Pharmacology Biochemistry & Behavior, Vol. 31, pp. 899–904. © Pergamon Press plc, 1989. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

Effects of 5-HT and Alpha$_1$ Adrenoceptor Antagonists on Kappa Opioid-Induced Sedation

G. E. LEIGHTON, R. G. HILL AND J. HUGHES

Parke-Davis Research Unit, Addenbrookes Hospital Site, Hills Road, Cambridge, CB2 2QB

Received 10 February 1988

LEIGHTON G. E., R. G. HILL AND J. HUGHES. *Effects of 5-HT and alpha$_1$ adrenoceptor antagonists on kappa opioid-induced sedation.* PHARMACOL BIOCHEM BEHAV 31(4) 899–904, 1988.—The kappa opioid agonists PD-117302 and U-50488 were found to produce dose-dependent reductions in spontaneous locomotor activity in mice. The magnitude of the response to a given dose of each kappa agonist was found to be clearly potentiated by pretreating the animals with either ketanserin (1 mg/kg) or prazosin (0.5 mg/kg). Pretreatment with the selective 5-HT$_2$ receptor antagonist ritanserin given at a high dose (1 mg/kg), the nonselective 5-HT antagonist methysergide or the 5-HT synthesis inhibitor parachlorophenylalanine did not alter the magnitude of the response to the kappa agonist. These results suggest that 5-HT systems are not involved in the sedative effects of kappa opioid agonists and that the potentiating effect seen in animals pretreated with ketanserin is due to the alpha$_1$ blocking properties of this compound since the effect was mimicked by the alpha$_1$ antagonist prazosin.

Locomotor activity Kappa agonists 5-HT antagonists Prazosin

THERE is now considerable evidence supporting the existence of at least three types of opioid receptors namely mu, delta and kappa. The original classification of mu and kappa receptors was based on observations of the behavioural effects in the dog that characterised agents acting at these different receptors (28). In addition to analgesia, one of the properties ascribed to ketocyclazocine, the prototypic kappa agonist, was sedation. Although it is now well recognised that a variety of kappa opioid agonists produce sedation in animals (9, 11, 18), the neural mechanism underlying this sedative effect is not known nor is the location in the central nervous system where kappa agonists act to produce sedation. Kappa binding sites have been localized in the deep layers of the cerebral cortex using in vitro autoradiography techniques (11) and it has been suggested on the basis of these findings that kappa agonists may produce their sedative effects by acting in this region although there is no functional evidence to support this hypothesis. In vivo studies in the dog have led to the proposal that an action of kappa agonists in the reticular activating system may be involved in the production of sedation since injections of kappa agonists into the fourth cerebral ventricle resulted in drowsiness followed by sleep in these animals (18).

The control of locomotor activity is extremely complex with many regions of the brain and many neurotransmitter systems probably involved. Monoamine systems certainly play a very important role in the control of activity as can be shown by various surgical and pharmacological manipulations of these systems which result in alterations in levels of activity. The nucleus accumbens is a region which is believed to play an important role as an interface between limbic structures and the motor system (cf. (36)]. Many putative neurotransmitters have been suggested to be involved in the initiation and regulation of locomotor activity by this brain region including dopamine, 5-HT, acetylcholine and gamma-aminobutyric acid (17). Opioid binding sites of the mu, delta and kappa types have been located in the nucleus accumbens (10,11) and recent evidence suggests that it may be by acting within this nucleus that the mu agonist morphine produces a suppression of locomotor activity (13). Injections of high doses of the kappa agonist Mr2033 into this nucleus, however, were without effect on locomotor activity suggesting that kappa agonists produce their effects on locomotor activity at some other site in the brain (13).

Apart from dopaminergic systems, two other monoamine neurotransmitter candidates which have been strongly implicated in the control of locomotor activity are noradrenaline and 5-HT. Amphetamine is well known to be a stimulant of locomotor activity [cf. (13)] and although amphetamine stimulates the release of both noradrenaline and dopamine, recent evidence suggests that it is the noradrenaline releasing action of amphetamine that is responsible for its locomotor stimulant effects since these are blocked by the alpha$_1$ adrenoceptor antagonist prazosin. Direct injection of the postsynaptic alpha$_1$ agonists phenylephrine and methoxamine into the cerebral ventricles produce increases in locomotor activity, these effects also being blocked by prazosin (14).

