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The serotonin/noradrenaline reuptake inhibitor venlafaxine attenuates acquisition, but not maintenance, of intravenous self-administration of heroin in rats ☆

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Abstract

Opioids and antidepressants are frequently used for the treatment of various pain conditions. A combination of both drug classes may be more effective than either treatment alone, and combined treatment with an antidepressant may result in an opiate-sparing effect. Although it has been shown that antidepressants can attenuate self-administration of psychomotor stimulant and depressant drugs, it is not known whether they also attenuate self-administration of opiates. To determine whether venlafaxine, a serotonin/noradrenaline reuptake inhibitor with antidepressive and analgesic properties, affects acquisition and maintenance of intravenous heroin self-administration in rats, male Long–Evans rats were trained to press a lever in order to receive heroin (0.05 mg/kg/infusion) under a fixed ratio or a progressive ratio schedule. A control group was trained in a fixed ratio food-reinforced operant procedure. The effect of venlafaxine on operant responding for heroin and food was assessed both during acquisition and, in separate groups of rats, during maintenance (i.e., after acquisition) of self-administration behaviour. Daily treatment with venlafaxine (10 mg/kg i.p.) before the operant session attenuated the acquisition of responding for heroin, but not for food. However, when tested during the maintenance phase in rats showing stable responding, acute treatment with venlafaxine only marginally affected operant responding for heroin under a fixed ratio:10 schedule of reinforcement, and neither acute nor subchronic (once daily during 4 weeks) venlafaxine treatment affected responding under a progressive ratio schedule. Thus, daily treatment with an antidepressant attenuates the acquisition of heroin self-administration in a behaviourally specific manner, while having only marginal effects on maintenance of heroin self-administration.

Keywords: Addiction; Analgesics; Antidepressant; Drug abuse; Operant behaviour; Opioid; Reinforcement

1. Introduction

Because of their well-established analgesic properties, opioids are broadly used for the treatment of moderate to severe pain (Stein, 1999). Unfortunately, opioid medication often coincides with development of tolerance to the analgesic effects, as well as with psychological and physical dependence. Moreover, their clinical use can be compromised by concomitant side-effects, like constipation, cognitive impairment and respiratory depression (Martin, 1983). Preclinical and clinical studies have indicated that a number of antidepressants, including the tricyclic desipramine, and selective serotonin/noradrenaline reuptake inhibitors, such as venlafaxine and duloxetine, have intrinsic analgesic properties (Briley, 2004; Mochizucki, 2004). Because these compounds do not share the abuse liability of opioids and are considered to have a less severe side-effect profile, they are generally viewed as an attractive treatment alternative for particular chronic pain conditions, such as neuropathic pain (Tzschentke, 2002; Briley, 2004). In addition, it has been suggested that combination of antidepressants with opioids can improve analgesic efficacy and/or reduce dosing of opioids (Malseed and Goldstein, 1979; Panerai et al., 1991).

Moreover, it was reported that antidepressants can attenuate self-administration of drugs with high abuse liability, such as

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psychomotor depressants and stimulants. For example, selective serotonin reuptake inhibitors, such as fluoxetine, citalopram, fluvoxamine or paroxetine were found to attenuate oral or intravenous self-administration of ethanol in rats and humans (e.g., Lyness and Smith, 1992; Naranjo et al., 1994; Le et al., 1999; Maurel et al., 1999a,b). Fluoxetine was also reported to attenuate reinstatement of extinguished cocaine-seeking behaviour (Baker et al., 2001) and to decrease the rate of responding maintained by intravenous cocaine or amphetamine in rats (Yu et al., 1986; Carroll et al., 1990). While these studies suggest that antidepressants with a serotonergic mechanism of action can attenuate self-administration of abused drugs, it has also been reported that reboxetine, an antidepressant which selectively inhibits the reuptake of noradrenaline, attenuated self-administration of nicotine (Rauhut et al., 2002). Therefore, it appears that antidepressants which block reuptake of either serotonin or noradrenaline (or both) interfere with self-administration of psychomotor depressants and stimulants. Although it remains unclear whether these antidepressants can directly affect self-administration of opioid analgesics, it is interesting to note that fluoxetine improved the beneficial effect of the opioid receptor antagonist naltrexone on relapse prevention in heroin-dependent patients (Landabaso et al., 1998).

