986) for the treatment of cancer pain. When dihydrocodeine became available as a slow-release preparation, prolonging the duration of action of the drug (Wotherspoon et al., 1991), it began to replace codeine in this respect.

Codeine exhibits about one tenth of the antinociceptive effectiveness of morphine and has an extremely low affinity for opioid receptors compared with morphine (Pert and Snyder, 1974) without selectivity toward the μ, δ or κ subtypes (Hennies et al., 1988). Because it is demethylated ≤10% to morphine in the organism (Adler et al., 1955; Findlay et al., 1978), it has been suggested that the analgesic effect of codeine is largely due to its conversion to morphine (Adler, 1963; Findlay et al., 1978; Sanfilippo, 1948; Way and Adler, 1962; cf. fig. 1). Likewise, it has been suggested that depression of pain sensation caused by dihydrocodeine might not develop unless the drug is metabolized to dihydromorphine (Rowell et al., 1983)

Dihydrocodeine differs in its chemical structure from codeine by the saturation of the double bond between C7 and C8 (fig. 1) and possesses, like codeine, antitussive and analgesic properties. However, no data from opioid receptor binding assays are available for dihydrocodeine. In various tests of nociception, dihydrocodeine was either half as effective, equally effective or twice as effective as codeine (Eddy et al., 1969). The therapeutic doses to produce analgesia are the same for codeine and dihydrocodeine (i.e., 60 mg), but according to early reports, the analgesic effectiveness of dihydrocodeine is higher than that of codeine and nearly equal to that of morphine (10 mg) in postoperative (Gravenstein et al., 1956; Keats et al., 1957) and tumor (Seed et al., 1958) pain when both morphine and dihydrocodeine were administered systemically. These clinical observations are in accord with results obtained when comparing the effects of dihydrocodeine with those of codeine and morphine on nociceptive activity elicited in neurons of the rat thalamus (Jurna and Carlsson, 1989).

It was the aim of the present study to assess whether dihydrocodeine itself produces analgesia or the analgesic effect results from biotransformation of dihydrocodeine to dihydromorphine. This was done by recording nociceptive activity in thalamic neurons evoked by electrical stimulation of

ABBREVIATIONS: VPL, ventral posterolateral nucleus; VPM, ventral posteromedial nucleus.
afferent nerve fibers in the sural nerve of the rat and blocking specifically cytochrome P-450 activity and thereby inhibiting O-demethylation of dihydromorphone after intravenous and intrathecal injection of the two compounds. The procedure of recording nociceptive activity from thalamic neurons in the rat was chosen because electrical stimulation of afferent C fibers causes pain in humans, the ventrobasal complex of the thalamus plays an important role in the generation of pain sensation (Willis, 1985) and analgesic agents, opioids as well as nonopioids, depress the activity at doses used in patients with pain (Carlsson et al., 1988; Jurna et al., 1992, 1993, 1996; Jurna and Brune, 1990).

Methods

Animals. The experiments were carried out on 138 rats of either sex (Wistar; Charles River, Margate, Kent, UK; 250–300 g b.wt.). The animals were housed in Macrolon cages (6 animals to a cage) and offered standard diet (Altromin) and tap water ad libitum. They received an intraperitoneal injection of urethane (1.2 g/kg) to induce and maintain anesthesia for surgery and the experimental procedure. At the end of surgery, an additional subcutaneous injection of urethane (120 mg/kg) was administered. In separate experiments performed on the righting reflex, it was found that sleeping time achieved by this treatment was ~6 hr. Preparing the animals, searching for neurons and recording activity before and after injection of drugs took ≤3 hr. The animals breathed spontaneously. Body temperature was monitored in the rectum and maintained between 37.5° and 38°C with radiant heat.

Injection, stimulation and recording. The procedure to prepare the animals for the experiment and to elicit and record C fiber-evoked activity from thalamic neurons has been described previously (Carlsson et al., 1988; Jurna et al., 1996). A cannula was inserted into a tail vein for intravenous injections. For intrathecal injections, a laminectomy was performed at the level of T-8 to T-10, and a polyethylene catheter (o.d., 0.4 mm; length inserted into the spinal canal, 14–20 mm) was introduced into the subarachnoid space of the lumbosacral spinal cord, with its outer end fitted with a 20-gauge injection needle to a microinjection syringe (Jurna et al., 1996). The exposed cord was covered with warm agar that, when cooling, sealed the spinal canal and fixed the intrathecal catheter. The left sural nerve was prepared for electrical stimulation with a pair of platinum wire electrodes and cut distal to the electrodes. The nerve was stimulated using single rectangular impulses delivered from a Grass stimulator (model S4; Grass Instruments, Quincy, MA) with stimulus isolation unit at a frequency of 0.1 Hz and an impulse duration of 0.5 msec. The stimulation strength was 2- to 2.5-fold higher than that producing maximum responses and supramaximal for afferent C fibers (42–68 V) in the sural nerve. These stimulation parameters have been used in a previous investigation (Jurna and Heinz, 1979) in which activity in single axons of the rat spinal cord was elicited by electrical stimulation of the sural nerve. (A more detailed description of C fiber-evoked activity is given below.)

