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Differential sensitivity of models of antinociception in the rat, mouse and guinea-pig to μ- and κ-opioid receptor agonists

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1 A range of opioid receptor agonists were tested for activity in five antinociceptive models: the acetylcholine-induced abdominal constriction, tail-flick and hot plate tests in the mouse and the paw pressure test in the rat and guinea-pig.

2 Agonists acting preferentially at the κ-opioid receptor were significantly more potent in the guinea-pig than in the rat paw pressure test, whereas μ-receptor preferring agonists were equipotent in the two tests. The mouse abdominal constriction test was of equal sensitivity to the guinea-pig pressure test for both types of agonist.

3 The mouse tail-flick and hot plate tests were progressively less sensitive than the other three tests, particularly to κ-receptor preferring agonists.

4 The efficacy of an agonist can also markedly affect its activity in antinociceptive tests. Thus, partial κ-agonists were weak or inactive in the rat paw pressure test, and partial agonists at both μ- and κ-opioid receptors were relatively weak in the tests in which heat was the noxious stimulus, particularly the mouse hot plate test.

5 The mouse abdominal constriction test is suggested as the most appropriate antinociceptive model for testing a broad range of opioid agonists, whilst the relative potency of a drug in the rat and guinea-pig paw pressure tests may indicate the degree to which it is selective for κ-opioid receptors *in vivo*.

Introduction

Agonists at both μ- and κ-opioid receptors are antinociceptive in animals (Martin *et al.*, 1976; Tyers, 1980), whereas the involvement of δ-opioid receptors in antinociception is more controversial (Chaillet *et al.*, 1984; Galligan *et al.*, 1984). Several rodent models have been developed that detect the central antinociceptive activity of μ- and κ-opioid receptor agonists, but the spectrum of drugs which are active differs markedly between models. For example, μ-selective opioid agonists have been reported to be more effective than κ-selective agonists in tests in which heat is the nociceptive stimulus, whereas tests in which pressure or chemical stimuli are used do not differentiate between the two groups (Tyers, 1980; Upton *et al.*, 1982). More information is now available on the relative μ:κ selectivity of opioids, as are a number of newly developed agonists, and it is appropriate to review this hypothesis in the light of the new data. In this study we have compared the activity of a range of opioid agonists with varying degrees of receptor selectivity on two tests using heat as the nociceptive stimulus (tail flick and hot plate tests in the mouse) with the paw pressure test in the rat and the acetylcholine-induced abdominal constriction test in the mouse. In addition, we have examined a new model, the paw pressure test in the guinea-pig. Receptor binding studies indicate that the guinea-pig brain contains a much higher proportion of κ-opioid receptors than the rat brain (Kosterlitz *et al.*, 1981; Gillan & Kosterlitz, 1982), including high levels in the pons and midbrain where nociceptive information processing is believed to occur (Tam, 1985), suggesting that an appropriate antinociceptive model in this species might be particularly sensitive to κ-opioid agonists.

Methods

Antinociceptive tests in the mouse and rat were performed as described by Tyers (1980) and are briefly summarised below. The following animals were used: male albino CRH mice (17–25 g); weanling PVG random-bred hooded male rats (35–70 g); and weanling male Dunkin-Hartley guinea-pigs (180–220 g).

All drugs were administered subcutaneously 30 min before testing, a time which is close to the maximal effect for most opioid agonists (Pearl *et al.*, 1968, and our own unpublished observations). Drugs were colour-coded so that the operators were unaware of which animal received drug or vehicle. Individual tests were carried out with dose groups of 6 animals. For the guinea-pig paw pressure test, data from one day were analysed; for the other tests, data were accumulated from two or three individual tests carried out on different days such that the final dose-groups comprised 12 or 18 animals.

Hot plate test in the mouse

The latency to a 'front paw lick' response was measured for mice placed on a copper plate heated to 55 ± 0.2°C. The cut-off time for non-responding animals was 60 s. The ED_{100} value was defined as the dose which doubled the latency measured in saline-treated control animals.

Tail flick test in the mouse

A beam of light was focused onto the tail, eliciting a reflex withdrawal after a certain latency. The ED_{100} value was defined as the dose which doubled the control latency. The cut-off time for non-responding animals was 10 s.