It was the aim of the present study to investigate whether the selective serotonin/nordrenaline reuptake inhibitor venlafaxine affects the acquisition and maintenance of intravenous self-administration of heroin in rats. Venlafaxine was selected since this antidepressant was reported to attenuate the reacquisition of morphine-induced conditioned place preference, as well as most morphine withdrawal signs in rats (Lu et al., 2001), without producing rewarding or aversive effects by itself (Subhan et al., 2000a). Furthermore, since at the outset of the experiments it was not known whether serotonergic or noradrenergic reuptake inhibition would be more relevant, a drug was chosen that combined both mechanisms of action to maximize the chance to see effects in these initial experiments. The first experiment examined the effect of daily pretreatment with venlafaxine on acquisition of heroin self-administration under a fixed ratio schedule of reinforcement. Behavioural specificity of the pretreatment effect was assessed in a food-reinforcement paradigm. The second experiment investigated the effect of acute venlafaxine pretreatment on the maintenance of heroin self-administration under a fixed ratio: 10 schedule, and, again, specificity of the effect was assessed in a corresponding food-reinforcement paradigm. Finally, effects of both acute and subchronic (4 week) venlafaxine treatment on maintenance of heroin self-administration under a progressive ratio schedule was investigated.

2. Materials and methods

2.1. Subjects

A total of 122 male Long Evans rats (Janvier Laboratories, Le Genest St. Isle, France), weighing 180–250 g at the start of the experiments, were used in these experiments. The animals were housed in groups of 5 in polycarbonate-cages before surgery, under the following standardized conditions: 12 h light/dark cycle (0600–1800 h light), room temperature 20–24 °C, relative humidity 35–70%, 15 air changes per hour, and air movement <0.2 m/s. Initially, the animals had free access to standard laboratory chow (ssniff R/M-Haltung, ssniff GmbH, Soest, Germany). There were at least 5 days between delivery of the animals and the onset of the experiments. All experiments were conducted during the light phase and were in accordance with international guidelines for animal care (NIH publication No. 85-23, revised 1985) and approved by the local authorities (Bezirksregierung Köln, AZ 23.203.2).

2.2. Apparatus

Six standard operant test chambers (TSE, Bad Homburg, Germany), housed in ventilated enclosures, were used. Each chamber was equipped with a stainless-steel grid floor and two levers. A house-light was positioned above the food-hopper, which was placed between the 2 levers. A yellow stimulus light was located above each lever. An infusion pump (Razel Scientific Instrument, Stamford, USA) was connected to the catheter via polyethylene tubing (PE90). The animals were allowed free movement inside the chamber by means of a liquid swivel which was connected to a pedestal on the top of the skull of the animal via a tether. One lever was designated “drug active” and scheduled pressing on this lever resulted in activation of the infusion pump and presentation of the yellow stimulus light (for the duration of the infusion). Heroin was infused in a volume of 0.25 ml/10 s, 1 s per 100 g body weight.

When behaviour was reinforced by food, scheduled pressing on the active lever resulted in presentation of the yellow stimulus light and delivery of a 45 mg food pellet (Noyes precision pellets, Bilaney, Düsseldorf, Germany) to the food hopper. The white house light was on during the whole test session. Responses on the inactive lever had no programmed consequences.

2.3. Surgery

Rats were implanted with a catheter in the right jugular vein under deep anaesthesia produced by a mixture of medetomidin (0.15 mg/kg), midazolam (2 mg/kg) and fentanyl (0.005 mg/kg), injected intramuscularly. The external jugular vein was isolated, and the catheter was inserted and secured to the vein with two sutures. The distal end of the catheter was passed subcutaneously to an exposed top portion of the skull, where it was attached to a connector pedestal anchored to the skull with three surgical screws and dental cement. Each day the catheters were flushed with 0.15 ml of a sterile saline solution containing heparin (1.25 U/ml) to prevent clotting and to maintain catheter patency. The pedestal tips were covered with a plastic cap when not in use. After surgery, the rats were allowed 5–7 days to recover.

When necessary, catheter patency was verified by infusion of 0.1 ml 1% methohexical natrium (10 mg/ml). Methohexical is an ultra-short-acting barbiturate and produces a rapid loss of muscle tone when administered intravenously. Animals with non-patent catheters were excluded from the experiments.

2.4. Procedure

2.4.1. Food deprivation schedule

In order to facilitate acquisition of operant behavior, food was restricted to 12 g/day in all rats during two to three weeks before the start of the operant sessions (De Vry et al., 1989a) in order to maintain rats at approx. 85% of their free-feeding weight. Water was available ad libitum.

2.4.2. Experiment 1.1. Daily pretreatment with venlafaxine during acquisition of heroin self-administration

Venlafaxine (10 mg/kg i.p.; $n=10$) or saline ($n=15$) was administered 30 min before each daily operant session. Individuals without prior operant experience were trained to lever-press for heroin (0.05 mg/kg/infusion) under a fixed ratio schedule of reinforcement, where the ratio requirements increased progressively during 4 consecutive 4 h daily sessions (day 1: fixed ratio:1, day 2: fixed ratio:3, day 3: fixed ratio:5, day 4: fixed ratio:10). The maximum possible infusion number was 30.