Tungsten microelectrodes (tip diameter, 1 μm; resistance, 10 MΩ) attached to a micromanipulator with a stereotaxic device were used to record activity from single neurons in the ventrobasal complex of the thalamus. For ipsilateral and contralateral recordings, a hole was drilled into the skull on both sides for introduction of the microelectrode. The coordinates for recording activity in the VPL and VPM were A, 2.3 to 2.6 mm; L, 2.8 mm and V, 5.2 to 6.8 mm (Paxinos and Watson, 1986).

The activity of single neurons was amplified (WPI preamplifier model DAM-5A; Sarasota, FL) and evaluated with a Cambridge electronic design computer interface (model 1401 A, Science Products, Frankfurt) together with a personal computer (Tandon XT 10) and MRATE software M., Germany. The number of addresses used was 256, with the duration of each address being 4 or 8 msec. Peristimulus histograms consisting of 10 consecutive responses were summed each time and electronically integrated. Spontaneous and evoked activities were
treated separately. The integrations of activity were pooled for statistical evaluation. Four to six determinations were made before drug administration, and these served as controls when they were stable. If evoked activity changed by >10% of the mean value before drug administration, the neuron was abandoned and another one was sought. Only one neuron was tested in one animal; therefore, the number of neurons or axons, experiments and rats used are identical.

After the end of the experiments, the position of the microelectrode tip was marked by passing current of −0.2 mA for 3 sec (Grass Lesion Maker). The animals were killed with an overdose of pentobarbital, and the brain was perfused by an intraarterial injection of a 10% formaldehyde solution. The brain was removed, fixed in Bouin’s solution and embedded in paraplast. Serial sections (10 μm) were stained with galloycyanin-chromalum (Einarson, 1951) and counterstained with phloxin.

**Statistical analysis.** Significant differences were established by applying Student’s t test for unpaired samples. In addition, the Friedman test was used in combination with the Wilcoxon-Wilcoxon test. Finally, the times were determined at which the values before and after drug application differed by using a multivariate analysis of variance. (These values are represented by open symbols in figs. 4, 6, 7 and 8; this was done to avoid unreadable curves when the time course of the dose-dependent depression of evoked activity is presented with S.E.M. values.)

**Drugs.** The drugs used were cimetidine hydrochloride (Smith-Kline and Beecham, München, Germany), dihydrocodeine hydrochloride (Knoll, Ludwigshafen, Germany), dihydromorphine hydrochloride (Mundipharma, Limburg, Germany), metyrapone (Sigma Chemie, Deisenhofen, Germany), morphine hydrochloride (Merck, Darmstadt, Germany), naloxone hydrochloride (Sigma) and urethane (Riedel-De Haen, Seelze, Germany). Physiological NaCl solution was used as solvent. Intrathecal injections were made with a volume of 10 μl at a rate of 20 μl/min. All doses are indicated as the salts.

**Fig. 2.** Location of cells in the ventrobasal complex of the thalamus responding to ipsilateral and contralateral stimulation of afferent C fibers in the left sural nerve. Cells were plotted on frontal planes from slices and adapted to the stereotaxic atlas of Paxinos and Watson (1986). Numbers, distance of the planes from bregma. F, fornix; HB, habenular nuclei; MD, mediodorsal nucleus; PV, paraventricular nucleus; ZI, zona incerta.