Acetylcholine-induced abdominal constriction in the mouse

Mice were injected intraperitoneally with 0.25 ml of a solution of acetylcholine iodine (0.75 mg ml^{-1}) and were then observed for 5 min during which time the number of abdominal constrictions was counted. The ED_{50} value was defined as the dose that reduced the mean number of constrictions to 50% of the control value.

Paw pressure test in the rat

The nociceptive threshold was determined with an 'Analgesymeter' (Ugo Basile, Milan) using a 25 g load. The ED_{30} value was defined as the dose that increased the threshold by 30% above that for the control group.

Paw pressure test in the guinea-pig

The nociceptive threshold was determined in the same way as in the rat, except that a 75 g load was used on the Analgesymeter. As with the rat paw pressure test, the end-point is determined subjectively, and it is essential for each complete test to be performed by a single operator who is unaware of the drug treatment. The typical end-point response is a marked increase in muscle tone or a withdrawal of the paw.

Rotarod test for sedation and motor incapacitation

Mice were placed on a revolving drum which accelerated linearly up to 50 revolutions per min over a 5 min period (Hayes & Tyers, 1983). The ED_{50} value was defined as the dose that halved the control latency for losing position on the drum.

Statistics

The methods of Finney (1964) were used to determine regression slopes, linearity and parallelism for dose-response curves and also antinociceptive activities (ED_x values where x is defined above) with 95% confidence limits.

Drugs

Few opioid receptor agonists can be considered highly selective for the μ- or κ-receptor. Most act preferentially at one receptor type but at higher concentrations will activate the other receptor. With this caveat in mind, the drugs used in this study have been classified as μ-preferring or κ-preferring on the basis of several criteria, including the pA_2 values for antagonism by naloxone in the guinea-pig isolated ileum preparation (Hutchinson *et al.*, 1975; Lord *et al.*, 1977; and our own unpublished observations); selective antagonism of μ-opioid agonists in the guinea-pig ileum by β-funaltrexamine (Hayes *et al.*, 1985) and selective antagonism of κ-opioid agonists in the guinea-pig ileum using β-chlornaltrexamine in combination with μ-receptor protection (Sheehan *et al.*, 1985); and the effect on urine output in the rat *in vivo*, μ-opioid agonists being antidiuretic and κ-opioid agonists diuretic (Leander, 1983a, b; Skingle *et al.*, 1985). The degree of efficacy was defined as follows: high efficacy κ-agonists are able to inhibit completely the twitch of the field-stimulated rabbit vas deferens preparation (Oka *et al.*, 1981) and cause a maximal diuretic effect in the rat, medium efficacy κ-agonists partially inhibit the twitch of the rabbit vas deferens but still cause maximal diuresis, and low efficacy κ-agonists do not inhibit the twitch of the rabbit vas deferens and produce low maximum diuresis. High efficacy μ-agonists inhibit completely the twitch of the field-stimulated rat vas deferens preparation (Smith & Rance, 1983) and cause maximal respiratory depressant and constipating effects in the rat *in vivo* (Hayes & Tyers, 1983), medium efficacy μ-agonists partially inhibit the twitch of the rat vas deferens but still cause maximal respiratory depression and constipation, and low efficacy μ-agonists do not inhibit the twitch of the rat vas deferens and produce low maximum res-

piratory depression and constipation.

The drugs tested are listed below (Table 1) with the abbreviations used in Figures 1 and 2, the company from which they were received, and our classification of their μ/κ selectivity and efficacy.

Table 1 Drugs tested and classification of their μ/κ-opioid receptor preference and efficacy

