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Motivational Effects of Opioids: Evidence on the Role of Endorphins in Mediating Reward or Aversion

I. P. STOLERMAN

Departments of Pharmacology and Psychiatry, Institute of Psychiatry De Crespigny Park, London SE5 8AF, U.K.

STOLERMAN, I. P. *Motivational effects of opioids: Evidence on the role of endorphins in mediating reward or aversion.* PHARMACOL BIOCHEM BEHAV **23**(5) 877–881, 1985.–It has been suggested that endogenous peptides with opiate-like effects may contribute to the mediation of reward or aversion. One line of evidence relating to these hypotheses derives from studies of the motivational effects of opioids. The ability of opioid agonists and antagonists to serve as positively reinforcing or aversive stimuli is reviewed, with results compared across several different behavioural procedures. The results for rewarding effects are consistent and independent of procedure: in self-administration, conditioned place preference and conditioned taste preference studies, opioid agonists are consistently effective whereas antagonists are inactive. Results for indices of aversive effects are more difficult to interpret because they are, to some extent, dependent on the procedure used. Neither agonists nor antagonists seem able to support operant escape/avoidance conditioning. Agonists can support taste aversion and place aversion conditioning to some extent, whereas antagonists are clearly active in both procedures. The results provide some support for the involvement of enkephalins or endorphins in reward and aversion, but there are significant gaps and contradictions in the evidence.

Opioids Reward Aversion Self-administration Brain-stimulation-reward
Place preference/aversion Taste preference/aversion Escape/avoidance

SPECULATIONS on the pleasures and pains of opiate use have occupied scientists and laymen for centuries. Both users and abusers of the drugs can claim benefits, however illusory they may be in the latter case, and the pains of withdrawal are too well-known to need elaboration here. More recently, behavioural scientists, stimulated by the discovery of enkephalins and endorphins, have sought parallels to these effects within the realms of neuroscience. Pleasure and pain are, for better or worse, perceived as related to reward and aversion processes and, operationally, as correlates of positive and negative reinforcement or punishment. Thus, the idea has been developed that endogenous substances with opiate-like effects are involved in the mediation within the CNS of these behavioural processes. This article reviews some of the work relating to such ideas, and especially emphasizes the importance of drawing together findings from different behavioural paradigms which are thought to measure basically similar effects. Bozarth [4] has discussed exciting attempts to localise mechanisms of reward to particular regions of the brain, and Iversen [9] has provided a broader review with a different perspective.

THE REWARD HYPOTHESIS

Belluzzi and Stein proposed that enkephalins may mediate a drive-reducing reward function which they linked to states of satisfaction, euphoria and well-being [3]. This bold suggestion was based on two pieces of evidence from studies in rats. Firstly, it was shown that intraventricular administrations of leucine-enkephalin or methionine-enkephalin maintained bar-pressing at rates above those maintained by a control solution. The same peptides suppressed rather than facilitated responding for other positive reinforcers, suggesting that self-administration was probably not just a reflection of non-specific behavioral stimulation. These were important early observations but nevertheless, the lack of control studies with an opioid antagonist must not be overlooked.

Secondly, it was reported that the antagonist naloxone reduced rates of responding for intracranial electrical stimulation [3]. The electrodes were aimed at the pontine central grey matter, an area rich in enkephalins and from which analgesia may be obtained. Doses of naloxone from 1.0–10 mg/kg reduced response rates by 60%. Such an effect in a classic animal model for reward mechanisms suggested that the reward process involved enkephalins or endorphins. It was not shown whether this effect had any behavioural specificity or if it was characteristic of opioid antagonists generally. These initial observations encouraged other workers to test further the general notion that enkephalins or endorphins were involved in motivational processes.

These seminal observations have received only partial support from workers in other laboratories. The principle that opioid peptides have positive reinforcing effects was confirmed by Woods, Herling and Young, who showed that monkeys would self-administer two synthetic met-enkephalin analogues (FK 33-824 and FW 34-569) by the intravenous route [25]. It is, of course, firmly established

that many other alkaloidal opioid agonists have powerful positive reinforcing effects in such experiments [10]. However, other workers were not able to confirm that naloxone suppressed intracranial self-stimulation behaviour in rats, using electrodes implanted in two different enkephalin-rich brain areas [24]. Only with extremely large, 40–160 mg/kg doses of naloxone was there any suppression of responding and effects at such massive doses could not be attributed to actions at opioid receptors. Esposito, Perry and Kornetsky were unable to demonstrate that naloxone enhanced the threshold currents needed to maintain self-stimulation [7].

THE REWARD-AVERSION HYPOTHESIS

Assuming that the basal release of opioid peptides maintains a form of motivational neutrality, then administering drugs such as naloxone should shift the balance of CNS functioning to a relatively aversive state. Thus, if enkephalins mediate positive reinforcement, then opioid antagonists should have the opposite type of action, and should be able to support conditioning in negative reinforcement, conditioned place aversion and conditioned taste aversion paradigms.

