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Fluoxetine-Induced Conditioned Place Preference: A Preliminary Study

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Fluoxetine, a selective serotonin (5-HT) uptake inhibitor, is now one of the most commonly prescribed antidepressant drugs (ADs); it is also used to treat some anxiety and eating disorders as well as drug abuse (Messiha, 1993), though the antidepressant effects of fluoxetine (FLX) do not completely account for its popularity. Recently, we have demonstrated that chronic administration of FLX shared with most ADs the ability to elicit behavioural sensitisation of D_2/D_3 receptors in the mesolimbic DA system (Serra et al., 1992). Thus, chronic FLX, as well as other ADs, potentiates quinpirole-induced locomotor hyperactivity but not stereotyped responses (Collu et al., in preparation). Moreover, both FLX and imipramine, administered chronically, elicited conditioned place preference (CPP) for a single dose of cocaine ineffective in control rats (Collu et al., 1994, 1996). Finally, further evidence for the increased sensitivity of DA receptors following FLX administration has been recently reported by Simon and Appel (1995), who have demonstrated that FLX potentiated the discriminability of 2.5 mg/kg cocaine in drug discrimination experiments. Taken together, these observations suggest that FLX potentiates DAergic transmission particularly in the mesolimbic system, which is strongly involved in mediating the rewarding properties of both physiological and external stimuli (Fibiger, 1993). Moreover, although there are conflicting results on this issue, it has been suggested that FLX reduces cocaine and amphetamine self-administration in rats by increasing the reinforcing effects of these substances (Carrol et al., 1990; Richardson and Roberts, 1991). However, the observation that FLX partially substitutes for cocaine as a discriminative stimulus in rats (Winters and Sliter, 1989) supports the hypothesis that FLX may have reinforcing effects by itself (Carrol et al., 1990). To test this hypothesis, we have studied the effect of FLX treatment on CPP paradigm in rats, a behavioural model widely used to test reinforcing properties of drugs.

Subjects were 68 male Sprague-Dawley rats (Charles River, Italy) weighing 125–150 g at the beginning of the experiment, kept four per cage under standard conditions (12-h light/dark cycle; temperature 22 ± 2°C) and given free access to food and water. CPP was assessed in eight identical Plexiglas shuttle-boxes (80 × 25 × 35 cm). Each box was divided into two compartments identical in size, separated by a removable guillotine door and differing in wall pattern and floor texture (solid brown vs. black and white strip walls and wire mesh vs. parallel bars, respectively). Conditioning and testing procedures were carried out under dim illumination (60 W) with a white noise generator. A videocamera and VCR were used to record pretest and test sessions. During the preconditioning phase (3 days), rats were placed into one of the compartments (start-side, S-side) and allowed to explore both compartments for 15 min. The choice of the S-side was counterbalanced across both animals and different box patterns and floor texture, remaining the same for each animal every day. On the third day, the time spent in one compartment was recorded. The conditioning phase (10 days) consisted of twenty 30-min sessions during which the animals were confined to one compartment by blocking the guillotine door. Saline and drug pairings occurred on the same day with 6 hr intervals. In the morning, a saline or vehicle injection was paired to the S-side, while in the evening a drug injection was paired to the non-start-side (NS-side). A control group received saline or vehicle in both compartments. The postconditioning test occurred on the test day, 36 hr after the final trial, by placing the rats in the S-side with access to explore freely for 15 min. All videotapes were later analysed without knowledge of each animal's treatment and the time spent in each compartment was recorded using hand-held stop-watches. Three groups of rats were as follows: group 1 received vehicle paired with both sides (n = 30) 1 h before the conditioning sessions; group 2 received vehicle (S-side) or FLX

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(NS-side; 1, 2.5 and 5 mg/kg) 1 h before conditioning. Fluoxetine HCl (in the form of the commercially available oral solution, Prozac®, Ely-Lilly) was diluted in distilled water and administered at the volume of 5 ml/kg by intragastric gavage (pediatric feeding tube, Medico Plast, Germany). The control group received 5 ml/kg vehicle (0.3 mg benzoic acid, 375 mg saccarose, 125 mg glycerine, 1.3 mg mint flavour in 5 ml) intragastrically.