Injections of a monoamine oxidase inhibitor and tryptophan (12) or injections of the 5-HT$_{1B}$ agonist RU24969 (31) produce marked elevations in spontaneous activity in rodents suggesting an important role for 5-HT in the control of motor behaviour. Since both catecholamines and in-

doleamines are known to be involved in the regulation of the level of consciousness and the control of locomotor activity, it was decided to investigate the possible interactions between both monoamine systems and the sedative effects of kappa opioid agonists.

One method available for obtaining a quantitative measure of sedation is to measure locomotor activity in mice. This method, however, will not discriminate between the effects of, for example, a sedative compound and one that causes immobility as a result of a muscle relaxant action. Since the kappa agonist ketocyclazocine has been reported to produce sedation in man (19), and bremazocine, also a kappa agonist, produces deep sedation in the dog as evidenced by a shift in the power spectrum of the EEG (9), it seems likely that the reduction in locomotor activity and in rearing and grooming in mice reported to occur following treatment with the selective kappa agonist U-50488 (34) is a consequence of a sedative effect. We have, therefore, used a locomotor activity monitor to investigate the possible involvement of 5-HT and alpha$_1$ adrenergic mechanisms in the sedative effects of kappa opioid agonists.

METHOD

The sedative effects of kappa agonists were measured in mice using an automated locomotor activity monitoring system (27) consisting of twelve individual polycarbonate cages each bisected by a single infrared beam. Male mice (CFLP, 35–50 grams, Interfauna, Huntingdon, UK) were housed under conditions of constant temperature (21±1°C) and humidity on a fixed twelve-hour light, twelve-hour dark cycle with food and water available ad lib. Mice were housed individually in the cages of the locomotor activity monitor for the duration of each experiment and all experiments were initiated at the beginning of the dark phase (18.00 hours).

The kappa agonists used in this study were PD-117302 [(±)-trans-N-methyl-N-[2-pyrrolidinyl)cyclohexyl]benzo[b]-thiophene-4-acetamide hydrochloride] (Parke-Davis) and U-50488 [(±)trans-3,4-dichloro-N-methyl-N-[2-(l-pyrrolidinyl)cyclohexyl]benzen-acetamide hydrochloride (synthesized at Parke-Davis). Other compounds used were ketanserin tartrate (Janssen), ritanserin (Janssen), methysergide maleate (Sandoz), prazosin hydrochloride (Pfizer), methiothepin maleate (Sigma) and parachlorophenylalanine (pCPA, Sigma). Test compounds were dissolved in saline (0.9% w/v NaCl solution), a small amount of tartaric acid being used initially to dissolve the prazosin and the ritanserin, and administered subcutaneously in a dose volume of 1 ml per 100 g body weight. The exception was pCPA which was suspended in 10% w/v carboxymethylcellulose and given by the intraperitoneal route. Kappa agonists were injected 5 minutes before the start of the test period. When pretreatments were used these compounds were injected 30 minutes prior to the kappa agonist. In those animals in which pCPA was given as a pretreatment the following dosing regime was used; day 1 200 mg/kg pCPA, day 2 and 3 100 mg/kg pCPA, day 4 test. Control animals were dosed with vehicle on days 1, 2 and 3. On the day after testing the animals were killed, the brains removed and assayed for 5-HT content using HPLC with electrochemical detection. Although locomotor activity was recorded over the entire twelve-hour dark period, the suppression of activity produced by the doses of kappa agonists used in this study was found to be maximal for the first two hours following administration and therefore the results shown are totals of activity seen in this first two-hour period. The animals were not allowed an acclimatization period in the locomotor activity boxes before the start of the test period, in order to maximize the initial period of exploratory behaviour and thus accentuate any suppression of activity produced by the test compounds. None of the animals were used more than once in any of these experiments.