Pilcher and Stolerman reported that naloxone could produce a conditioned taste aversion in rats which had never previously received any exogenous opioid [19]. In the initial experiments only, this was a weak effect, produced by a large, 10 mg/kg dose of naloxone and needing many animals to reach statistical significance. Similar results were obtained by LeBlanc and Cappell [13]. In later experiments, the threshold dose of naloxone for producing the effect was reduced ten-fold, to 1 mg/kg, and relatively strong, dose-related, aversions were produced by naloxone in doses of 3.2 and 10 mg/kg [23]. This improvement in sensitivity was obtained by optimizing the conditioning procedure according to well-established behavioural principles. Similar results were obtained with other antagonists (Mr 1452, (−)-BC-2860 and naltrexone). Negative results with stereoisomers of opioid antagonists (Mr 1453 and (+)-BC-2860) established the stereospecificity of the effect. The GABA antagonists bicuculline and picrotoxin were not potent agents for producing conditioned taste aversions [21]. It was argued that the taste aversion produced by naloxone was most probably due to blockade of endogenous enkephalins or endorphins, thus supporting the view that endogenous opioids were involved in aversive processes.

In later experiments, further attempts were made to find conditions in which the taste aversion effect of naloxone was more marked. In view of the proposed involvement of opioid peptides in responses to stress, conditioned taste aversion experiments were carried out in rats receiving moderate amounts of footshock [20]. This manipulation did not potentiate the response to naloxone, but overcrowding, another stress-inducing treatment, enhanced the effect [18]. Tests were carried out to determine whether a previous history of chronic morphine administration enhanced the response to naloxone, but the results were negative.

Mucha and Herz have confirmed that naloxone can produce marked, dose-related taste aversions and in this study, the effective doses of naloxone were in the range 0.1–2 mg/kg [14]; these observations show a further ten-fold increase in the potency of naloxone, as compared with previous work. The reasons for the enhanced potency were not established, but the use of the subcutaneous instead of the intraperitoneal route may be significant. Interestingly, on a mg/kg basis naloxone was rather more potent than lithium, a classical agent for producing conditioned taste aversions. This work provides further support for the view that the taste aversion effect of naloxone is mediated by blockade of endogenous opioids. Evidence from other behavioural paradigms thought to reflect the rewarding or aversive effects of drugs will now be assessed.

CONDITIONED PLACE PREFERENCES

Additional evidence suggestive of a role for endogenous opioids in reward mechanisms has been derived from studies using conditioned place preference procedures. This family of techniques involves administering a drug to an animal and then placing it in an environment with distinctive sensory features, usually visual and tactile. After a number of such conditioning trials, "preference" for or "aversion" to the environment is assessed by measuring the latency to enter it or time spent there, in comparison with a control environment associated with saline injections. Such experiments can provide evidence of the subjects' responses to environmental stimuli previously associated with the effects of a drug and thus, they relate indirectly to possible rewarding or aversive actions of the drug itself. The initial observations of Beach [1] and Kumar [12] showed that morphine administered chronically, in rather large doses, produced conditioned place preferences. Only recently have procedures of this type been subject to intensive systematic study, and the early findings have been confirmed and considerably extended.

Several workers have now shown that small acute doses of morphine can produce conditioned place preferences. For example, Mucha and Iversen [15] exposed rats to a distinctive environment for 1 hour beginning immediately after subcutaneous injection of morphine (0.04–5 mg/kg). Different environmental stimuli were paired with saline injections in the same rats, with drug-environment pairings counterbalanced to minimize the effects of any unconditioned preferences for one or the other environment. After four conditioning sessions with drug and four with saline, preferences were examined in 15-min tests; a clear, dose-related increase in the time spent in the morphine-paired environment was demonstrated for morphine doses of 0.1 mg/kg or more.

Similar effects of morphine have been found with procedural variations such as different designs of apparatus, routes of injection and numbers of conditioning trials [11, 15, 16]. The effect seems to be stereospecific and blocked by naloxone. Other opioid agonists have also been shown to support place preference conditioning; these compounds, etorphine, levorphanol, fentanyl and sufentanil, seem to act predominantly at the mu subtype of opioid receptor [14,16]. There is also preliminary evidence that intraventricular injections of an enkephalin analogue (D-Ala^{2}leu-enkephalinamide, 25 μg) can produce conditioned place preferences [11]. Opioid antagonists have not generally been found to produce conditioned place preferences. The antagonist methylnaltrexone can produce place preference, presumably through a peripheral mechanism [2].

