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Buprenorphine–cocaine Interactions in Mice: Effect on Locomotor Activity and Hole-dipping Behaviour

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Abstract—The effect of cocaine and the mixed μ-opioid partial agonist/κ-antagonist buprenorphine on locomotor activity and hole-dipping behaviour was investigated in mice. The drugs were given alone and in combination. Cocaine (7·5, 15, 30 mg kg^{-1}, i.p.) significantly increased locomotion in a dose-related manner in the hour following injection. The two highest doses also increased hole-dipping although this response was not consistently seen. Buprenorphine (0·5, 5 mg kg^{-1}, i.p.) produced an increase in locomotion which occurred 30–60 min after injection but did not alter hole-dipping behaviour. A lower dose (0·05 mg kg^{-1}) had no effect on either parameter. The locomotion induced by cocaine (15 mg kg^{-1}, i.p.) was not modified by buprenorphine (0·05, 0·5, 1, 5 mg kg^{-1}, i.p.; 5 min pretreatment). However, hole-dipping was almost completely abolished in animals given combinations of cocaine and buprenorphine (0·05–5 mg kg^{-1}, i.p.), although neither drug decreased hole-dipping when given alone. This observation, which was not simply due to the emergence of stereotyped behaviour, suggests an interaction between buprenorphine and cocaine.

Buprenorphine is an opioid that has been characterized pharmacologically as a partial agonist at μ-opioid receptors and an antagonist at κ-receptors. The μ-agonism is reflected, for example, by its being antinociceptive in rats and mice (Cowan et al 1977a). However, as a partial agonist it also antagonizes the antinociceptive effects of the opioid agonist morphine (Cowan et al 1977a). The antagonist action of buprenorphine at κ-opioid receptors has been shown by its ability to inhibit the diuretic and behavioural effects of κ-agonists in rats and squirrel-monkeys (Richards & Sadee 1985; Leander 1987; Negus & Dykstra 1988; Negus et al 1990, 1991). The blockade of the effects of full opioid agonists by buprenorphine has been demonstrated in man (Jasinski et al 1978) and has led to its being evaluated as a treatment of opioid abuse (Mello & Mendelson 1980; Mello et al 1982).

Over recent years, several studies have investigated the possibility that buprenorphine may also be useful in the treatment of addiction to other drugs of abuse. In particular buprenorphine has been reported to attenuate the behavioural effects of cocaine, although there are some conflicting results. For example, buprenorphine suppresses self-administration of cocaine in rhesus monkeys (Mello et al 1989) and several groups have reported that buprenorphine reduces the toxic effects of cocaine in mice—probably through a μ-opioid receptor mechanism (Shukla et al 1991; Witkin et al 1991). Conversely, others have noticed similarities between the behavioural and neurochemical effects of cocaine and buprenorphine, which itself possesses some abuse potential (Hammersley et al 1990), and in some tests buprenorphine potentiates the actions of cocaine. For instance, buprenorphine has been shown to enhance sensitivity to cocaine in squirrel-monkeys trained to discriminate cocaine from saline (Kamien & Spealman 1991). Moreover, additive effects of buprenorphine and cocaine have been detected in rats using the conditioned place preference test; an animal model of the rewarding properties of a drug (Brown et al 1991). Furthermore, both drugs increased dopamine release in the nucleus accumbens, an effect which was also enhanced when cocaine and buprenorphine were given together (Brown et al 1991).

It is thought that dopamine release underlies many of the actions of cocaine in the central nervous system. Thus it has been associated with the reinforcing properties of cocaine (see above) and also with its well-known behavioural stimulant effects (Johanson & Fischman 1989). Since increased locomotion is an indication of the effects of cocaine, it is surprising that there have been no other studies of buprenorphine's effects on this parameter. Consequently in the present study we have used the stimulation of locomotion and hole-dipping produced by cocaine to examine possible interactions between buprenorphine and cocaine.

Materials and Methods

Animals

Male mice of the TO strain (Bantin & Kingman North Humberside, UK), 28–35 g, were used in all experiments. Mice were housed in groups of 30 at 23 ± 2°C under a 14:10 h light–dark cycle (lights on at 0500 h) with free access to standard rat and mouse diet, and water. Animals were used on only one occasion.