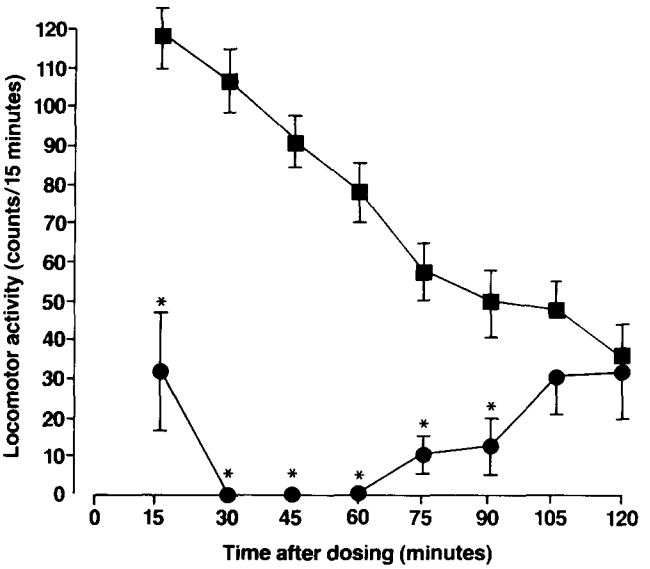

FIG. 1. Time course of the locomotor suppressant effect produced by a single dose (10 mg/kg PD-117302 SC). Results are shown as number of activity counts (i.e., beam breaks) occurring per 15 minute data analysis interval. (●) Saline-treated controls, n=24; (■) PD-117302, n=6. Results are shown as means±SEM. *$p<0.005$ (Mann-Whitney U-test) significant difference between the two groups.

Statistical analysis of data was performed using the Kruskal-Wallis one-way analysis of variance or the Mann-Whitney U-test as appropriate.

RESULTS

Effects of PD-117302 and U-50488 on Spontaneous Locomotor Activity

Clear dose-related reductions in locomotor activity were observed in animals treated with PD-117302 or U-50488. PD-117302 was more potent than U-50488 at producing this effect and this is consistent with the relative antinociceptive potencies of these compounds (20). The dose required to reduce locomotor activity counts by 50% over the two-hour test period was 6.5 mg/kg for PD-117302 and 14 mg/kg for U-50488. The time course of the effect seen with a single dose of PD-117302 is shown in Fig. 1. Locomotor activity was seen to return to control levels within the first two hours after dosing with 10 mg/kg PD-117302.

Effects of Antagonists Alone on Spontaneous Locomotor Activity

Apart from methiothepin none of the antagonists given alone produced any effect on locomotor activity even when tested at doses higher than those used in the interaction experiments. Results obtained in experiments in which animals

TABLE 1

THE EFFECT OF DIFFERENT ANTAGONIST PRETREATMENTS ON SPONTANEOUS LOCOMOTOR ACTIVITY IN GROUPS OF MICE TREATED WITH SALINE

Pretreatment		n	Locomotor Activity (counts per 2 hours)
Saline		6	410 ± 98
Ketanserin	0.33 mg/kg	6	557 ± 164
	1.0 mg/kg	6	344 ± 59
	3.0 mg/kg	6	382 ± 37
Saline		9	522 ± 63
Ritanserin	0.33 mg/kg	9	401 ± 50
	1.0 mg/kg	9	535 ± 66
	3.0 mg/kg	9	338 ± 59
Saline		9	522 ± 61
Methysergide	1.1 mg/kg	8	510 ± 52
	3.3 mg/kg	9	456 ± 63
	10.0 mg/kg	9	353 ± 77
Saline		9	427 ± 73
Prazosin	0.5 mg/kg	7	412 ± 50
Saline		3	525 ± 96
Methiothepin	1.1 mg/kg	3	51 ± 27*

Animals were treated subcutaneously with antagonist or saline 30 minutes before receiving a saline injection and then being placed in the locomotor activity monitor. Values represent mean ± S.E.M. Of the antagonists tested, only methiothepin produced an effect that was statistically different from a parallel control group (*$p<0.05$, Kruskal-Wallis one-way ANOVA).