CONDITIONED PLACE AVERSIONS

Experiments using place aversion procedures have consistently strengthened the evidence that opioid antagonists have aversive effects even in subjects which have never received any exogenous opioids. The procedure is essentially the same as that used for testing the conditioning of place

TABLE 1

SUMMARY OF MOTIVATIONAL EFFECTS OF OPIOIDS WHICH ACT MAINLY ON RECEPTORS OF THE MU TYPE*

Paradigm	Agonists	Antagonists
Rewarding Effects		
Self-administration†	Yes	No
Place preference‡	Yes	No
Taste preference‡	Yes (?)	No
Aversive Effects		
Negative reinforcement§	No (?)	No (?)
Place aversion‡	No	Yes
Taste aversion‡	No (?)	Yes

*Effects thought to result from peripheral drug actions have been excluded. Question marks indicate outcome based on very limited information.

†Schedules of response-contingent drug injections.

‡Assessed after drug-place or drug-taste pairings according to classical conditioning principles.

§Behaviour maintained by avoidance of or escape from drugs and associated stimuli.

preferences (see above). Mucha *et al.* showed that (−)-naloxone (0.1–45 mg/kg) produced conditioned place aversions in rats [16]. The stereoisomer (+)-naloxone was inactive, suggesting that the effect was stereospecific and possibly mediated through opioid receptors. In later studies, it was confirmed that (−)-naloxone (0.1–2 mg/kg) produced place aversions, and the magnitude of the effect was related both to the dose of naloxone and to the number of conditioning trials [14,15]. The dose-response curves for conditioned place aversions produced by naloxone are displaced to the right, as compared with those for conditioned taste aversions; this fits in with the well-known facilitation of conditioning to drug effects when gustatory stimuli are used instead of visual cues in rats.

Until recently, it appeared that narcotic agonists did not support place aversion conditioning at all. However, Bechara and van der Kooy have shown that a small dose of morphine (0.05 mg/kg) produced place aversion when injected intraperitoneally [2]. Subcutaneous injections did not produce the effect. Furthermore, the place aversion was absent after subdiaphragmatic vagotomy, suggesting a peripheral site of action. Vagotomy did not attenuate the place preference produced by a larger dose of morphine. If the interpretation of a peripheral site of action is correct, then one would expect that the place preference would be blocked by pretreatment with methylnaltrexone, but this remains to be shown.

CONDITIONED TASTE PREFERENCES

The importance that could be attached to experiments demonstrating conditioned taste aversions produced by naloxone was limited by knowledge that many drugs, including the classic opioid agonist morphine, could also produce the effect. One might expect morphine to produce conditioned taste preferences if the paradigm functioned in the manner originally proposed. Initially, preferences for a taste associated with morphine could only be produced in rats self-administering the drug by drinking solutions of it [22]. Some recent experiments have shed new light on the matter.

Very small doses of some opioid agonists have been reported to produce conditioned taste preferences, as shown by increased consumption of drug-paired flavoured solutions in direct tests against vehicle-paired flavoured solutions [14]. The active drugs were fentanyl (0.004 mg/kg), sufentanil (0.00025–0.0005 mg/kg) and morphine (0.15 mg/kg). Larger doses of all three drugs produced conditioned taste aversions. The effect of morphine was weaker than that of the other two agents. It remains to be determined whether these effects are stereospecific and blocked by opioid antagonists.

These significant new results raise the possibility that previous work [13,23] involved doses of morphine which were above the range producing conditioned taste preferences. Morphine may have been rather unrepresentative of opioids as a class, its status as a prototypical opioid agonist notwithstanding. There is also evidence that the taste aversion effect of morphine may be peripherally mediated [2]. The findings may help to resolve the contrast between the positive reinforcing effects of morphine in self-administration and place conditioning studies on the one hand, and its taste aversion effect on the other. Nevertheless, dose or site of action is very unlikely to account for the all taste aversion effects produced by abused drugs. Even extremely small doses of amphetamine, well below the range producing conditioned taste aversions, failed to produce conditioned taste preference [5]. Conditioned taste aversions produced by amphetamine also appear to be centrally mediated [22].

NEGATIVE REINFORCEMENT PROCEDURES

In studies using negative reinforcement procedures, intravenous infusions of drugs occurred according to a predetermined programme, unless the subject made a specified response. Rhesus monkeys were trained to press a lever to turn off a light associated with a drug infusion scheduled to occur 30 seconds after the light came on [8]. Each response while the light was on turned it off for 1 minute (avoidance), whereas responses during an infusion terminated the infusion (escape). Infusions of saline or of the narcotic agonist codeine maintained little avoidance or escape responding. Infusions of two mixed agonist-antagonists (nalorphine and cyclazocine) maintained avoidance/escape responding, although response rates seemed lower than those maintained when electric shock was used instead of the drugs. However, the effects of the drugs may not have been associated with their antagonist properties since the relatively pure antagonist naloxone (0.005–0.1 mg/kg per infusion) did not maintain avoidance/escape responding. In one later report, naloxone was found to maintain avoidance/escape responding in a rhesus monkey at doses of 0.3 mg/kg/min [6].