**Fig. 3.** Depression by dihydrocodeine of activity in a single neuron of the thalamus evoked by sural nerve stimulation. A, Recordings show spontaneous impulse discharge (a) and evoked impulse discharges before (b) and 20 min after intravenous injection of dihydrocodeine (2 mg/kg) (c). Supramaximal electrical stimulation (58 V) of the ipsilateral sural nerve produces an increase in impulse discharge (evoked activity). Dots under the recordings, stimulus artifacts. B, Recordings present the peristimulus histograms (10 trials each) of the activity determined before and after intravenous injection of dihydrocodeine in the neuron as in A. Hill-shaped curves in the histograms, electronic integrations of the impulse discharges. Dots under the recordings, stimulation.
Dihydrocodeine and morphine without and after pretreatment with metyrapone or cimetidine. Dihydrocodeine administered by intravenous injection reduced the activity evoked in thalamic neurons by afferent C fiber stimulation (fig. 3). This effect was dose dependent, and its maximum was reached between 5 and 10 min (fig. 4). The threshold dose is 0.25 mg/kg, and the dose producing the maximum effect (i.e., complete depression of evoked activity) is 2 mg/kg. The ED$_{50}$ of intravenous dihydrocodeine is 0.47 mg/kg. The effect of dihydrocodeine (2 mg/kg) was reversed by an intravenous injection of naloxone (0.2 mg/kg; fig. 5). In a previous study, it was found that an intravenous injection of naloxone increased C fiber-evoked activity in thalamic neurons at high doses (1 and 5 mg/kg), whereas at low doses (0.1, 0.2, and 0.5 mg/kg), it was reduced (Jurna, 1988). Therefore, it must be assumed that naloxone (0.2 mg/kg) reversed the depressant effect of dihydrocodeine by displacement of the latter from opioid receptor sites.

The dose of metyrapone that is usually used in metabolic studies is 50 mg/kg (Fantuzzi et al., 1993; Maser and Legrum, 1985; Usansky et al., 1984). This dose reduced the O-demethylation process for $\geq$2 hr by $\sim$70% when administered 15 min before the test agent, methacетin (Maser and Legrum, 1985). The doses of cimetidine administered for similar purposes range between 10 to 150 mg/kg (Chang et al., 1992; Mitchell et al., 1984; Mojaverian et al., 1982). Intraperitoneal injection of metyrapone (50 mg/kg) or cimetidine (50 mg/kg) had no effect on the evoked nociceptive activity in thalamic neurons up to 90 min after the administration (nine experiments for each drug).

When metyrapone (50 mg/kg i.p.) was administered 20 min before the intravenous injection of dihydrocodeine (1 or 2 mg/kg), it slightly reduced the early phase of the depressant effect of dihydrocodeine (fig. 6, A and B). This reduction, however, was not significant compared with the effect of dihydrocodeine without pretreatment. Likewise, administration of cimetidine (50 mg/kg i.p.) 20 min before intravenous injection of dihydrocodeine (1 mg/kg) failed to significantly change the depression of evoked nociceptive activity. After pretreatment with cimetidine, the depression of the evoked activity caused by dihydrocodeine (2 mg/kg) from 5 to 40 min after the injection was significantly less in comparison with the effect of dihydrocodeine alone. Still, the depression of evoked nociceptive activity was as significant after pretreatment as without prior injection of cimetidine. Naloxone (0.2 mg/kg) was injected intravenously at the end of the experiments carried out with cimetidine and dihydrocodeine (1 mg/kg) and abolished the depressant effect of the opioid.

Dihydromorphine and morphine without and after pretreatment with metyrapone or cimetidine. Dihydromorphine depressed the nociceptive activity evoked in thalamic neurons in a dose-dependent fashion (fig. 7). The lowest dose tested (0.5 mg/kg) produced a slight depression that was significant at 5 and 10 min after the injection. A dose of 4 mg/kg reduced the evoked activity in the mean by 90% of the controls, and the effect was significant from 5 min until the end of the experiment at 90 min after the injection. The ED$_{50}$ of dihydromorphine is 0.97 mg/kg and thus twice as high as that of dihydrocodeine.

Pretreatment with metyrapone had no effect on the depression caused by dihydromorphine (4 mg/kg; seven experiments). Likewise, pretreatment with metyrapone and cimetidine (both drugs injected intraperitoneally at a dose of 50 mg/kg) failed to change the depressant action of morphine (1 mg/kg i.v.) (seven experiments for each pretreatment). This
dose of morphine had been shown in two separate studies to be as effective as morphine (0.5 mg/kg) in causing a long-lasting and complete depression of evoked nociceptive activity (Carlsson et al., 1988; Jurna et al., 1996).

Intrathecal injection of dihydrocodeine and dihydromorphine. Local application of dihydrocodeine to the lumbosacral spinal cord by intrathecal injection reduced the nociceptive activity in thalamic neurons evoked by electrical stimulation of afferent C fibers in the sural nerve. The depressant effect was dose dependent (fig. 8A). Dihydromorphine and dihydrocodeine were equieffective when the two drugs were administered at a dose of 100 mg/kg, respectively, without pretreatment with metyrapone and are from figure 3. Other details are as in legend to figure 3.