Experimental procedures

All procedures were carried out in a quiet, air-conditioned laboratory between 0900 and 1600 h at an ambient temperature of 23 ± 2°C. Locomotor activity was measured using four automated activity boxes. Each consisted of an open transparent-perspex arena (60 × 60 × 30 cm). The floor of

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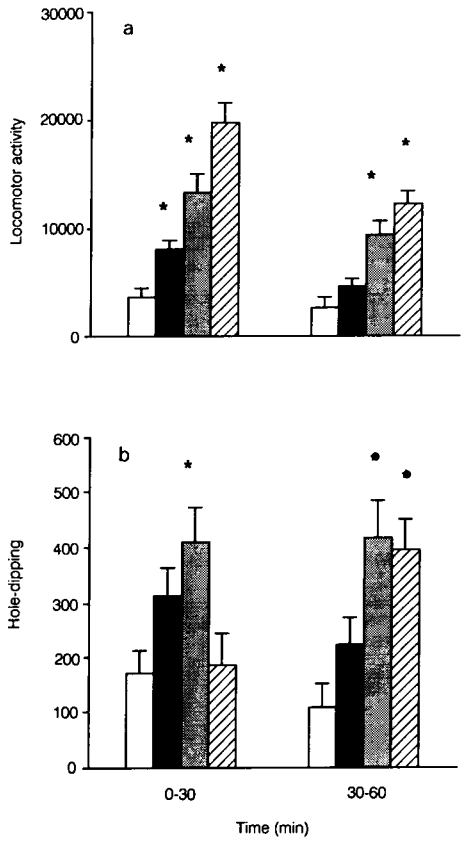

FIG. 1. Effect of cocaine on (a) locomotor activity and (b) hole-dipping behaviour in habituated mice. Animals were injected intraperitoneally with vehicle (open columns) or with doses of cocaine: 7·5 mg kg^{-1} (closed columns); 15 mg kg^{-1} (stippled columns); 30 mg kg^{-1} (hatched columns). Results represent mean counts ± s.e.m. for groups of eight animals. Significant differences from the vehicle-treated controls are denoted by $*P < 0{\cdot}05$.

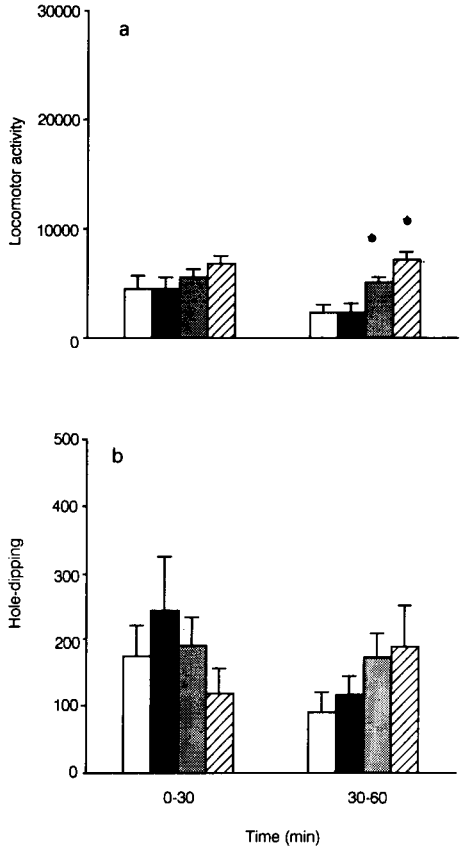

FIG. 2. Effect of buprenorphine on (a) locomotor activity and (b) hole-dipping behaviour in habituated mice. Animals were injected intraperitoneally with vehicle (open columns) or with doses of buprenorphine: 0·05 mg kg^{-1} (closed columns); 0·5 mg kg^{-1} (stippled columns); 5 mg kg^{-1} (hatched columns). Results represent mean counts ± s.e.m. for groups of eight animals. Significant differences from the vehicle-treated controls are denoted by $*P < 0{\cdot}05$.