CONCLUSIONS

It is now possible to compare the motivational effects of narcotic agonists and antagonists across a variety of behavioral procedures. The use of several quite different procedures can help to establish that effects are robust and that they are not due to procedure-specific artefacts; this is a long-established but often neglected principle in psychopharmacology. Confounding factors which may influence the results of one class of procedure may not be relevant to

another, and thus agreement across different conditions makes conclusions more convincing. Table 1 summarizes the evidence for rewarding and aversive effects of narcotic agonists and antagonists, each assessed with three classes of procedure.

Tests for rewarding effects of the drugs are yielding a fairly consistent pattern of results and these will be considered first. There are clear results from self-administration procedures of the conventional type, using the methods of operant conditioning. Opioid agonists serve as positive reinforcers whereas antagonists do not, under the conditions normally used. Only recently have tests of conditioned place preferences, based on classical conditioning, begun to come into common use; these procedures too suggest that opioid agonists but not antagonists have positive reinforcing effects. The situation with conditioned taste preferences is more complex since only very recently has there been any evidence that agonists can support this type of conditioning (see above). There is no evidence suggesting that antagonists can support taste preference conditioning. It is generally very difficult to obtain conditioned taste preferences with any type of drug and, therefore, the findings with opioid agonists are all the more impressive. Provided that these initial results prove robust and can be further validated, it may become possible to interpret the effects of opioid agonists as rewarding across the three distinct conditioning paradigms.

The results from tests for aversive effects of opioid agonists and antagonists have yielded a less consistent set of results (Table 1). Opioid agonists have not been reported to support avoidance/escape responding in operant conditioning procedures where the drugs are administered instead of a conventional stimulus such as shock. Although the lack of such effects fits in with the reward-aversion hypothesis, it has to be noted that few investigators have tested for them, probably because the idea that opioid agonists are rewarding has been so influential. Opioid antagonists have also not generally been found to support avoidance/escape responding in such procedures. This is a serious problem since such techniques provide the most direct evidence bearing on the putative aversive effects of the antagonists. The technical complexity and the initial, rather negative, results may have discouraged investigators from pursuing the idea further. Nevertheless, unless conditioning of this type can be supported convincingly by antagonists, the viability of the reward-aversion hypothesis must be questioned.

The results with place and taste conditioning techniques are less of a problem. Agonists do not generally support place aversion conditioning, whereas antagonists clearly do. The agonists can produce conditioned taste aversions, but the doses needed are appreciably larger than those which produce conditioned taste preferences, and peripheral mechanisms may be involved. Investigations with a wider range of drugs, across different conditions, will be needed to resolve the matter. Small doses of antagonists can also produce conditioned taste aversions which are dose-related and stereospecific. The results with these indirect measures are reasonably consistent with the reward-aversion hypothesis.

The aversive effects of naloxone are greatly increased in subjects receiving morphine chronically. This enhanced reaction, which has been found with negative reinforcement, conditioned place aversion and conditioned taste aversion techniques, will not be considered further because it probably reflects conditioning of a precipitated withdrawal reaction rather than a normal function of endorphins [6, 16, 19].

To summarize, tests of the motivational effects of opioid agonists and antagonists provide appreciable support for the initial reward hypothesis, and the reward-aversion notion cannot be discounted entirely. Before definite conclusions can be reached from these lines of investigation, further efforts will be needed to fill in some of the cells of the scheme outlined in Table 1. The data obtained to date are incomplete, especially since nearly all the information relates to alkaloidal opioids. Very little work in this area has been done with the opioid peptides. This is an important limitation since there are variations in the sub-populations of opioid receptors upon which different peptides and alkaloids act. No doubt the difficulty of carrying out behavioural work with peptides, most of which need to be injected directly into the brain, is largely responsible for this situation.

The important question of whether drug effects are of central or peripheral origin has also received less attention than might have been expected. This is especially important in view of the evidence that the rewarding and aversive effects of the drugs may be different at central and peripheral sites. Great care is also needed to take full account of such mundane variables as dose and route of injection, since effects of drugs may be prevented or even reversed by either manipulation.

Most of the evidence reviewed in this article applies to opioids that act primarily upon the mu-subtype of receptor, and clearly more studies with drugs thought to act on kappa, sigma or delta receptors are needed. There is also a serious, almost complete lack of studies on the release of endorphins in relation to reward or aversion processes, and on the effects of manipulating their concentrations by means of enzyme inhibitors or lesions. There is also very little evidence about their role in the reinforcement of behaviour maintained by conventional stimuli. It is to be hoped that interest in the field will continue to grow and that the limitations of present knowledge will encourage further work.

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