Drug	*Abbreviation*	*Source*	*μ or κ Preferring*	*Efficacy*
Bremazocine hydrochloride	Br	Sandoz	κ	high
Bromadoline tartrate	Bm	Upjohn	μ	high
Buprenorphine hydrochloride	Bu	Reckitt & Colman	μ	low
Butorphanol tartrate	Bt	Bristol-Myers	non-selective	low
Codeine phosphate	C	Macfarlan Smith	μ	medium
Codorphone hydrochloride	Cp	Miles	κ	low
Cyclorphan base	Cy	Hoffman-La Roche	κ	low
Ethylketocyclazocine methane sulphonate	E	Sterling Winthrop	κ	high
Fentanyl citrate	F	Janssen	μ	high
Ketocyclazocine base	K	Sterling Winthrop	κ	high
Meptazinol hydrochloride	Me	Wyeth	μ	medium[a]
Morphine hydrochloride	M	Macfarlan-Smith	μ	medium
Moxazocine tartrate	Mx	Bristol-Myers	κ	low
Mr2034[b]	Mr	Boehringer Ingelheim	κ	medium
Nalbuphine hydrochloride	N	DuPont	μ	low
Nalorphine hydrobromide	Na	Wellcome	κ	low
Oxilorphan tartrate	O	Bristol-Myers	κ	low
Pentazocine hydrochloride	Pe	Sterling Winthrop	μ	medium
Picenadol hydrochloride racemate	Pi	Lilly	μ	low
Profadol hydrochloride	Pf	Warner-Lambert	μ	medium
D-Propoxyphene hydrochloride	D	Lilly	μ	medium
Proxorphan tartrate	Pr	Bristol-Myers	κ	medium
Tifluadom hydrochloride	T	Kali-Chemie	κ	high
U50488[c]	U	Upjohn	κ	high

[a] See Pasternak *et al.* (1985).
[b] [(−)-α-(1R, 5R, 9R)-5,9-dimethyl-2-(L-tetrahydrofuryl)-2′-hydroxy-6, 7-benzomorphan]
[c] (*trans*-(±)-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl) cyclohexyl]-benzene-acetamide methane sulphonate)

Results

Antinociceptive ED_{50} values for μ-preferring opioid agonists in the mouse abdominal constriction test, rat paw pressure test and guinea-pig paw pressure test are shown in Table 2. All of the compounds tested, even those such as nalbuphine, buprenorphine and picenadol, which behave as partial agonists in some test systems, were able to produce maximal analgesia in all of these tests. In most cases, each compound has almost identical potency in all three tests (Figures 1 and 2, filled circles), although D-propoxyphene and buprenorphine were less potent in the guinea-pig paw pressure test and mouse abdominal constriction test respectively.

Less consistent activity was shown by the κ-preferring agonists across these three tests (Table 3). All except nalorphine were able to produce maximal analgesia in the mouse abdominal constriction test and guinea-pig paw pressure test; nalorphine did so on one test day in the mouse but on two other test days it produced a maximal increase above control of 21 and 72%. In the guinea-pig paw pressure test, nalorphine produced a maximal 37% increase in threshold response on the single test day. The rat paw pressure test was a system in which only high efficacy κ-opioid agonists could cause a maximal antinociceptive response: agonists of low efficacy (which also behave as partial agonists or antagonists in the rabbit vas deferens bioassay: Oka *et al.*, 1981; Hayes & Kelly, 1985) such as nalorphine and oxilorphan, were inactive in this test (see Figure 3d). Proxorphan, a partial agonist with somewhat higher efficacy than these three compounds, was active in the rat paw pressure test but

Table 2 Antinociceptive activities of μ-preferring opioid agonists in the mouse abdominal constriction test, rat paw pressure test and guinea-pig paw pressure test

	Antinociceptive activity ED_x (95% confidence limits) mg kg^{-1} s.c.		
Drug	*Mouse abdominal constriction test*	*Rat paw pressure test*	*Guinea-pig paw pressure test*
Morphine	0.47 (0.34–0.60)	0.44 (0.35–0.53)	0.54 (0.17–1.56)
Codeine	4.05 (2.24–7.74)	2.0 (1.5–2.7)	1.49 (0.50–3.16)
D-Propoxyphene	1.42 (0.87–2.12)	4.1 (2.6–6.0)	22.5 (6.2–131)
Fentanyl	0.004 (0.002–0.007)	0.003 (0.002–0.004)	0.004 (0.001–0.011)
Bromadoline	3.27 (2.32–4.62)	2.55 (1.86–3.38)	ND
Pentazocine	0.75 (0.17–2.34)	1.0 (0.1–10.8)	1.54 (0.49–4.68)
Nalbuphine	0.37 (0.18–0.76)	0.9 (0.4–1.7)	1.73 (0.09–3.22)
Buprenorphine	0.021 (0.010–0.033)	0.001[a] (0.0005–0.004)	0.003 (0.001–0.011)
Profadol	0.96 (0.068–1.35)	1.38 (0.90–1.99)	ND
Picenadol	0.38 (0.25–0.61)	0.98 (0.60–1.55)	ND

Doses are in mg kg^{-1} and were administered subcutaneously; the 95% confidence limits are in parentheses. ND: not determined. [a] Tyers, 1980.