2.4.3. Experiment 1.2. Daily pretreatment with venlafaxine during acquisition of lever-pressing for food

Venlafaxine (10 mg/kg i.p.; $n=10$) or saline ($n=10$) was administered 30 min before each daily operant session. Rats without prior operant experience were trained to lever-press for food during 4 consecutive 45 min daily sessions, where the fixed ratio requirements were increased progressively as in Experiment 1.1. (consecutive ratio requirements: 1, 3, 5, and 10 for each consecutive session, respectively).

2.4.4. Experiment 2.1. Acute pretreatment with venlafaxine during maintenance of heroin self-administration under a fixed ratio schedule

Rats from Experiment 1.1 that had been pretreated with vehicle before the 4 daily sessions of heroin self-administration and that showed reliable operant responding under a fixed ratio: 10 schedule of reinforcement after continuation of training (=12 infusions/session on 3 consecutive days) were randomly allocated to one of two groups. One group ($n=6$) was injected i.p. with 10 mg/kg venlafaxine, and the other group received saline ($n=9$). Thirty min later all subjects were allowed to lever-press for heroin (0.05 mg/kg/infusion) under a fixed ratio:10 schedule during a 3.5 h test session.

2.4.5. Experiment 2.2. Acute pretreatment with venlafaxine during maintenance of lever-pressing for food under a fixed ratio schedule

Rats without previous drug history were trained to perform under a fixed ratio:10 schedule for food reward. At the start of the experiment, they were trained to lever-press under a fixed ratio:1 schedule during daily 45 min sessions. After the rats reached criterion (at least 100 pellets per session), the response requirement was progressively increased to fixed ratio:10 (consecutive ratio requirements: 3, 5, 10), and session length was reduced to 15 min. Once responding was reliable ($\geq$100 pellets/session on 3 consecutive days), animals were randomly allocated to one of two groups. One group ($n=20$) was injected i.p. with 10 mg/kg venlafaxine, and the other group received saline ($n=21$). Thirty min later all subjects were allowed to lever-press for food under a fixed ratio:10 schedule during a 15 min test session.

2.4.6. Experiment 3.1. Acute pretreatment with venlafaxine during maintenance of heroin self-administration under a progressive ratio schedule

Rats were initially trained to lever press for food under a fixed ratio:1 schedule during daily 45 min sessions. After the rats reached criterion ($\geq$100 pellets per session), the response requirement was progressively increased to fixed ratio:10, as described in the previous experiment. Rats that showed 3 days of reliable responding ($\geq$100 pellets/session) were implanted with a catheter. After 4 to 6 days of recovery, during which they were fed ad libitum, rats were retrained to self-administer heroin (0.05 mg/kg/infusion) under a progressive ratio schedule. Under this paradigm, the ratio increased during each daily session, according to the following exponential progression: 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, 402, 492, 603, 737, 901 (see Richardson and Roberts, 1996). Sessions lasted 3.5 h or until 30 min passed without response. After 4 days of training under the progressive ratio schedule, rats were randomly allocated to one of two groups and were tested 30 min after pretreatment with venlafaxine (10 mg/kg i.p.; $n=6$) or vehicle ($n=11$) during a 3.5 h session (or until 30 min passed without response).

2.4.7. Experiment 3.2. Subchronic pretreatment with venlafaxine during maintenance of heroin self-administration under a progressive ratio schedule

Rats ($n=19$) were trained to self-administer heroin (0.05 mg/kg/infusion) under a progressive ratio schedule of reinforcement, according to the same procedure as described for Experiment 3.1. During the whole 4-week period (except on the day of surgery), rats received once daily (Monday to Friday) treatment with either venlafaxine (10 mg/kg i.p.; $n=10$) or vehicle ($n=9$). After 4 days of progressive ratio training rats received venlafaxine (10 mg/kg i.p.) or vehicle and, 30 min later, were allowed to lever-press for heroin as described for the test session of Experiment 3.1.

2.5. Data analysis

The mean number (+1 S.E.M.) of reinforcers (food pellets or heroin infusions) was calculated for data presentation. Data were subjected to a one-way analysis of variance (ANOVA) with post hoc Dunnett tests where appropriate. The level of significance was set at $P<0.05$. Asterisks in the figures indicate statistically significant differences between vehicle and venlafaxine treatment.

2.6. Drugs

Venlafaxine (synthesized at Grünenthal GmbH, Aachen, Germany) and the anaesthetic mixture which consisted of medetomidin (Dormitor®, Orion Pharma, Finland), midazolam (Dormicum®Roche, Germany) and fentanyl (Synopharm,

Germany) was dissolved in saline, and administered in an application volume of 1 ml/kg body weight. Heroin (Macfarlan Smith, Edinburg, UK) was dissolved in saline.