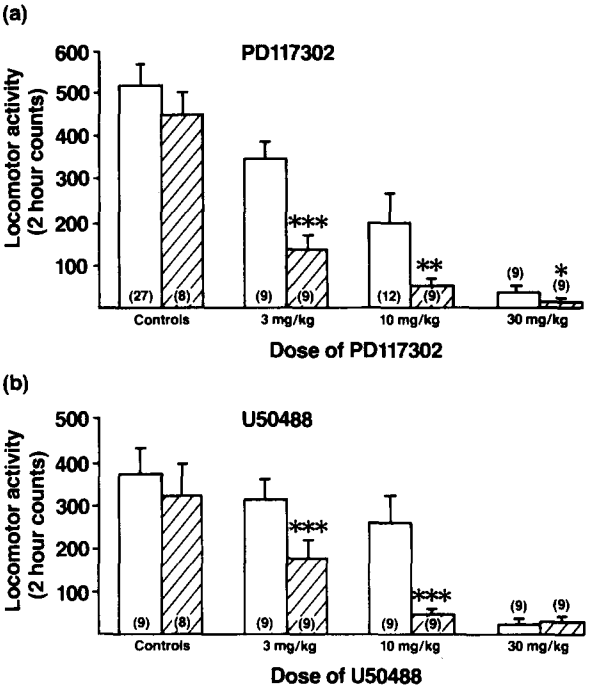

FIG. 2. Potentiation of the locomotor suppressant effect of (a) PD-117302 and (b) U-50488 by pretreatment with ketanserin (1 mg/kg). Results are shown as mean±SEM. Open bars represent animals pretreated with saline, hatched bars represent animals treated with ketanserin. *$p<0.05$, **$p<0.01$, ***$p<0.0005$ (Mann-Whitney U-test) significant difference between saline- and ketanserin-treated groups. The number of animals in each group is shown in parentheses.

treated with antagonist were compared with saline-treated controls are shown in Table 1. Methiothepin tested at doses of 1.1, 3.3 and 10 mg/kg produced a profound sedative effect which lasted for the entire two-hour test period. This reduction in locomotor activity may be attributable to the dopamine antagonist properties of this compound (25) and for this reason methiothepin was not used in any of the interaction studies.

Influence of Ketanserin on Kappa Opioid-Induced Hypomotility

Ketanserin (1 mg/kg), a 5-HT_2 antagonist, was found to potentiate the suppression of locomotor activity produced by PD-117302 and U-50488 (Fig. 2). This potentiation was observed throughout the entire two-hour data analysis period and therefore data are shown as total activity scores. Since ketanserin also possesses appreciable affinity for the $alpha_1$ receptor (21) and has been shown in vivo to block the stimulant effects of the $alpha_1$ agonist phenylephrine on the cardiovascular system (8), it was decided that the effects of ritanserin, a more selective 5-HT_2 antagonist than ketanserin, methysergide, a nonselective 5-HT antagonist with no $alpha_1$ antagonist activity, and prazosin, a selective $alpha_1$ antagonist, on the sedative effects of kappa agonists should be compared.

Influence of Different Antagonist Pretreatment on PD-117302-Induced Hypomotility

The effects of pretreatment with ketanserin, ritanserin, methysergide or prazosin on the hypomotility response to a single dose (3 mg/kg) of PD-117302 are shown in Fig. 3. There was slight day to day variability in the levels of activity shown by the control groups. Results have therefore been normalized so that the level of activity in the control group in each experiment is expressed as 100% and the activity in the PD-117302-treated group is expressed as a percentage of this control. Ketanserin (1 mg/kg) produced a clear potentiation of the response to 3 mg/kg PD-117302, an effect which was highly statistically significant ($p<0.01$, Mann-Whitney U-test), whereas ritanserin at the same dose produced a much less pronounced potentiation of PD-117302. The nonselective 5-HT antagonist methysergide (3 mg/kg) did not alter the response to PD-117302. The $alpha_1$ antagonist prazosin (0.5 mg/kg) produced a clear potentiation of the response produced by 3 mg/kg PD-117302.

Influence of Different Antagonist Pretreatment on U-50488-Induced Hypomotility

The effects of pretreatment with ketanserin, ritanserin, methysergide and prazosin on the hypomotility response to U-50488 were the same as those seen with PD-117302. The effect of prazosin pretreatment on the response produced by U-50488 (10 mg/kg) is shown in Fig. 4. The response to U-50488 was clearly potentiated by prazosin given at a dose that by itself did not alter baseline levels of activity.

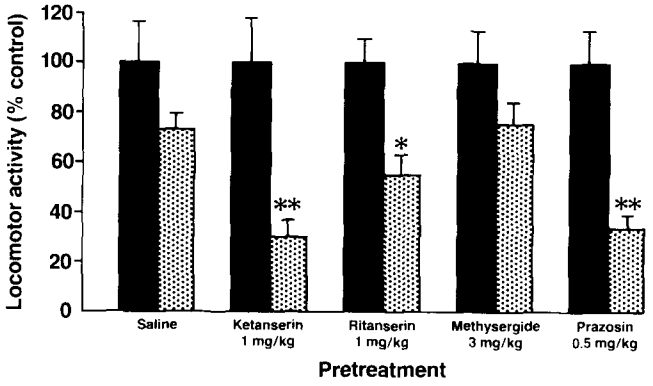

FIG. 3. Mean locomotor activity (as percentage of control) for groups of animals receiving a saline or antagonist pretreatment 30 minutes before saline (filled bars) or 3 mg/kg PD-117302. *$p<0.05$, **$p<0.01$ (Mann-Whitney U-test) significant difference between antagonist-pretreated and saline-pretreated groups. n=9 per group.