As shown in Figure 1, the time spent in the drug-paired (NS) side by 2.5 mg/kg FLX-treated rats was significantly higher than that spent by animals receiving 1 or 5 mg/kg FLX as well as by vehicle-treated rats [$F_{(3,64)} = 8.32$; $P < 0.01$]. This finding indicates that FLX can elicit CPP in rats, suggesting that besides its ability to potentiate the rewarding effects of cocaine (Collu et al., 1996) it possesses reinforcing properties by itself. The dose-response curve of FLX-induced CPP is quite similar to that observed with amphetamine and 8-OH-DPAT (Bardo et al., 1995; Papp and Willner, 1991). It is likely that FLX at high doses could possess aversive effects which counterbalance its reinforcing properties. Indeed, as observed with high doses of 8-OH-DPAT, the high dosage of FLX could induce some components of the 5-HT syndrome (Sternbach, 1991).

Much experimental evidence has been accumulated on the important role of the mesolimbic dopamine system in controlling rewarded behaviour (Fibiger, 1993). Accordingly, the FLX ability to induce CPP could be related to its effects on the mesolimbic DA receptors mediating locomotor activity and reward, but seems to stimulate the neuronal activity of VTA cells (Ashby et al., 1995). Several behavioural studies suggest that a reduction of serotonergic activity may play an important role in activating mesolimbic DA neurons involved in reward (Fletcher et al., 1995). CPP induced by selective 5-HT_{1A} receptor agonists has been ascribed to the inhibition of 5-HT transmission due to stimulation of the raphe somatodendritic autoreceptors, which in turn results in the release of mesolimbic DA transmission from the inhibitory control of 5-HT (Arborelius et al., 1993; Prisco et al., 1994). Consistent with this hypothesis, CPP induced by selective agonist of 5-HT_{1A} receptor, 8-OH-DPAT, is reversed by DA antagonists (Papp and Willner, 1991). Thus, it may be suggested that a small dose of FLX indirectly stimulates 5-HT_{1A} somatodendritic receptors in the raphe nuclei (Blier and de Montigny, 1994), resulting in the activation of the mesolimbic DA system. On the other hand, the failure of high doses of FLX to induce CPP could be explained by stimulation of postsynaptic 5-HT receptors which counterbalance the effect on 5-HT_{1A} autoreceptor activation. However, it must be pointed out that interaction between DA and 5-HT is complex mainly because of the large number of 5-HT receptor subtypes whose functional role still remains to be clarified. Further work will therefore be needed to assess the neurochemical mechanisms by which FLX induces CPP. Whatever the mechanism involved, the finding that FLX elicits CPP in rats provides a convincing explanation for its ability to decrease cocaine and amphetamine self-administration in rats (Carroll et al., 1990), as well as for its efficacy in improving cocaine outcome and craving as recently observed in humans (Washburn et al., 1995; Batki et al., 1995). Finally, our results raise the question as to whether FLX produces rewarding effects in humans. However, further studies using different animal models will be needed to address this important issue.

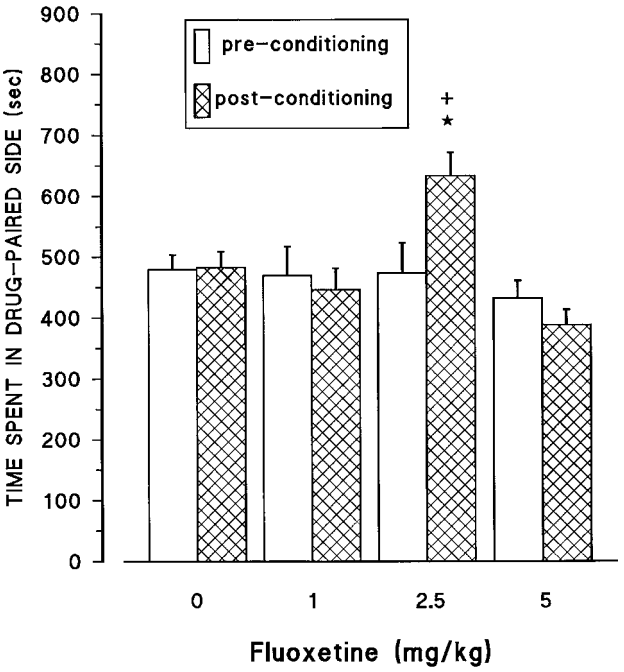

Fig. 1. Effects of vehicle and fluoxetine on the time spent in the drug-paired (non-start) compartment before and after conditioning. Values represent the mean ± S.E. of vehicle- (n = 30, pooled) or fluoxetine-treated (1, 2.5 and 5 mg/kg: n = 12, 14 and 12 animals, respectively) rats. Since following an initial ANOVA, the preconditioning values for the time spent on the non-start side did not differ between groups [$F_{(3,64)} = 0.26$, not significant); one-way ANOVA between groups has been performed on postconditioning values for the time spent on the non-start side (see text). *$P < 0.01$ vs. all other groups (Newman-Keuls test) and †$P < 0.05$ vs. preconditioning values of FLX 2.5 mg/kg (paired Student's t test).