3. Results

3.1. Experiment 1.1. Daily pretreatment with venlafaxine during acquisition of heroin self-administration

Venlafaxine produced a robust attenuation of heroin self-administration across all fixed ratio requirements tested [fixed ratio:1: $F(1,19)=10.8$, $P<0.01$; fixed ratio:3: $F(1,17)=13.7$, $P<0.01$); fixed ratio:5: $F(1,11)=6.7$, $P<0.05$; fixed ratio:10: $F(1,11)=2222.1$, $P<0.0001$; Fig. 1A]. The observed decrease in heroin intake tended to be dependent on the ratio requirement, such that the attenuation was more pronounced at higher ratio requirements [$F(3,23)=2.84$, $P=0.07$].

3.2. Experiment 1.2. Daily pretreatment with venlafaxine during acquisition of lever-pressing for food

Venlafaxine did not affect the acquisition of lever-pressing for food across all fixed ratio requirements tested (Fig. 1B).

3.3. Experiment 2.1. Acute pretreatment with venlafaxine during maintenance of heroin self-administration under a fixed ratio schedule

Acute pretreatment with venlafaxine produced a small, but statistically significant, attenuation of heroin self-administration under a fixed ratio:10 schedule of reinforcement [$F(1,13)=4.8$, $P=0.0495$; Fig. 2A].

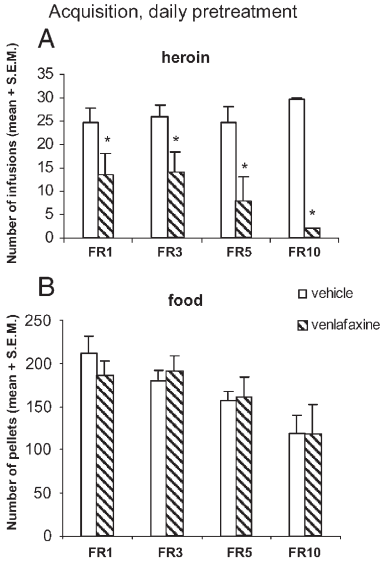

Fig. 1. Effect of daily pretreatment with venlafaxine (10 mg/kg i.p.) on the acquisition of (A) self-administration of heroin (0.05 mg/kg/infusion) and (B) lever-pressing for food under a fixed ratio (FR) schedule with increasing ratio requirements for each consecutive daily session (FR1 to FR10). Data are expressed as mean ± S.E.M. number of (A) infusions, and (B) food pellets obtained per session. * $P<0.05$ as compared to vehicle pretreatment.

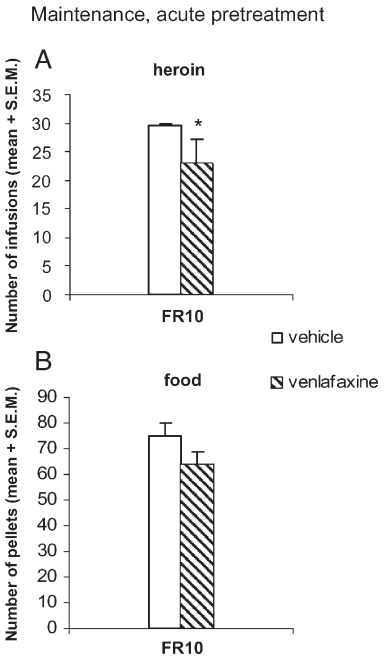

Fig. 2. Effect of acute pretreatment with venlafaxine (10 mg/kg i.p.) on the maintenance of (A) self-administration of heroin (0.05 mg/kg/infusion) and (B) lever-pressing for food under a fixed ratio (FR10) schedule. Data are expressed as mean ± S.E.M. number of (A) infusions, and (B) food pellets obtained per session. * $P<0.05$ as compared to vehicle pretreatment.

3.4. Experiment 2.2. Acute pretreatment with venlafaxine during maintenance of lever-pressing for food under a fixed ratio schedule

Acute pretreatment with venlafaxine did not affect lever-pressing for food under a fixed ratio:10 schedule of reinforcement (Fig. 2B).

3.5. Experiment 3.1. Acute pretreatment with venlafaxine during maintenance of heroin self-administration under a progressive ratio schedule

Acute pretreatment with venlafaxine did not affect responding for heroin under a progressive ratio schedule of reinforcement (Fig. 3).

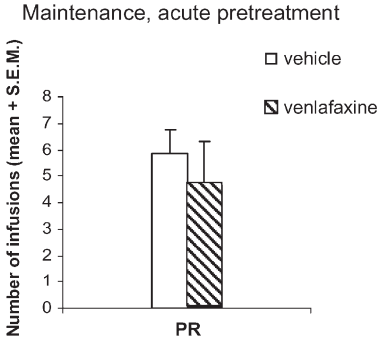

Fig. 3. Effect of acute pretreatment with venlafaxine (10 mg/kg i.p.) on responding for heroin (0.05 mg/kg/infusion) under a progressive ratio (PR) schedule. Data are expressed as mean ± S.E.M. number of infusions.