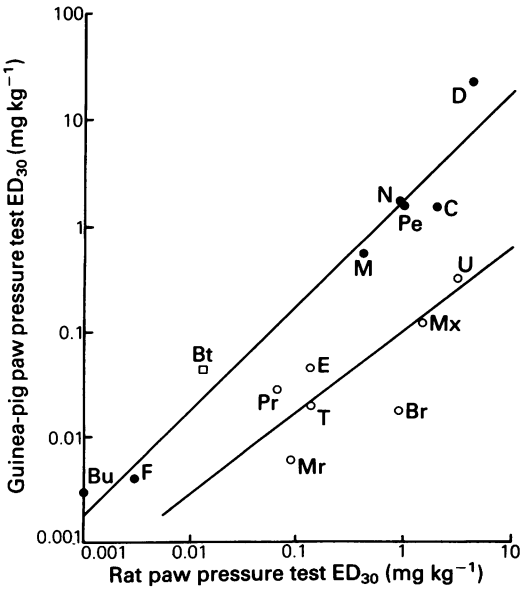

Figure 1 Comparison of ED_{30} values for μ-preferring (●) and κ-preferring (○) opioid agonists in the rat and guinea-pig paw pressure tests, plotted on the abscissa and ordinate scales respectively. Abbreviations are explained in the Methods section. Some κ-preferring agonists were inactive in the rat paw pressure test and thus do not appear on the graph. The selectivity of butorphanol has not been unequivocally characterized *in vitro* and so it has been plotted as an open square and omitted from the statistical analysis. For κ-preferring agonists the ratio (ED_{30} in the rat/ED_{30} in the guinea-pig) with 95% confidence limits is 7.1 (3.8–13.0), $P < 0.001$. For μ-preferring agonists the ratio is 0.56 (0.30–1.023), $P > 0.05$.

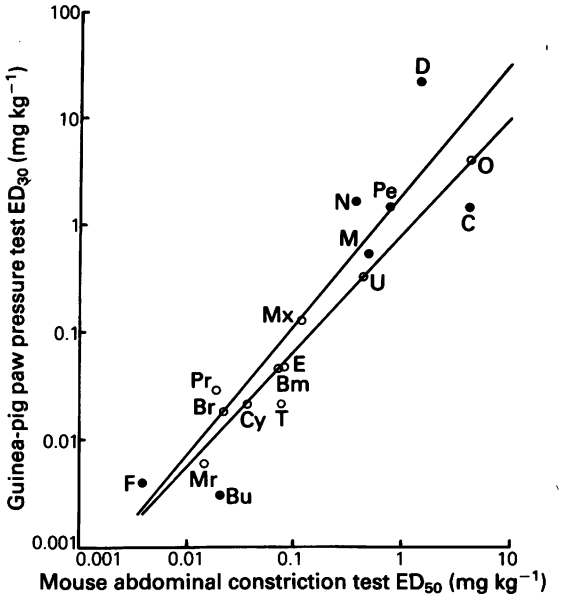

Figure 2 Comparison of ED_x values for μ-preferring (●) and κ-preferring (○) opioid agonists in the mouse abdominal constriction and guinea-pig paw pressure tests. Abbreviations are explained in the Methods section. The regression lines are not significantly different ($P > 0.05$).

