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CCK_B receptor antagonism attenuates naloxone-induced morphine withdrawal conditioned place aversion and escape behaviour

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It has been proposed that cholecystokinin (CCK) neurones are implicated in anxiety and may be activated in abnormal (anxiogenic) circumstances (Hughes et al., 1990). Moreover, CCK_B antagonists may be useful in anxiety treatment and also in the management of withdrawal associated with drugs of abuse such as cocaine, nicotine and alcohol (Costall et al., 1991). It has since been reported that blockade of CCK_B receptors by CI 988 potentiates both the analgesic (Valverde et al., 1994) and rewarding effects of morphine and RB 101, a mixed inhibitor of enkephalin catabolism (Valverde et al., 1996). Thus, we have tested the effect of CI 988 on naloxone (NLX)-precipitated morphine withdrawal place aversion in rats. A three compartment apparatus as described earlier (Hutcheson et al., 1995) was used for the study. Rats were initially assessed for compartment occupancy in the apparatus over a 20 min period (pre-test time) and then placed on a standard morphine dependence-inducing dosing protocol. This was initiated at a dose of 8 mg/kg (twice daily i.p.) increasing to 45 mg/kg (twice daily) over a period of 6 days (Hutcheson et al., 1995). On day 5 or 6 of the dependence schedule, animals were dosed with either NLX (0.25 mg/kg s.c.) and paired with their most preferred compartment, or saline and paired with their least preferred compartment. This procedure was counter-balanced such that half the animals received saline on day 5 and NLX on day 6 and then the remaining half NLX on day 5 and saline on day 6. The day after pairing, compartment occupancy was evaluated over a 20 min test period (post-test time). Aversion times were calculated from (post-test) - (pre-test) times. As shown in table 1, animals that underwent morphine withdrawal in their initially preferred compartment, displayed significant compartment aversion (i.e. minus values) compared to controls. Administration of the CCK_B antagonist, CI 988 (3 mg/kg and 5 mg/kg) 30 min before NLX withdrawal conditioning attenuated withdrawal aversion times. This was statistically significant at the 5 mg/kg dose level compared to the morphine-only group. The escape behaviour (as measured by the incidence of jumps) was also significantly attenuated after both 3 and 5mg/kg CI 988 treatment (table 1).

These results suggest that CI 988 may be a useful agent in reducing the severity of morphine abstinence syndrome, possibly through a mechanism involving increased endogenous enkephalin levels (Maldonado et al., 1995). This increase in enkephalin may subsequently displace the binding of NLX (a competitive opioid antagonist) to opioid receptors thus reducing the aversive effects of NLX induced morphine withdrawal.

Table 1: Effect of CI 988 on NLX-induced morphine (MP) withdrawal place aversion and escape behaviour. Results are expressed as mean ± s.e.m. (n = 8-14).

TREATMENT GROUPS	AVERSION TIME (s)	NO. OF JUMPS
SAL + NLX	-111 ± 55	0.0 ± 0.0
MP + NLX	-362 ± 69	7.6 ± 1.6
MP + CI 988 (3 mg/kg) + NLX	-211 ± 80	3.5 ± 1.4*
MP + CI 988 (5 mg/kg) + NLX	-188 ± 47**	4.0 ± 0.62*

Values are significantly different for aversion time ($F_{3,42} = 4.592$, **$P<0.01$) and jumps ($F_{3,41} = 3.773$, *$P<0.05$) as compared to morphine group (one- way ANOVA with Dunnett's post hoc analysis)

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