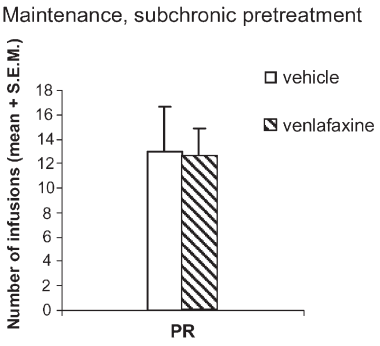

Fig. 4. Effect of subchronic pretreatment with venlafaxine (10 mg/kg i.p., once daily for 2 weeks prior to surgery and operant testing) on responding for heroin (0.05 mg/kg/infusion) under a progressive ratio (PR) schedule. Data are expressed as mean±S.E.M. number of infusions.

3.6. Experiment 3.2. Subchronic pretreatment with venlafaxine during maintenance of heroin self-administration under a progressive ratio schedule

Subchronic pretreatment with venlafaxine did not affect responding for heroin under a progressive ratio schedule of reinforcement (Fig. 4).

4. Discussion

While being of broad clinical utility, opioid analgesics carry the risk of dependence development and abuse. Therefore, when considering co-administration of opioids with antidepressants for the treatment of chronic pain, information about the abuse liability of the drug combination may be clinically relevant. There are a number of animal studies suggesting that repeated administration of antidepressants can enhance the behavioural and neurochemical effects of psychostimulants and direct dopamine agonists (Papp et al., 1992; Stewart and Rajabi, 1996; Collu et al., 1997; D'Aquila et al., 2000, 2003). Moreover, Subhan et al. (2000b) have shown that fluoxetine enhances the rewarding effect of morphine as assessed in a conditioned place preference paradigm. There are also anecdotal clinical reports of abuse of antidepressant drugs (e.g. fluoxetine: Pagliaro and Pagliaro, 1993; amitriptyline: Delisle, 1991). On the other hand, various antidepressants were found to reduce the intake of psychostimulants and sedatives in animals and man (see Introduction). To our knowledge, the present study is the first that investigated the influence of an antidepressant on opioid self-administration.

The serotonin/noradrenaline reuptake inhibitor venlafaxine was selected for this study for several reasons. First, the compound is a clinically effective antidepressant with analgesic properties (for review, see Briley, 2004). In rat experiments, the dose used in the present study (10 mg/kg i.p.) was shown to have moderate, but significant analgesic effects in chronic pain models (e.g. Iyengar et al., 2004; own unpublished results). In addition, venlafaxine was found to attenuate the reinstating effect of morphine in a conditioned place preference paradigm (Lu et al., 2001). Subhan et al. (2000a) showed that venlafaxine, at the dose and application conditions used in the present study (i.e., 10 mg/kg i.p., injected 30 min prior to testing), failed to produce either conditioned place preference or aversion. This suggests that the compound is "motivationally neutral", and that a potential attenuation of heroin self-administration does not result from a simple additive effect of combining a rewarding and an aversive drug effect. Furthermore, it was reported that venlafaxine attenuates subjective effects of cocaine in humans (Foltin et al., 2003). Finally, since it remains unclear from previous studies whether serotonin or noradrenaline reuptake inhibition is more relevant for affecting drug intake (see Introduction), we selected a compound which combines both mechanisms of action.

The present study showed that venlafaxine had an attenuating effect on the acquisition of heroin self-administration, as assessed in a fixed ratio paradigm. The effect of venlafaxine on heroin intake was considered to be behaviourally specific, as the compound did not affect acquisition of lever-pressing for food in a similar paradigm. However, once behaviour was well established under a fixed ratio:10 schedule, the same dose of venlafaxine only had a very small (albeit significant) effect on responding for heroin (while having no effect on responding for food). When using individual doses of a rewarding drug, decreases in drug intake could in principle be due to either an increase or a decrease in the rewarding effects of the drug. To circumvent this potential uncertainty, we also examined the effects of venlafaxine on heroin self-administration under a progressive ratio schedule of reinforcement. Here, acute treatment with venlafaxine had no influence on lever-pressing for heroin. In the progressive ratio experiment with acute pretreatment rats showed relatively low break point values; therefore, there might have been the potential risk of floor effects interfering with possible venlafaxine effects on heroin self-administration. However, in the subchronic pretreatment experiment, break point values were higher, and still no effect was seen. Thus, interference by floor effects does not appear to be an issue for the acute experiment. Since clinical experience (e.g., Morishita and Arita, 2003), as well as preclinical data (e.g., Lu et al., 2001), indicates that the effect of antidepressants can increase with repeated administration, it was tested in a further experiment whether subchronic pretreatment with venlafaxine would lead to a more pronounced effect on the maintenance of heroin self-administration. Again, as assessed in the same progressive ratio paradigm, repeated administration of venlafaxine failed to affect responding for heroin. Taken together, these results suggest that venlafaxine attenuates acquisition, but not (or only marginally) maintenance, of heroin self-administration.