Table 3 Antinociceptive activities of κ-preferring opioid agonists in the mouse abdominal constriction test, rat paw pressure test and guinea-pig paw pressure test

	Antinociceptive activity ED_x (95% confidence limits) mg kg^{-1} s.c.		
Drug	*Mouse abdominal constriction test*	*Rat paw pressure test*	*Guinea-pig paw pressure test*
EKC	0.08 (0.04–0.15)	0.14[a] (0.07–0.27)	0.046 (0.010–0.114)
Ketazocine	0.29[a] (0.10–0.80)	0.37[a] (0.1–0.9)	ND
U50488	0.41 (0.23–0.70)	3.1 (1.2–8.6)	0.33 (0.077–0.99)
Tifluadom	0.079 (0–0.32)	0.14 (0.06–0.29)	0.02 (0.007–0.058)
Bremazocine	0.022 (0.011–0.047)	0.19 (0.05–0.58)	0.018 (0.012–0.026)
Mr2034	0.015 (0.004–0.026)	0.09 (0.05–0.166)	0.006 (0.001–0.014)
Codorphone	1.77 (0.87–3.52)	NSE at 0.13–10	ND
Proxorphan	0.019 (0.013–0.029)	0.067 but SDR (0.036–0.128)	0.029 (0.006–0.091)
Nalorphine	0.34 but SDR (0.06–1.01)	NSE at 0.12–10	SDR, range 0.01–0.037, Emax 37%
Oxilorphan	4.16 (1.11–8.76)	NSE at 0.1–30	4.26 (1.61–10.4)
Cyclorphan	0.037 (0.023–0.058)	ND	0.021 (0.004–0.077)
Moxazocine	0.12 (0.05–0.22)	1.49 (0.73–2.61)	0.125 (0.061–0.228)
Butorphanol	0.077 (0.02–0.24)	0.014 (0.001–0.13)	0.043 (0.009–0.532)

ND: not determined. NSE: no significant effect over the dose range shown. SDR: shallow dose-response curve. An ED_{50} value is given where this could be calculated; otherwise the active dose-range is given, together with the maximum percentage increase in threshold over the control group (E_{max}).

[a] Tyers, 1980.