REFERENCES

Arborelius, L., Chergui, K., Murase, S., Nomikos, G.G., Höök, B.B., Chouvet, G., Hacksell, U., and Svensson, T.H. (1993) The 5-HT1A receptor selective ligands, (R)-8-OH-DPAT and (S)-UH-301, differentially affect the activity of midbrain dopamine neurons. Naunyn-Schmiedeberg's Arch. Pharmacol., 347:353–362.

Ashby, C.R., Jr., Minabe, Y., Ramachandran, C., Strecker, R.E., and Dewey, S.L. (1995) The effect of acute and chronic administration of (±) FLX on spontaneously active midbrain dopamine neurons: An in vivo electrophysiological study. Soc. Neurosci. Abstr., Vol. 21, Part 1:153.2.

Bardo, M.T., Rowlett, J.K., and Harris, M.J. (1995) Conditioned place preference using opiate and stimulant drugs: A meta-analysis. Neurosci. Biobehav. Rev., 19:39–51.

Batki, S.L., Washburn, A., Manfredi, L., Murphy, J., Herbst, M.D.,

Delucchi, K., Jones, T., Nanda, N., Jacob III, P., and Jones, R.T. (1995) Fluoxetine in primary and secondary cocaine dependence: Outcome using quantitative benzoylecgonine concentration. In: NIDA Res. Monograph 153. Problems of Drug Dependence, Vol. II, p. 140.

Blier, P., and deMontigny, C. (1994) Current advances and trends in the treatment of depression. TIPS 15:220–226.

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

Collu, M., Pani, L., Gessa, G.L., and Serra, G. (1994) Chronic imipramine potentiates cocaine-induced CPP. Polish J. Pharmacol., 46:315–316.

Collu, M., Poggiu, A.S., and Serra, G. (1996) Antidepressants sensitize the dopamine mesolimbic system mediating reward. Behav. Pharmacol. 7 (Suppl. 1):18–19.

Fibiger, H.C. (1993) Mesolimbic dopamine: An analysis of its role in motivated behaviour. Semin. Neurosci., 5:321–327.

Fletcher, P.J., Tampakeras, M., and Yeomans, J.S. (1995) Median raphe injections of 8-OH-DPAT lower frequency thresholds for lateral hypothalamic self-stimulation. Pharmacol. Biochem. Behav., 52:65–71.

Messiha, F.S. (1993) Fluoxetine: A spectrum of clinical applications and postulates of underlying mechanisms. Neurosci. Biobehav. Rev., 17:385–396.

Papp, M., and Willner, P. (1991) 8-OH-DPAT-induced place preference and place aversion: Effects of PCPA and dopamine antagonists. Psychopharmacology, 103:99–102.

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

Richardson, N.R., and Roberts, D.C.S. (1991) Fluoxetine pretreatment reduces breaking points on a progressive ratio schedule reinforced by intravenous cocaine self-administration. Life Sci., 49:833–840.

Serra, G., Collu, M., D'Aquila, P.S., and Gessa, G.L. (1992) Role of the mesolimbic dopamine system in the mechanism of action of antidepressants. Pharmacol. Toxicol., 71 (Suppl. 1):72–85.

Simon, B.B., and Appel, J.B. (1995) Dopaminergic and serotonergic properties of FLX. Soc. Neurosci. Abstr., Vol. 21, Part 2:445.2.

Sternbach, H. (1991) The serotonin syndrome. Am. J. Psichiatry, 148:705–713.

Washburn, A.M., Batki, S.L., Delucchi, K., Murphy, J., Jones, T.A., and Nanda, N. (1995) Predictors of outcome in a clinical trial of FLX treatment of primary cocaine dependence. In: NIDA Res. Monograph 153. Problems of Drug dependence, Vol. II, p. 139.

Winters, T.A., and Slifer, B.L. (1989) Discriminative stimulus properties of cocaine. Is there mediation by serotonin? FASEB J. 3:295.