6-hydroxydopamine (Melamed et al 1980). The explanation has been proposed that when tyrosine hydroxylase is activated, its affinity for the cofactor, tetrahydrobiopterin, is increased so that the enzyme is no longer limited by tetrahydrobiopterin concentration but instead becomes limited by L-tyrosine availability (Sved & Fernstrom 1981). In these circumstances, exogenous tyrosine can increase dopamine synthesis. Our findings extend the list of pharmacological models in which this effect of tyrosine has been demonstrated.

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Suppression of ethanol consumption by MET-enkephalin in rats

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Recent experimental studies on the interactions between opiates and ethanol have been focused on the ability of the acute effects of opiate agonists to reduce the volitional consumption of ethanol in rats (Sinclair et al 1973; Ho et al 1976, 1980) and in hamsters (Ross et al 1976) whereas ethanol consumption is increased following opiate withdrawal (Ho 1980). With the identification of the opiate receptors and the detection and characterization of the endogenous opiate-like peptides, the enkephalins and endorphins (Hughes et al 1975; Goldstein 1973), it is reasonable to suspect that some of these endogenous opioids may alter ethanol consumption in a way similar to the opiates. We now present some preliminary data to show that met-enkephalin injected into the rat lateral ventricle under conscious states, significantly suppressed the volitional consumption of ethanol and the effect was partially reversed by naltrexone.

Adult male Long-Evans hooded rats, 200 to 250 g, were kept in individual cages at a constant temperature (20 °C) and humidified room. Two graduated glass drinking tubes (Richter type, Kimax Instrument Co.) were fitted on to the outside of each cage, one filled with water and the other with 5% v/v ethanol (diluted from 95% ethanol with deionized water). The rats were put on a training schedule and were allowed 2 h (from 1 to 3 p.m.) for fluids (water and ethanol) and food ingestion each day. After a stable base-line of consumption was established, the animals were anaesthetized with sodium pentobarbitone (35 mg kg^{-1} i.p.) supplemented by ether during surgery when necessary and were stereotactically implanted in the horn of the lateral ventricle with permanent hollow stainless steel cannulae 5 mm long. Coordinates employed were from bregma 0·6 P., 1·8 L and from the surface of the brain 3·1 mm. A minimum of 7 days postoperative recuperation was allowed before they were put back on a food and water/ethanol training schedule. After a stabilizing period to re-establish a base-line of consumption the rats ($n = 8$) were injected under conscious conditions with 20 μl with a vehicle solution of either artificial cerebrospinal fluid (c.s.f.) or 0·9% NaCl 30 min before the food and water/ethanol session. The administrations of the vehicle solution were repeated several times so as to avoid the initial stress induced by the treatment procedure. Met-enkephalin (supplied by Peninsula Laboratory, California) was dissolved in 20 μl artificial c.s.f. at three different concentrations (40, 80 and 200 μg) and injected under conscious states into the ventricle. Fig. 1 shows that following a met-enkephalin in 200 μg injection, a significant ($P < 0{\cdot}005$) reduction was observed in ethanol consumption which lasted for at least 2 days. At the lower concentrations of 40 and 80 μg/rat, there was only a small and transient reduction in ethanol intake. The rats appeared to be normal in their gross behaviour and in good general condition following an intraventricular injection; there was no significant loss in weight. The lack of response at the lower dose levels may be attributed to the rapid inactivation of met-enkephalin by peptidases in the c.n.s. and thus reducing its availability at the opiate receptors. No significant reduction in ethanol consumption was observed in the 'sham' operated controls given equal

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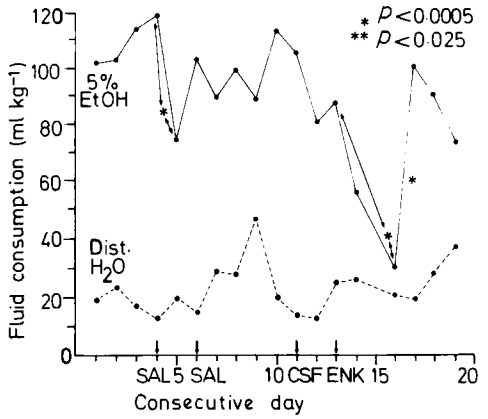

FIG. 1. Effects of met-enkephalin (ENK) on ethanol selections in the Long-Evans Hooded Rats. ENK (200 μg/rat) was infused into the lateral ventricle through an indwelling canula, 30 min before a 2-h daily session of ethanol (5%), water and food. Data are expressed as mean daily consumption, 8 rats used for each group, injection days indicated as (↑), SAL = saline, CSF = artificial cerebral spinal fluid.

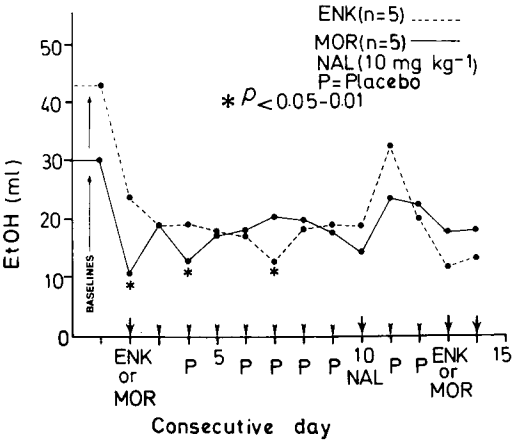

FIG. 2. Effects of enkephalin (200 μg/rat) and morphine (60 mg kg^{-1} s.c.) on daily consumption of ethanol. Treatment protocol as described in Fig. 1. NAL: naltrexone (10 mg kg^{-1} s.c.) given with morphine or enkephalin as indicated(↑).

volume of artificial c.s.f. (data not shown). To study whether this effect can be compared with morphine and blocked by a long acting opiate antagonist, naltrexone, we selected a group of 10 rats and established a baseline consumption for ethanol (5%) and water. Five rats were injected with met-enkephalin (200 μg/rat) and the other 5 morphine (60 mg kg^{-1} s.c.) was given 30 min before the session. Ethanol consumption was reduced significantly ($P < 0{\cdot}05$–$0{\cdot}01$) for both enkephalin and morphine respectively. Daily injection of the vehicle solution (P) was given for 7 days. On day 8, naltrexone (10 mg kg^{-1} s.c.) was given twice a day, with the last injection at 30 min before the treatment with met-enkephalin or morphine. Naltrexone by itself reversed the decrease in ethanol consumption induced by both morphine and met-enkephalin (Fig. 2). Independently, naltrexone produced little effect on the selection of ethanol. There was no significant difference in water and food consumption between the treated and the control rats. These findings on the suppression of ethanol consumption by acute met-enkephalin appear to be consistent with our earlier observations that acute treatment with opiate agonists suppress ethanol consumption and the effect is blocked by antagonists, naloxone or naltrexone. It is conceivable that the other endogenous opioids, such as leu-enkephalin and β-endorphin may act as modulators on the volitional consumption of ethanol.

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