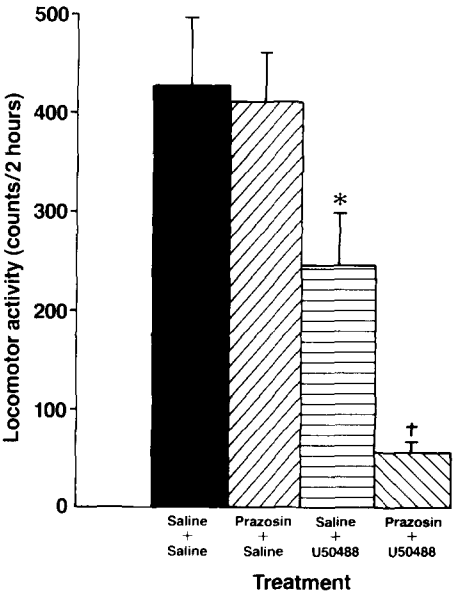

FIG. 4. Potentiation of the U-50488- (10 mg/kg) induced suppression of locomotor activity in mice by the alpha$_1$ antagonist prazosin (0.5 mg/kg). *$p<0.05$ compared to saline + saline-treated group, †$p<0.01$ compared to the saline + U-50488-treated group. Results are shown as mean±SEM. n=9 per group.

Depletion of 5-HT With p-Chlorophenylalanine

Treating animals for three days with the tryptophan hydroxylase inhibitor pCPA resulted in a statistically significant reduction ($p<0.01$, Mann-Whitney U-test) in brain 5-HT content to 11.0±1.0 pmoles/mg protein compared to the control level of 18.8±2.9 pmoles/mg protein (n=6 per group). This reduction in brain 5-HT levels did not alter the response to 3 mg/kg PD-117302 (Table 2).

TABLE 2

EFFECT OF SALINE OR pCPA PRETREATMENT ON THE SUPPRESSION OF LOCOMOTOR ACTIVITY PRODUCED BY A LOW DOSE OF PD-117302 (3 mg/kg)

Pretreatment Day 1–3	Treatment Day 4	n	Locomotor Activity (counts per two hours)
Saline	saline	9	409 ± 23
pCPA	saline	8	471 ± 80
Saline	PD-117302	9	337 ± 29
pCPA	PD-117302	9	402 ± 49

DISCUSSION

The 5-HT antagonist ketanserin was found to produce a marked potentiation of the locomotor suppressant effects of PD-117302 and U-50488. Although this compound is highly selective for 5-HT$_2$ receptors as opposed to other types of 5-HT receptors, it also has high affinity for the alpha$_1$ adrenoceptor and is capable of displacing ligands from this site at concentrations only five times greater than those that interact with 5-HT$_2$ binding sites (21). Since doses of ketanserin of between 0.0625 and 1 mg/kg (IV) have been shown to be effective at blocking the pressor response to the alpha agonist phenylephrine in the pithed rat (8), the dose of ketanserin used in this study is likely to be blocking alpha$_1$ adrenoceptors as well as 5-HT$_2$ receptors. In order to determine whether the effects produced by ketanserin were due to antagonism at 5-HT$_2$ or alpha$_1$ adrenoceptors, or both, we decided to investigate the effects of ritanserin. Ritanserin is much more selective for 5-HT$_2$ receptors than ketanserin (the IC$_{50}$ obtained in in vitro binding assays for alpha$_1$ binding sites is 107 times higher than that for 5-HT$_2$ sites), it is also more potent in vivo and shows extremely good CNS penetration (22). It would be expected, therefore, that if the potentiation of the sedative effects of kappa agonists produced by ketanserin was due to blockade of 5-HT$_2$ receptors, then ritanserin should be more effective than ketanserin given at the same dose. It has been shown that following a single subcutaneous dose of 0.1 mg/kg [^{3}H] ritanserin the resulting 5-HT$_2$ binding site occupancy in the cerebral cortex is high (22). It has also recently been demonstrated that the effects of 5-HT on food intake can be antagonised using doses of ritanserin as low as 0.01 mg/kg (29). Given in a dose 100 times greater than this, ritanserin was found not to potentiate the depressant effect of U-50488 on locomotor activity although a slight potentiation of the effect of PD-117302 was seen. These results strongly suggest that it was not the 5-HT$_2$ receptor-blocking property of ketanserin that was producing the potentiation of the locomotor suppressant actions of the kappa agonists. A further study using the 5-HT antagonist methysergide, which, although it does not discriminate between 5-HT$_1$ and 5-HT$_2$ receptors, possesses no affinity for the alpha$_1$ adrenoceptor (3) supports the supposition that blockade of 5-HT receptors is not involved in the effect produced by ketanserin since methysergide had no effect on either the response produced by PD-117302 or that produced by U-50488. No potentiation of the effect of PD-117302 was seen in animals which had been treated with the 5-HT depleting agent pCPA even though these animals were found to have reduced levels of brain 5-HT following this treatment, further suggesting that 5-HT mechanisms are not