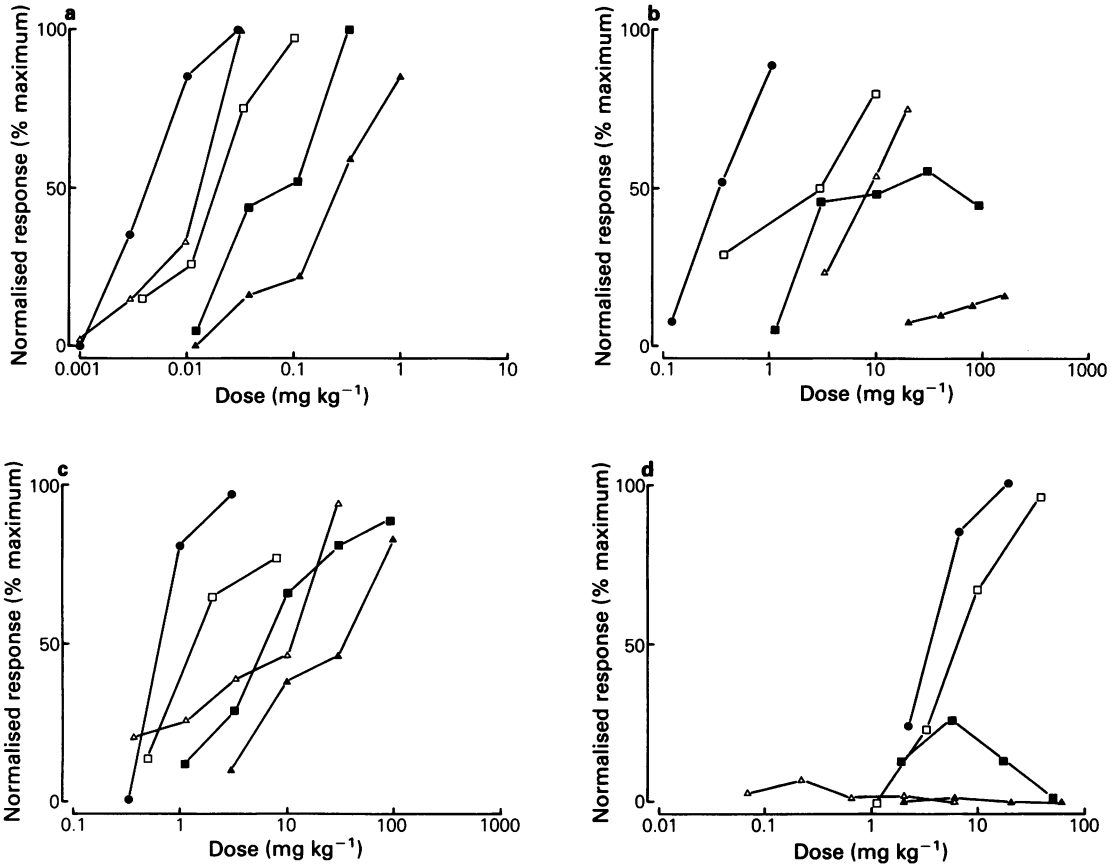

Figure 3 Dose-response curves for opioid agonists in five antinociceptive models. The curves were normalized by setting the control response in each test to zero and the maximum (or cut-off point) to 100%. The agonists are (a) the μ-preferring full agonist fentanyl, (b) the μ-preferring partial agonist nalbuphine, (c) the κ-preferring full agonist U50488, and (d) the κ-preferring partial agonist oxilorphan. Key to symbols: (●) mouse abdominal constriction test; (□) guinea-pig paw pressure test; (△) rat paw pressure test; (■) mouse tail flick test; (▲) mouse hot plate test.

produced a shallow dose-response curve with a low maximum response of 50%. A comparison of the ED_{30} values for opioid agonists which were active in the rat paw pressure test with their ED_{30} values in the guinea-pig paw pressure test demonstrates that the latter test is significantly more sensitive to κ-preferring agonists, and thus a clear separation is apparent between the activity of μ-preferring and κ-preferring agonists in the two tests (Figure 1). In contrast, there was no significant difference in the potency of a κ-preferring agonist between the mouse abdominal constriction test and guinea-pig paw pressure test (Figure 2).

The two tests in which heat was the noxious stimulus were, in general, less sensitive to the antinociceptive effects of opioids than the non-heat tests. Antinociceptive ED_{100} values for μ-preferring agonists are given in Table 4 and for κ-preferring agonists in Table 5, while Figure 3 compares the dose-response curves for example of high and low efficacy μ- and κ-opioid agonists in each test. All μ-preferring agonists were antinociceptive in the mouse tail flick test but higher dose-levels (usually about 3–4 fold greater) were necessary to achieve a similar percentage change in the response as in the three non-heat tests. Moreover, among the partial μ-receptor agonists, nalbuphine produced a low maximum antinociceptive response and picenadol a shallow dose-response curve. The mouse hot plate test was even less sensitive towards opioid agonists: μ-preferring opioids of medium to high efficacy, such as morphine or fentanyl, were about half as potent as in

Table 4 Antinociceptive activities of μ-preferring opioid agonists in the mouse tail flick and hot plate tests, and sedative activity in the Rotarod test

Drug	*Antinociceptive activities* ED_{100} (95% confidence limits) mg kg^{-1} s.c.		*Rotarod* ED_{50} value *(95% conf.* limits) mg kg^{-1} s.c.
	Mouse tail flick test	*Mouse hot plate test*	
Morphine	1.35 (0.43–3.64)	2.22 (0.76–5.54)	14.2[b] (6.7–42.1)
Codeine	14.0 (3.5–28.0)	20.8 (6.2–61.9)	110 (61–234)
D-Propoxyphene	9.4 (5.0–19.2)	13.3 (8.1–21.3)	36.4 (25.2–63)
Fentanyl	0.045 (0.017–0.105)	0.088 (0.012–0.254)	0.81 (0.26–3.56)
Bromadoline	4.05 (2.16–7.30)	11.9 (7.0–19.7)	23.3 (10.6–94.5)
Pentazocine	4.3 (2.1–8.5)	21.8 (14.8–31.7)	42.8 (20–107)
Nalbuphine	1.85 (but E_{max} 56%) (0.81–4.23)	SDR, range 20–160, E_{max} 17%	NSE at 18–300
Buprenorphine	0.024 (0.011–0.048)	SDR, range 0.003–0.1 E_{max} 26%	E_{max} 27% increase*
Profadol	ND	7.8 (but SDR) (0.09–190)	39.9 (28.2–66.6)
Picenadol	14.1 (but SDR) (2.6–186)	SDR, range 1.85–16.7 E_{max} 19%	26.1 (15.2–60.6)