each box contained 64 (8 × 8) equally spaced holes (1·8 cm in diam.) through which a mouse could extend its head. Fifteen infra-red emitters and receivers located 1·5 cm above floor level recorded locomotion, while 15 infra-red emitters and receivers located just below the level of the holes recorded hole-dips. The infra-red beams were interfaced to a computer which recorded continuously the number of beam breaks per unit time. Four identical sets of equipment were used so that the locomotor and hole-dipping behaviour of animals from each of four different treatment groups was monitored concurrently. Animals were tested individually and two animals from each treatment group were tested in each of the four boxes to allow for variability in either the activity boxes or their environment. Hence, each treatment group contained eight animals. Animals were given a 40 min habituation period since this is the time required for mice to fully explore the novel activity boxes and for their activity levels to stabilize (I. J. Griffin, unpublished observations). Locomotor activity and hole-dipping behaviour was recorded in the periods 0–30 min and 30–60 min following drug administration.

Drugs

Cocaine hydrochloride was purchased from Sigma (Poole, UK). Buprenorphine hydrochloride was synthesized at Reckitt & Colman, Hull (UK). Both drugs were dissolved in saline (which was acidified to pH 3 in the case of buprenorphine) and were administered intraperitoneally in a dose volume of 10 mL kg^{-1}. Mice were treated with either cocaine (7·5, 15, 30 mg kg^{-1}), buprenorphine (0·05, 0·5, 5 mg kg^{-1}) or a combination of cocaine (15 mg kg^{-1}) and buprenorphine (0·05, 0·5, 1, 5 mg kg^{-1}). The 15 mg kg^{-1} dose of cocaine was chosen for the interaction experiments to enable detection of either inhibition or potentiation of activity. Buprenorphine was injected 5 min before treatment with cocaine or vehicle. All experiments contained appropriate vehicle-treated control groups which were tested concurrently with each drug treatment group.

Statistical analysis

Locomotor activity counts and number of hole-dips per 30 min period were statistically compared using the non-parametric one-way analysis of variance (Kruskal-Wallis; $P < 0{\cdot}05$; $H > 7{\cdot}81$) followed by the Mann-Whitney U-test (2-tailed; $P < 0{\cdot}05$; U values < 13; $n = 8$). Results are expressed as treatment group means (± s.e.m. to give an indication of the spread of the data).

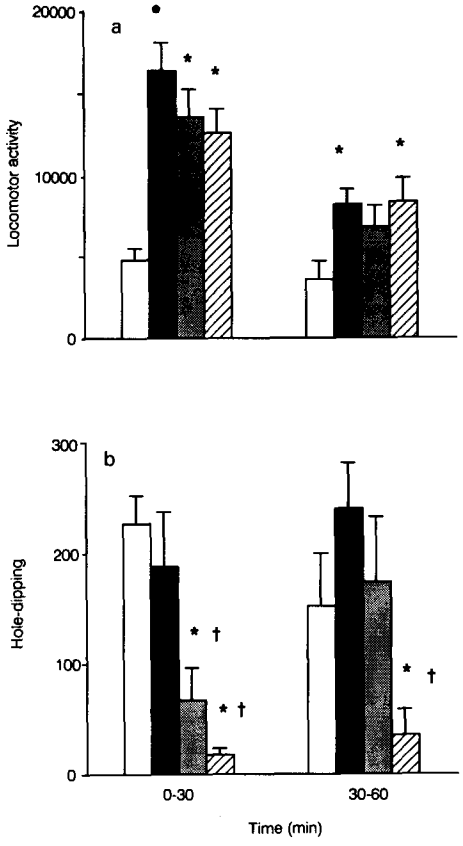

FIG. 3. Effect of a combination of cocaine and buprenorphine on (a) locomotor activity and (b) hole-dipping behaviour in habituated mice. Animals were injected intraperitoneally with vehicle (open columns); cocaine 15 mg kg^{-1} (closed columns); cocaine 15 mg kg^{-1} plus buprenorphine 0·05 mg kg^{-1} (stippled columns) or cocaine 15 mg kg^{-1} plus buprenorphine 0·5 mg kg^{-1} (hatched columns). Results represent mean counts ± s.e.m. for groups of eight animals. Significant differences from the vehicle-treated controls are denoted by $*P<0·05$ and from the cocaine-treated controls by $\dagger P<0·05$.