involved in the potentiation of the response to kappa agonists produced by ketanserin.

In order to further examine the possibility that ketanserin was producing its effects by blocking alpha$_1$ adrenoceptors, the effects of the alpha$_1$ antagonist prazosin on the responses to PD-117302 and U-50488 were investigated. Prazosin has no demonstrable affinity for the alpha$_2$ adrenoceptor, but possesses marked affinity and selectivity for alpha$_1$ adrenoceptors (4) and unlike phentolamine, yohimbine and phenoxybenzamine does not increase the stimulated release of radiolabelled noradrenaline from the rat pulmonary artery preparation. Prazosin shows good CNS penetration and has been show to antagonise the stimulation of locomotor activity produced by amphetamine (30) or by the directly acting alpha$_1$ adrenoceptor agonists phenylephrine and methoxamine (14), but not that produced by the dopamine uptake blocker buproprion (30). In our experiments a low dose of prazosin produced a clear potentiation of the locomotor suppression produced by low doses of PD-117302 and U-50488.

There are several reports in the literature claiming that kappa agonists are capable of inhibiting the release of noradrenaline from brain slices (16,23). If this were to occur in a region of the brain in which activity of noradrenergic neurones normally plays an important role in the initiation or maintenance of locomotor activity, it is possible that kappa agonists may be sedative by way of inhibiting noradrenaline release and thus reducing the amount of noradrenaline available to act at postsynaptic excitatory alpha$_1$ adrenoceptors. This effect could then be potentiated by an alpha$_1$ antagonist such as prazosin or ketanserin. The cerebral cortex has been shown to possess kappa opioid (11) and alpha$_1$ (15) binding sites and to be an area in which kappa agonists are capable of acting presynaptically to inhibit noradrenaline release (23), and this may be the region of the brain in which such an interaction between kappa agonists and alpha$_1$ antagonists occurs. A possible alternative site of action for kappa agonists in the production of sedation is the locus coeruleus. In vitro electrophysiology studies have shown that kappa agonists produce a concentration-dependent depression of the excitatory postsynaptic potential evoked by electrical stimulation of afferent inputs to the locus coeruleus (26). Autoradiography studies have confirmed the existence of kappa opioid binding sites in this brain region (26). Since the majority of noradrenergic fibres projecting to the cortex are believed to originate in the locus coeruleus (5,24), it is possible that by inhibiting excitatory input to these neurones kappa agonists are able to reduce levels of spontaneous locomotor activity. An action of kappa agonists within the locus coeruleus to produce sedation would be consistent with the observation (18) that kappa agonists produce sedation when injected into the fourth ventricle due to a local action on brainstem periventricular structures.

In conclusion, the results described here show that the alpha$_1$ adrenoceptor antagonist prazosin potentiates the locomotor suppressant effect of kappa agonists. Although the 5-HT$_2$ antagonist ketanserin also potentiates kappa sedation experiments with ritanserin and with the nonselective 5-HT antagonist methysergide (which does not have any affinity for the alpha$_1$ adrenoceptor and does not potentiate the hypolocomotor activity of the kappa agonists PD-117302 and U-50488) suggest that blockade of the 5-HT$_2$ receptor is not involved.

ACKNOWLEDGEMENTS

The authors wish to express their gratitude to Mrs. W. Turner for assistance with the locomotor activity experiments, to Ms. S. Dawson for measuring brain levels of 5-HT, to Dr. D. Horwell and colleagues for the synthesis of PD-117302 and U-50488 and to the following pharmaceutical companies for their kind donations of drugs: Janssen (ketanserin and ritanserin) and Pfizer (prazosin).