dihydrocodeine suppressed completely this activity when injected at a sufficiently high dose. This dose was 2 mg/kg for dihydrocodeine in the present experiments and 0.5 mg/kg for morphine in preceding studies. The ED50 of dihydrocodeine determined in the present study was 0.47 mg/kg and thus 10 times higher than that of morphine determined previously (0.044 mg/kg) (Carlsson et al., 1988; Jurna et al., 1996). On the basis of an average body weight of 70 kg for the adult patient, the ED50 of dihydrocodeine corresponds with a dose of 30 mg, which is actually at the low end of the therapeutic dose range. Thus, dihydrocodeine is as effective as morphine in depressing nociceptive activity evoked in thalamic neurons and might therefore substitute for morphine on step 3 of the analgesic ladder of the World Health Organization (1986). However, dihydrocodeine is less potent than morphine. In comparison with codeine, which failed to suppress completely the nociceptive activity evoked in thalamic neurons at doses as high as 3 mg/kg (Jurna et al., 1993), dihydrocodeine is more effective and more potent. These results obtained in the animal experiments agree with older clinical observations (for references, see the introduction) when both morphine and dihydrocodeine were injected intravenously. Unfortunately, however, no recent data from controlled studies comparing dihydrocodeine with morphine or codeine in pain patients are available. Furthermore, dihydrocodeine is currently administered orally, and conflicting results were obtained in pharmacokinetic studies. In one study that used a radioimmunoassay, dihydrocodeine administered orally was found to undergo so extensive presystemic elimination that the mean bioavailability was only 21% (Rowell et al., 1983). The levels of acidic metabolites were significantly higher after oral than after intravenous administration. The acidic metabolites were not determined separately, but they were assumed to be dihydromorphine, dihydrocodeine-6-glucuronide, dihydromorphine-3-glucuronide and N-dealkycodeine. Dihydromorphine-6-glucuronide will not be formed; even if it were, it presumably would not have been more effective than dihydromorphine or dihydrocodeine in producing analgesia because it has recently been shown that al-

Discussion

Dihydrocodeine administered by intravenous injection to rats depressed the nociceptive activity in neurons of the ventrobasal complex of the thalamus that was evoked by electrical stimulation of afferent C fibers in the sural nerve. Like morphine (Carlsson et al., 1988; Jurna et al., 1996),
et al. (Hoskin was high-performance liquid chromatography; the bioavailability of dihydrocodeine tablets by the application of the same route, and the ED₅₀ of dihydrocodeine (0.47 mg/kg i.v.) is about half that of dihydromorphine (0.97 mg/kg i.v.). If dihydrocodeine acted by way of transformation to dihydromorphine, it should be less potent than dihydromorphine, not more. Furthermore, it is unlikely that amounts of dihydromorphine had been formed from dihydrocodeine that were sufficient to produce the maximum of depression at the same time at which the maximum depression occurred after an intravenous injection of dihydrocodeine (5–10 min after the administration).

Dihydrocodeine and dihydromorphine were equieffective when administered by intrathecal injection at a dose of 100 µg. Although brain tissue is capable of metabolizing opioids, this activity is very low (Samuelsson et al., 1993; Wahlström et al., 1988). It is therefore highly improbable that dihydrocodeine, after biotransformation to dihydromorphine, produces the same amount of depression as dihydromorphine administered directly to the spinal cord at the same dose as dihydrocodeine. It is also incompatible with the view of dihydrocodeine as a prodrug that the time courses of the effects of dihydrocodeine and dihydromorphine, each injected intrathecally at a dose of 100 µg, are identical from 5 to 20 min (see fig. 8B). Finally, the duration of the effect of dihydrocodeine (100 µg) was significantly shorter than that of dihydromorphine (100 µg). If the depression by dihydrocodeine is produced indirectly by the formation of dihydromorphine, its duration should be longer. It is worth noting in this context that morphine and dihydrocodeine are capable of producing a maximum depression of 50% to 60% of this activity when administered by intrathecal injection (for morphine, see Jurna et al., 1996). This means that maximum analgesia cannot be established from the spinal cord alone but results only when all levels of the nociceptive system are acted on by the opioids.

Finally, one cannot neglect the surprising result that dihydrocodeine is more effective than dihydromorphine in depressing nociceptive activity evoked in thalamic neurons, because masking the phenolic hydroxyl group (position 3, e.g., morphine-3-glucuronide) generally reduces the analgesic effectiveness of hydromorphone compared with morphine. Removal of the double bond between position 7 and 8, however, causes a change in the molecular configuration that might contribute to the increase in analgesic effectiveness of hydromorphone compared with morphine and of oxycodone or dihydrocodeine compared with codeine. The impact of the constitutional change in the opioid molecules on the activation of the opioid receptors will need clarification.

From the results presented, it is concluded that dihydro-
codeine produces analgesia by an action of its own and that
this action is due to binding to opioid receptors because it is
reversed by naloxone.

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