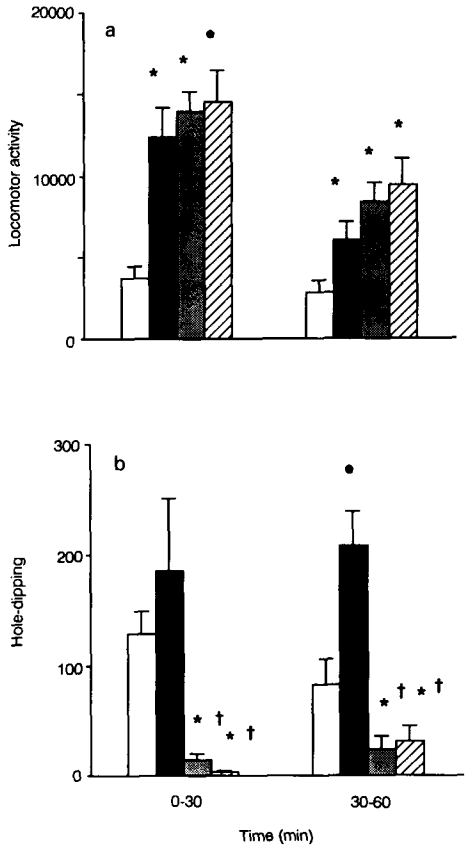

FIG. 4. Effect of a combination of cocaine and buprenorphine on (a) locomotor activity and (b) hole-dipping behaviour in habituated mice. Animals were injected intraperitoneally with vehicle (open columns); cocaine 15 mg kg^{-1} (closed columns); cocaine 15 mg kg^{-1} plus buprenorphine 1 mg kg^{-1} (stippled columns) or cocaine 15 mg kg^{-1} plus buprenorphine 5 mg kg^{-1} (hatched columns). Results represent mean counts ± s.e.m. for groups of eight animals. Significant differences from the vehicle-treated controls are denoted by $*P<0·05$ and from the cocaine-treated controls by $\dagger P<0·05$.

Results

Cocaine (7·5, 15, 30 mg kg^{-1}) increased the locomotor activity of habituated mice in a dose-dependent manner as shown in Fig. 1a. The locomotor activity scores of animals treated with all doses of cocaine were significantly greater than controls during the first 30 min after injection. The two highest doses (15, 30 mg kg^{-1}) also significantly increased locomotion during the following 30 min period. Cocaine at 7·5 mg kg^{-1} had no effect on hole-dipping (Fig. 1b). However, the two higher doses of cocaine significantly increased this parameter. Cocaine at 15 mg kg^{-1} produced a significant increase in hole-dipping throughout the hour following injection. On the other hand, cocaine at 30 mg kg^{-1} did not increase this response until the second half of the experiment.

Buprenorphine at 0·5 and 5 mg kg^{-1} also significantly increased locomotor activity in mice, although this did not occur until the 30–60 min period as shown in Fig. 2a. The lower dose of buprenorphine (0·05 mg kg^{-1}) did not modify locomotor activity. Hole-dipping behaviour in mice was not significantly altered by buprenorphine (0·05, 0·5, 5 mg kg^{-1}; Fig. 2b) in the hour following drug administration.

Buprenorphine (0·05, 0·5, 1, 5 mg kg^{-1}) did not significantly antagonize nor potentiate the increase in locomotor activity induced by cocaine (15 mg kg^{-1}) in mice as shown in Figs 3a and 4a. In these two experiments cocaine (15 mg kg^{-1}) tended to increase hole-dipping, although this response was not always evident until the 30–60 min period (Figs 3b, 4b) and did not always reach levels of significance. However, hole-dipping was virtually abolished in animals given a combination of cocaine (15 mg kg^{-1}) and buprenorphine (0·5, 1, 5 mg kg^{-1}). This was apparent during the first 30 min of the experiment and also during the following 30 min period. Hole-dipping was also significantly reduced at 30 min in animals given cocaine and the lowest dose of buprenorphine (0·05 mg kg^{-1}). The hole-dipping scores of animals given cocaine and buprenorphine were significantly lower than both the vehicle-treated control group and also the group of animals given cocaine alone (Figs 3b, 4b).

Discussion

Three interesting findings emerged from the current study. The first is that buprenorphine has a small locomotor

stimulant effect but that this is delayed. The second is that buprenorphine did not increase or decrease the locomotor effects of cocaine and the third is that buprenorphine and cocaine in combination markedly inhibited hole-dipping behaviour.