Abbreviations are as defined in Table 2. * indicates that buprenorphine had a bell-shaped dose-response curve over the dose-range 0.3–10 mg kg^{-1} with maximal effect at 1 mg kg^{-1} (Tyers, 1980). [b] Hayes & Tyers, 1983.

the mouse tail flick test, whereas low efficacy compounds produced shallow dose-response curves usually with very low maximum effects. The ED_{100} values for full agonists were nevertheless lower than the doses necessary to cause sedation in the rotarod test (Table 4, column 3).

For κ-preferring agonists the lower sensitivity of the heat tests was even more marked. Full agonists were active in the tail-flick test, while partial agonists were usually much weaker than in the non-heat tests. The ED_{100} value for active drugs was generally lower than doses causing sedation (Table 5, column 3). In the mouse hot plate test, most κ-preferring partial agonists were inactive, and most full agonists were active only at doses close to or greater than their sedative ED_{50} in the rotarod test. Notable exceptions were EKC and Mr2034, which were active at doses significantly lower than those causing sedation.

Discussion

Each of the five tests compared in this study showed a different pattern of selectivity to μ and κ-preferring opioid agonists. The novel test, the guinea-pig paw pressure test, gave results in accord with the prediction that it would be particularly sensitive to κ-opioid agonists. On average, κ-agonists were seven times more active in the guinea-pig than in the rat, which is in agreement with the relative densities of κ-binding sites in the brain (Kosterlitz *et al.*, 1981; Gillan & Kosterlitz, 1982).

Furthermore, some κ-preferring agonists of low efficacy, such as oxilorphan and nalorphine, were inactive in the rat paw pressure test but were able to produce maximal analgesia in the guinea-pig. These tests were equally sensitive to μ-preferring agonists. The mouse abdominal constriction test was the most widely sensitive to opioids, in that all drugs tested were able to inhibit the response fully, although nalorphine did not always do so. In terms of sensitivity, the mouse abdominal constriction test was similar to the guinea-pig paw pressure test for κ-agonists, while for μ-preferring agonists all three tests were similar.

The mouse tail flick test was in general less sensitive than the previous three tests, but not consistently so. The sensitivity was least for κ-preferring agonists but, except for tifluadom, antinociceptive activity was achieved without overt motor impairment. In contrast, in the mouse hot plate test, which was the least

Table 5 Antinociceptive activities of κ-preferring opioid agonists in the mouse tail flick and hot plate tests, and sedative activity in the Rotarod test

Drug	*Antinociceptive activities* ED_{100} (95% confidence limits) $mg\,kg^{-1}$ s.c.		*Rotarod* ED_{50} value *(95% conf.* limits) $mg\,kg^{-1}$ s.c.
	Mouse tail flick test	*Mouse hot plate test*	
EKC	0.15 (0.07–0.30)	0.51 (0.27–0.82)	1.59 (0.86–3.82)
Ketazocine	ND	NSE at 12.5–50	SDR, E_{max} 20% at 50
U50488	0.52 (0–3.79)	5.5 (1.1–22.7)	6.3 (1.8–25.5)
Tifluadom	2.01 (0.93–3.85)	1.86 (1.40–2.39)	0.4 (0–1.59)
Bremazocine	0.019 (0.011–0.030)	3.2 (0.02–100)	0.74[b] (0.34–1.64)
Mr2034	ND	0.26 (but SDR) (0.03–1.81)	10.4[b] (5.2–29.1)
Codorphone	1.81 (1.18–2.78)	87.9 (71.3–109)	65.3 (39.9–129)
Proxorphan	0.133 (0.055–0.278)	NSE at 1.1–90	83 (26–824)
Nalorphine	ND	NSE at 5–40	NSE[b] 0.12–40
Oxilorphan	SDR, range 1.85–50 E_{max} 26%	NSE at 1.85–50	28.3 (16.0–75.7)
Cyclorphan	SDR, range 0.078–0.67 E_{max} 55%	NSE at 0.078–18	ND
Moxazocine	ND	4.03 (2.0–9.5)	4.4 (2.4–9.2)
Butorphanol	ND	35.3 (25–48)	26 (12–64)