REFERENCES

1. Baraben, J. M.; Aghajanian, G. K. Suppression of firing activity of 5-HT neurones in the dorsal raphe by alpha-adrenoceptor antagonists. Neuropharmacology 19:355–363; 1980.
2. Bevan, P.; Bradshaw, C. M.; Szabadi, E. The pharmacology of adrenergic neuronal responses in the cerebral cortex: evidence for excitatory alpha and inhibitory beta receptors. Br. J. Pharmacol. 59:635–641; 1977.
3. Bradley, P. B.; Engel, G.; Feniuk, W.; Fozard, J. R.; Humphrey, P. P. A.; Middlemiss, D. N.; Mylecharne, E. J.; Richardson, B. P.; Saxena, P. R. Proposals for the classification and nomenclature of functional receptors for 5-hydroxytryptamine. Neuropharmacology 25:563–576; 1986.
4. Cambridge, D.; Davey, M. J.; Massingham, R. Prazosin: a selective antagonist of postsynaptic alpha adrenoceptors. Br. J. Pharmacol. 59:514P–515P; 1977.
5. Clavier, R. M.; Routtenberg, A. Brainstem self-stimulation attenuated by lesions of medial forebrain bundle but not by lesions of locus coeruleus or caudal ventral norepinephrine bundle. Brain Res. 101:251–271; 1976.
6. Cole, S. O. Brain mechanisms of amphetamine-induced anorexia, locomotion and stereotypy: A review. Neurosci. Biobehav. Rev. 2:89–100; 1978.
7. Davey, M. J. Alpha adrenoceptors an overview. J. Mol. Cell. Cardiol. 18(Suppl. 5):1–15; 1986.
8. Fozard, J. F. Mechanism of the hypotensive effect of ketanserin. J. Cardiovasc. Pharmacol. 4:829–838; 1982.
9. Freye, E.; Hartung, E.; Schenk, G. K. Bremazocine: An opiate that induces sedation and analgesia without respiratory depression. Anaesth. Analg. 62:483–488; 1983.
10. Goodman, R. R.; Snyder, S. H.; Kuhar, M. J.; Young, W. S. Differentiation of delta and mu opiate receptor localizations by light microscopic autoradiography. Proc. Natl. Acad. Sci. USA 77:6239–6243; 1980.
11. Goodman, R. R.; Snyder, S. H. K-opiate receptors localized by autoradiography to deep layers of the cerebral cortex: relation to sedative effects. Proc. Natl. Acad. Sci. USA 79:5703–5707; 1982.
12. Grahame-Smith, D. G. Studies in vivo on the relationship between brain tryptophan, brain 5-HT synthesis and hyperactivity in rats treated with a monoamine oxidase inhibitor and L-tryptophan. J. Neurochem. 18:1053–1066; 1971.
13. Havemann, U.; Kuschinsky, K. Locomotor activity of rats after injection of various opioids into the nucleus accumbens and the septum mediale. Naunyn Schmiedebergs Arch. Pharmacol. 331:175–180; 1985.
14. Heal, D. J. Phenylephrine-induced activity in mice as a model of central a_1-adrenoceptor function. Neuropharmacology 23:1241–1251; 1984.
15. Hornung, R.; Presek, P.; Glossman, H. Alpha adrenoceptors in rat brain: Direct identification with prazosin. Naunyn Schmiedebergs Arch. Pharmacol. 308:223–230; 1979.