The animals treated with cocaine alone showed the expected increase in locomotor activity, greater in the first 30 min than in the second. A less consistent stimulation of hole-dipping was observed, that was only significant in some experiments, perhaps because of the inverted U-shaped dose-response curve revealed in Fig. 1. Buprenorphine stimulated locomotor activity but only to a significant degree in the second 30 min. However, this was dose-related. Similar findings have been reported by others although the time course of this effect was not examined closely (Cowan et al 1977b). The results with buprenorphine are consistent with the actions of the μ-agonist morphine in the same paradigm which also produces an increase in activity following an initial delay (H. C. Jackson; unpublished observations).

In comparison with cocaine, buprenorphine produced less locomotor stimulation, which is in accordance with microdialysis studies that show it to be a less efficacious releaser of dopamine in the nucleus accumbens in the hour following injection (Brown et al 1991). The time course of both cocaine and buprenorphine on dopamine release correlates with that of the locomotor activity observed in the present study. This supports the contention that the effects of buprenorphine on locomotor activity are mediated through the release of dopamine. Moreover, there is evidence that μ-opioid receptors are involved in the modulation of dopamine function (Di Chiara & Imperato 1986; Spanagel et al 1990), and dopamine antagonists block the effects of morphine on locomotion (Carroll & Sharp 1972; Longoni et al 1987).

The interaction studies between cocaine and buprenorphine revealed that buprenorphine neither increased nor decreased the locomotor effects of cocaine. A number of studies have shown that buprenorphine potentiates some of the behavioural effects of cocaine such as its drug discrimination action (Kamien & Spealman 1991) and its rewarding effects in conditioned place preference (Brown et al 1991). Furthermore, the study in rats (Brown et al 1991) showed an immediate potentiation of the dopamine-releasing effects of cocaine by buprenorphine, despite the drugs having very different time courses when given alone. It is not clear why there was no potentiation of cocaine-induced locomotion by buprenorphine either early or late in the test. Because an increase in dopamine release can produce stereotypes which could interfere with locomotion, the behaviour of the mice was observed. However, there was no evidence of altered behaviour in the mice given the buprenorphine–cocaine combination compared with mice given cocaine alone.

On the basis of other studies (Mello et al 1989; Shukla et al 1991; Witkin et al 1991) it might have been predicted that buprenorphine would reduce the actions of cocaine. However, there was no sign of this on locomotion, although the combination markedly reduced hole-dipping. Buprenorphine itself did not alter this behaviour and the effects of cocaine alone were somewhat inconsistent. An explanation of the effect of the drug combination could derive from our observation that cocaine has an inverted U-shaped dose-response relationship to hole-dipping. This suggests that increased dopamine release can inhibit hole-dipping and since buprenorphine may acutely increase cocaine-induced dopamine release (Brown et al 1991), it may effectively shift the cocaine dose-response curve to the left (see also Kamien & Spealman 1991). Supporting evidence for this concept is given by the very recent report from self-administration studies that the first dose of buprenorphine markedly reduces cocaine intake in rats (Carroll & Lac 1992). In this study, for instance, a dose of 0·1 mg kg^{-1} buprenorphine intravenously produced a response to the 0·1 mg kg^{-1} cocaine dose equivalent to that of 0·4 mg kg^{-1} cocaine. However, this explanation must be interpreted with caution since it would be predicted to increase locomotor activity in our experiments, and this did not occur. Moreover, behavioural observation of the mice showed that stereotyped behaviours were not interfering with the hole-dipping response. The mice approached the holes as normal but did not dip. Thus the reasons why buprenorphine reduced hole-dipping in cocaine-treated animals are presently unclear.

Taken together the current data demonstrate some similarities in the actions of cocaine and buprenorphine which may be of relevance to the human situation. The effects of chronic administration of buprenorphine on the rewarding or reinforcing properties of cocaine have been investigated by a number of groups. Some studies have shown that it is more effective when given chronically (see Mello et al (1989) and discussion in Kosten et al (1991), whereas others have reported the development of tolerance (Carroll & Lac 1992). Following these discrepancies it would be of interest to repeat the current buprenorphine–cocaine interaction studies in mice given chronic treatments with these drugs.

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