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The effect of chronic administration of nefazodone on 8-OH-DPAT-induced hyperphagia in fasted rats

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We have previously reported that the suppressant effect of the 5-HT_{1A} receptor agonist 8-OH-DPAT on feeding in food-deprived rats or non-deprived rats given access to palatable food (see Ebenezer *et al*., 2003) is abolished following chronic treatment with antidepressants, such as fluoxetine and sertraline, that selectively inhibit the reuptake of 5-HT (Tite *et al.*, 2003, Burki *et al*., 2005) and have suggested that this effect is due to desensitisation of central 5-HT_{1A} receptors. The present study was undertaken to extend these observations and investigate the effect of chronic administration of the antidepressant drug nefazodone on 8-OH-DPAT-induced hypophagia in rats. Nefazodone is a serotonin antagonist and reuptake inhibitor (SARI). The principle antidepressant mechanism of SARIs is to potently inhibit 5-HT_{2A} receptors combined with a less potent blockade of 5-HT and noradrenaline re-uptake (Davis et al., 1997). Male Wistar rats (b.wt. 215 – 310 g; n=12) were randomly divided into 2 equal groups and were deprived of food in their home cages for 22 h each day. Rats in Group 1 (Control Group) were injected i.p. once daily with physiological saline solution for 27 days, while rats in Group 2 (Treatment Group) were injected i.p. once daily with nefazodone (60 mg kg^{-1}). On day 28 the animals in both groups were injected s.c. with 8-OH-DPAT (100 μg kg^{-1}) and placed singly in experimental cages with free access to food and water (Ebenezer **et al**., 2003) and food intake measured at 30 min. On day 27 a similar experimental protocol as described for day 28 was used except that the animals in both groups were injected with saline instead of 8-OH-DPAT in order to establish a control feeding baseline. The results were analysed by 2-way ANOVA and *post-hoc* Dunnett's test. The mean ± s.e.mean food intake per 100g body weight for the rats chronically treated with saline (Group 1) was 2.5 ± 0.2 g after saline and 0.7 ± 0.3 g ($P<0.01$) after 8-OH-DPAT. The mean ± s.e.mean food intake per 100 g body weight for the rats chronically treated with nefazodone (Group 2) was 2.2 ± 0.1 g after saline and 1.6 ± 0.2 g ($P<0.05$) after 8-OH-DPAT. ANOVA revealed that there was a significant interaction between the two groups of rats and their responses to saline and 8-OH-DPAT ($F_{(1,10)} = 8.7605$, $P<0.01$), and post-hoc tests indicate that chronic treatment with nefazodone (60 mg kg^{-1}) significantly reverses the hypophagic effect of 8-OH-DPAT in fasted rats ($P<0.05$). These findings extend previous observations and show that chronic administration of a SARI reverses the inhibitory effects of 8-OH-DPAT in fasted rats presumable by desensitising central 5-HT_{1A} receptors (see Tite *et al*., 2004). Thus, these data, taken together with those obtained previously (Tite *et al*., 2004, Burki *et al*, 2005, Burki *et al*., 2009), suggest that the method described here may be useful as anl *in vivo* test to assess psychoactive compounds for potential antidepressant activity.

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