Although it remains unclear why venlafaxine differentially affected both phases of heroin self-administration, it can be hypothesized that it relates to differential effects of the compound on the underlying motivation to self-administer heroin during both experimental phases. It can be assumed that self-administration of heroin during acquisition mainly results from the positive reinforcing (most likely ´euphorigenic´, or rewarding) effects of the drug (for discussion, see De Vry et al., 1989b); on the other hand, it can be speculated that during maintenance, it might also have resulted (at least in part) from the negative reinforcing effects of heroin (i.e., suppression of

withdrawal symptoms resulting from the development of physical dependence induced by repeated administration of heroin). According to this hypothesis, venlafaxine is able to attenuate the positive reinforcing effects of heroin, and therefore, attenuates acquisition of self-administration. If, on the other hand, physical dependence contributed to the maintenance of heroin self-administration under the present experimental conditions, and venlavaxine has no effect on development or expression of physical dependence, this speculation could explain why venlafaxine had no (or only a minor) effect during the maintenance phase.

In operant paradigms, there is always the underlying concern that drug-induced changes in activity levels (in particular inhibition of activity) may affect the outcome of the experiments. In the present study we recorded responses on the inactive lever but have omitted that data because there were always very few responses on the inactive lever, thus making this measure unsuitable to detect a potential unspecific reduction in activity. In the above-mentioned unpublished CPP studies we found that venlafaxine (10 mg/kg i.p.), heroin (0.5 mg/kg i.p.) as well as the combination of both reduced locomotor activity only very slightly.

Opioids produce their positive reinforcing or rewarding effect predominantly via disinhibition of dopaminergic neurons in the ventral tegmental area (VTA), resulting in increased extracellular levels of dopamine in the nucleus accumbens (Johnson and North, 1992). Both the serotonergic raphe nuclei and the noradrenergic locus coeruleus project to the VTA (Hervé et al., 1987; Phillipson, 1979), and an increase of extracellular levels of serotonin and noradrenaline can inhibit dopaminergic neurons in the VTA via 5-$HT_{1B/1C}$ and/or 5-$HT_{2B/2C}$ receptors (Prisco et al., 1994; Prisco and Esposito, 1995), and adrenergic α_1 receptors (Paladini and Williams, 2004), respectively. Thus, by elevating extracellular levels of serotonin and/or noradrenaline, venlafaxine may enhance the inhibitory influence of these transmitters on dopamine neurons and consequently counteract or attenuate the stimulatory effects of heroin on these neurons. If venlafaxine counteracts the heroin-induced activation of dopamine release in the nucleus accumbens, this would reduce the rewarding effect of heroin, resulting in an attenuated acquisition of self-administration. This assumption is indirectly supported by the finding that the selective serotonin reuptake inhibitor fluoxetine reduces brain stimulation reward (Lee and Kornetsky, 1998; Harrison and Markou, 2001). We are currently testing the hypothesis that venlafaxine attenuates the rewarding effect of heroin, as assessed in a conditioned place preference procedure.

As it may seem paradoxical that a compound which reverses deficits in the ability to experience pleasure (anhedonia) in depressed patients also is able to attenuate the rewarding effect of heroin, it is hypothesized that venlafaxine ´stabilizes´ the function of the brain reward system. According to this hypothesis, the direction of effect of venlafaxine would depend on the state of the reward system. When the function of this system is impaired, venlafaxine is hypothesized to enhance its reactivity to rewarding stimuli. On the other hand, when the system is (over)activated by external stimuli (e.g., heroin or electrical stimulation), the compound is expected to dampen the activity of the system. Obviously, since the responding for food was not affected, this latter assumption can only be applied to excessive and artificial (i.e. non-physiological) activation of the reward system.

In conclusion, venlafaxine was found to attenuate the acquisiton of intravenous self-administration of heroin in a behaviourally specific manner; while having very little effect on responding for heroin in the maintenance phase. Thus, venlafaxine appears to moderately attenuate the abuse liability of heroin. On the other hand, it should be noted that the study did not find any indication for an enhanced intake of heroin. Therefore, it can be postulated that adding an antidepressant drug, such as venlafaxine, to an opioid for the treatment of pain would not be expected to enhance the abuse liability of the opioid (if anything, the combination might have a reduced abuse liability). It should be kept in mind that heroin is a strong opioid with very high abuse liability. If antidepressants like venlafaxine exert only a moderate modulating effect on the reinforcing/rewarding effect of opioids, the effects of heroin may be too potent to obtain clear and consistent effects of venlafaxine across different experimental conditions.

