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 NA 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 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 an in vivo test to assess psychoactive compounds for potential antidepressant activity.