16. Jackisch, C. H.; Geppert, M.; Illes, P. Characterisation of opioid receptors modulating noradrenaline release in the hippocampus of the rabbit. J. Neurochem. 46:1802–1810; 1986.
17. Jones, D. L.; Mogenson, G. J.; Wu, M. Injections of dopaminergic, cholinergic, serotonergic and GABAergic drugs into the nucleus accumbens: Effects on locomotor activity in the rat. Neuropharmacology. 20:29–37; 1981.
18. Kamerling, S. G.; Martin, W. R.; Wu, K. M.; Wettstein, J. G. Medullary k hyperalgesic mechanisms II. The effects of ethylketocyclazocine administered into the fourth cerebral ventricle of the dog. Life Sci. 33:1839–1843; 1983.
19. Kumor, K. M.; Haertzen, C. A.; Johnson, R. E.; Kocher, T.; Jasinski, D. Human psychopharmacology of ketocyclazocine as compared with cyclazocine, morphine and placebo. J. Pharmacol. Exp. Ther. 238:960–968; 1986.
20. Leighton, G. E.; Johnson, M. A.; Meecham, K. G.; Hill, R. G.; Hughes, J. Pharmacological profile of PD-117302, a selective kappa opioid agonist. Br. J. Pharmacol., in press.
21. Leysen, J. E.; Awouters, F.; Kennis, L.; Laduron, P. M.; Vandenberk, J.; Janssen, P. A. J. Receptor binding profile of R 41 468, a novel antagonist at 5-HT_2 receptors. Life Sci. 28:1015–1022; 1981.
22. Leysen, J. E.; Gommeren, W.; Van Gompel, P.; Wynants, J.; Janssen, P. A. J.; Laduron, P. M. Receptor binding properties in vitro and in vivo of ritanserin: A very potent and long acting serotonin-S_2 antagonist. Mol. Pharmacol. 27:600–611; 1985.
23. Limberger, M.; Spath, L.; Holting, Th.; Starke, K. Mutual interaction between $alpha_2$-adrenoceptors and opioid K-receptors at the noradrenergic axons of the rabbit brain cortex. Naunyn Schmiedebergs Arch. Pharmacol. 334:166–171; 1986.
24. Lindvall, O.; Bjorklund, A. The organization of the ascending catecholamine neuron systems in the rat brain as revealed by the glyoxylic acid fluorescence method. Acta Physiol. Scand. [Suppl.] 412:1–48; 1974.
25. Lloyd, K. G.; Bartholini, G. The effect of methiothepin on cerebral monoamine neurones. Adv. Biochem. Psychopharmacol. 10:305–308; 1974.
26. McFadzean, I.; Lacey, M. G.; Hill, R. G.; Henderson, G. Kappa opioid receptor activation depresses excitatory synaptic input to rat locus coeruleus neurons in vitro. Neuroscience 20:231–239; 1987.
27. Marshal, R. W.; Sparks, M. G.; Davies, J. A. A microcomputer system for long-term monitoring and analysis of locomotor activity. In: Redfern, P. H.; Campbell, I. C.; Davies, J. A.; Martin, K. F., eds. Circadian rhythms in the central nervous system. 1985:263–269.
28. Martin, W. R.; Eades, C. G.; Thompson, J. A.; Huppler, R. E.; Gilbert, P. E. The effects of morphine- and nalorphine-like drugs in the nondependent and morphine dependent chronic spinal dog. J. Pharmacol. Exp. Ther. 197:517–532; 1976.
29. Massi, M.; Marini, S. Effect of the 5-HT_2 antagonist ritanserin on food intake and on 5-HT induced anorexia in the rat. Pharmacol. Biochem. Behav. 26:333–340; 1987.
30. Menkes, D. B.; Baraban, J. M.; Aghajanian, G. K. Prazosin selectively antagonises neuronal responses mediated by $alpha_1$ adrenoceptors in brain. Naunyn Schmiedebergs Arch. Pharmacol. 317:273–275; 1981.
31. Oberlander, C.; Blaquiere, B.; Pujol, J-F. Distinct functions for dopamine and serotonin in locomotor behaviour: Evidence using the 5-HT_1 agonist RU24969 in globus pallidus-lesioned rats. Neurosci. Lett. 67:113–118; 1986.
32. Snoddy, A. M.; Tessel, R. E. Prazosin: Effect on psychomotor cues and locomotor activity in mice. Eur. J. Pharmacol. 116:221–228; 1985.
33. Tyler, T. D.; Tessel, R. E. Norepinephrine uptake inhibitors as biochemically and behaviourally selective antagonists of the locomotor stimulation induced by indirectly acting sympathomimetic amines in mice. Psychopharmacology (Berlin) 69:27–34; 1980.
34. Ukai, M.; Kameyama, T. Multi-dimensional analysis of behaviour in mice treated with U-50488H, a purported kappa (non-mu) opioid agonist. Brain Res. 337:352–356; 1985.
35. Ukai, M.; Kameyama, T. Effects of ethylketocyclazocine on behaviours in mice using multidimensional behavioural analysis. Pharmacol. Biochem. Behav. 28:43–46; 1987.
36. Yim, C. Y.; Mogenson, G. J. Response of nucleus accumbens to amygdala stimulation and its modification by dopamine. Brain Res. 239:401–415; 1982.