References

Baker, D.A., Tran-Nguyen, T.L., Fuchs, R.A., Neisewander, J.L., 2001. Influence of individual differences and chronic fluoxetine treatment on cocaine-seeking behavior in rats. Psychopharmacology 155, 18–26.

Briley, M., 2004. Clinical experience with dual action antidepressants in different chronic pain syndromes. Hum. Psychopharmacol. Clin. Exp. 19, S21–S25.

Carroll, M.E., Lac, S.T., Asencio, M., Kragh, R., 1990. Fluoxetine reduces intravenous self-administration in rats. Pharmacol. Biochem. Behav. 35, 237–244.

Collu, M., Poggiu, A.S., Devoto, P., Serra, G., 1997. Behavioural sensitization of mesolimbic dopamine D2 receptors in chronic fluoxetine-treated rats. Eur. J. Pharmacol. 322, 123–127.

D'Aquila, P.S., Collu, M., Devoto, P., Serra, G., 2000. Chronic lithium chloride fails to prevent imipramine-induced sensitization to the dopamine D(2)-like receptor agonist quinpirole. Eur. J. Pharmacol. 395, 157–160.

D'Aquila, P.S., Peana, A.T., Panin, F., Grixoni, C., Cossu, M., Serra, G., 2003. Reversal of antidepressant-induced dopaminergic behavioural supersensitivity after long-term chronic imipramine withdrawal. Eur. J. Pharmacol. 458, 129–134.

Delisle, J.D., 1991. A case of amitriptyline abuse. Am. J. Psychiatry 148, 297–298.

De Vry, J., Donselaar, I., van Ree, J.M., 1989a. Food deprivation and acquisition of intravenous cocaine self-administration in rats: effect of naltrexone and haloperidol. J. Pharmacol. Exp. Ther. 251, 735–740.

De Vry, J., Donselaar, I., van Ree, J.M., 1989b. Intraventricular self-administration of heroin in the rat: reward seems dissociated from analgesia and physical dependence. Eur. J. Pharmacol. 161, 19–25.

Foltin, R.W., Ward, A.S., Collins, E.D., Haney, M., Hart, C.L., Fischman, M.W., 2003. The effects of venlafaxine on the subjective, reinforcing, and cardiovascular effects of cocaine in opioid-dependent and non-opioid-dependent humans. Exp. Clin. Psychopharmacol. 11, 123–130.

Harrison, A.A., Markou, A., 2001. Serotonergic manipulations both potentiate and reduce brain stimulation reward in rats: involvement of serotonin-1A receptors. J. Pharmacol. Exp. Ther. 297, 316–325.

Hervé, D., Pickel, V.M., Joh, T.H., Beaudet, A., 1987. Serotonin axon terminals in the ventral tegmental area of the rat: fine structure and synaptic input to dopaminergic neurones. Brain Res. 435, 71–83.

Iyengar, S., Webster, A.A., Hemrick-Luecke, S.K., Xu, J.Y., Simmons, R.M.A., 2004. Efficacy of duloxetine, a potent and balanced serotonin–norepinephrine reuptake inhibitor in persistent pain models in rats. J. Pharmacol. Exp. Ther. 311, 576–584.

Johnson, S.W., North, R.A., 1992. Opioids excite dopamine neurons by polarization of local interneurons. J. Neurosci. 12, 483–488.

Landabaso, M.A., Iraurgi, I., Jimenez-Lerma, J.M., Sanz, J., Fernandez, C., Araluce, K., Calle, R., Gutierrez-Fraile, M., 1998. A randomized trial of adding fluoxetine to a naltrexone treatment programme for heroin addicts. Addiction 93, 739–744.

Le, A.D., Poulos, C.X., Harding, S., Watchus, J., Juzytsch, W., Shaham, Y., 1999. Effects of naltrexone and fluoxetine on alcohol self-administration and reinstatement of alcohol seeking induced by priming injections of alcohol and exposure to stress. Neuropsychopharmacology 21, 435–444.

Lee, K., Kornetsky, C., 1998. Acute and chronic fluoxetine treatment decreases the sensitivity of rats to rewarding brain stimulation. Pharmacol. Biochem. Behav. 60, 539–544.

Lu, L., Su, W.J., Yue, W., Ge, X., Su, F., Pei, G., Ma, L., 2001. Attenuation of morphine dependence and withdrawal in rats by venlafaxine, a serotonin and noradrenaline reuptake inhibitor. Life Sci. 69, 37–46.