Abbreviations are as defined in Table 2. [b] Hayes & Tyers, 1983.

sensitive to opioid drugs of all the tests under study, most of the κ-preferring agonists were active only at doses that cause overt motor impairment, suggesting that sedation or ataxia may contribute to their apparent antinociceptive activity, as proposed previously (Tyers, 1980). The only κ-preferring agonists which showed activity in the mouse hot-plate test at doses significantly lower than their ED_{50} in the rotarod test were EKC, which may reflect activity at μ- rather than κ-opioid receptors in this instance (Tyers, 1980; Ward & Takemori, 1983), and Mr2034, which produced a shallow dose-response curve.

The results of this study indicate that the order or sensitivity of the five tests towards μ- and κ-opioids agonists is as follows:-

μ-agonists

mouse abdominal constriction = guinea-pig paw pressure = rat paw pressure > mouse tail flick > mouse hot plate

κ-agonists

mouse abdominal constriction = guinea-pig paw pressure > rat paw pressure > mouse tail flick >> mouse hot plate

The efficacy of an agonist was also shown to be important in determining the response in these tests. High efficacy μ-opioid agonists were active in all tests. Partial μ-opioid agonists such as nalbuphine, buprenorphine and picenadol were inactive in the mouse hot plate test and had reduced activity or low maximum effects in tail flick. Full κ-opioid agonists were active in the tail-flick but, as previously mentioned, may not be truly antinociceptive in the hot plate test. Partial κ-opioid agonists such as oxilorphan and nalorphine were inactive in the mouse hot plate and paw pressure tests, and tended to need relatively high doses for activity in the mouse tail flick test. Only the mouse abdominal constriction and guinea-pig paw pressure tests reliably detected the antinociceptive activity of

partial κ-agonists. The ability of partial agonists to produce a maximum response indicates that there is efficient receptor-effector coupling or high receptor density for μ- and κ-opioid receptors in the physiological systems which mediate antinociception in these tests. As defined by Kenakin (1986), these systems have a high 'effective receptor reserve'. Conversely, antinociceptive tests such as the mouse hot plate test, in which partial agonists are inactive and full agonists are less potent, are indicative of a lower effective receptor reserve. It is interesting that the effective receptor reserve in the five tests studied seems to vary in a similar way for both μ- and κ-receptor agonists although, since it is not possible to compare the efficacy of μ- and κ-agonists directly, the absolute magnitude cannot be quantified.

A number of simplifying assumptions have been made in this study which may not be valid for all drugs tested. No account has been taken of any contribution to the antinociceptive response that may be mediated by δ-opioid receptors, although most of the compounds tested show little affinity for these receptors (Magnan *et al.*, 1982; Miller & Shaw, 1985; Sheehan *et al.*, 1986). Furthermore, in classifying drugs into those which are μ- or κ-preferring, no mention has been made of the degree of selectivity. Clearly, a compound that is only slightly selective for one receptor type may exert a considerable part of its agonist effect at the other receptor if the concentration or coupling efficiency of the second receptor is greater. Indeed, pentazocine and EKC appear to show such marginal selectivity for μ- and κ-opioid receptors respectively (Sheehan *et al.*, 1985). Drugs may also be metabolized *in vivo* to compounds with a different selectivity. It is thus unwise to assume that a drug which appears κ-selective *in vitro* will invariably be acting predominantly at κ-opioid receptors when tested *in vivo*.

The results presented here demonstrate that the mouse abdominal constriction test detects the greater range of agonists with the greatest sensitivity and also the greatest separation between doses causing antinociception and motor impairment, upholding the pioneering work of Collier *et al.* (1968). It is thus the most appropriate test for general purposes although, surprisingly, the less sensitive tail flick and hot plate tests are also used extensively. The guinea-pig paw pressure test is equally sensitive, but requires much more compound than tests in the mouse. However, if an opioid drug has a greater potency in the guinea-pig paw pressure test than in the rat paw pressure test, this may indicate that it is κ-selective *in vivo*.

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