Lyness, W.H., Smith, F.L., 1992. Influence of dopaminergic and serotonergic neurons on intravenous ethanol self-administration in the rat. Pharmacol. Biochem. Behav. 42, 187–192.

Malseed, R.T., Goldstein, F.J., 1979. Enhancement of morphine analgesia by tricyclic antidepressants. Neuropharmacology 18, 827–829.

Martin, W.R., 1983. Pharmacology of opioids. Pharmacol. Rev. 35, 283–323.

Maurel, S., De Vry, J., Schreiber, R., 1999a. 5-HT receptor ligands differentially affect operant oral self-administration of ethanol in the rat. Eur. J. Pharmacol. 370, 217–223.

Maurel, S., De Vry, J., Schreiber, R., 1999b. Comparison of the effects of the selective serotonin-reuptake inhibitors fluoxetine, paroxetine, citalopram and fluvoxamine in alcohol-preferring cAA rats. Alcohol 17, 195–201.

Mochizucki, D., 2004. Serotonin and noradrenaline reuptake inhibitors in animal models of pain. Hum. Psychopharmacol. Clin. Exp. 19, S15–S19.

Morishita, S., Arita, S., 2003. Differential period of onset of action of fluvoxamine, paroxetine and milnacipran for depression. Hum. Psychopharmacol. 18, 479–482.

Naranjo, C.A., Poulos, C.X., Bremner, K.E., Lanctot, K.L., 1994. Fluoxetine attenuates alcohol intake and desire to drink. Int. Clin. Psychopharmacol. 9, 163–172.

Pagliaro, L.A., Pagliaro, A.M., 1898. Fluoxetine abuse by an intravenous drug user. Am. J. Psychiatry 150.

Paladini, C.A., Williams, J.T., 2004. Noradrenergic inhibition of midbrain dopamine neurons. J. Neurosci. 24, 4568–4575.

Panerai, A.E., Bianchi, M., Sacerdote, P., Ripamonti, C., Ventafridda, V., De Conno, F., 1991. Antidepressants in cancer pain. J. Palliat. Care 7, 42–44.

Papp, M., Muscat, R., Willner, P., 1992. Additive effects of chronic treatment with antidepressant drugs and intermittent treatment with a dopamine agonist. Eur. Neuropsychopharmacol. 2, 121–125.

Phillipson, O.T., 1979. Afferent projections to the ventral tegmental area of Tsai and interfascicular nucleus: a horseradish peroxidase study in the rat. J. Comp. Neurol. 187, 117–143.

Prisco, S., Esposito, E., 1995. Differential effects of acute and chronic fluoxetine administration on the sponteneous activity of dopaminergic neurones in the ventral tegmental area. Br. J. Pharmacol. 116, 1923–1931.

Prisco, S., Pagannone, S., Esposito, E., 1994. Serotonin-dopamine interaction in the rat ventral tegmental area: an electrophysiological study in vivo. J. Pharmacol. Exp. Ther. 271, 83–90.

Rauhut, A.S., Mullins, S.N., Dwoskin, L.P., Bardo, M.T., 2002. Reboxetine: attenuation of intravenous nicotine self-administration in rats. J. Pharmacol. Exp. Ther. 303, 664–672.

Richardson, N.R., Roberts, D.C.S., 1996. Progressive ratio schedules in drug self-administration studies inrats: a method to evaluate reinforcing efficacy. J. Neurosci. Methods 66, 1–11.

Stein, C., 1999. Opioids in Pain Control. Basic and Clinical Aspects. Cambridge University Press, Cambridge, UK.

Stewart, J., Rajabi, H., 1996. Initial increases in extracellular dopamine in the ventral tegmental area provide a mechanism for the development of desipramine-induced sensitization within the midbrain dopamine system. Synapse 23, 258–264.

Subhan, F., Deslandes, P.N., Pache, D.M., Sewell, R.D.E., 2000a. Do antidepressants affect motivation in conditioned place preference? Eur. J. Pharmacol. 408, 257–263.

Subhan, F., Pache, D.M., Sewell, R.D.E., 2000b. Potentiation of opioid-induced place preference by the selective serotonin reuptake inhibitor fluoxetine. Eur. J. Pharmacol. 390, 137–143.

Tzschentke, T.M., 2002. NA and 5-HT reuptake inhibitors and α2 agonists. In: Buschmann, H., et al. (Ed.), Analgesics — From chemistry and pharmacology to clinical application. Wiley-VCH, Weinheim, Germany, pp. 265–284.

Yu, D.S., Smith, F.L., Smith, D.G., Lyness, W.H., 1986. Fluoxetine-induced attenuation of amphetamine self-administration in rats. Life Sci. 39, 1383–1388.