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THE ENKEPHALINASE INHIBITOR ACETORPHAN BUT NOT CARFECILLIN SHOWS EXCITOLOCOMOTOR ACTIVITY

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Enkephalins are rapidly metabolised by aminopeptidases and enkephalinase (neutral endopeptidase EC 3.4.24.11) (De La Baume et al 1981). An effect observed after administration of opioid peptides is an increase in spontaneous locomotor activity (SLA) Broekkamp et al (1979), and this response is blocked by the opioid antagonist naltrexone suggesting an opioid receptor involvement. Our previous work has shown that certain penicillins have inhibitory activity against the enzyme enkephalinase but are less potent in vitro than one of the estabished inhibitors, acetorphan (Livingston et al 1989). This study shows that acetorphan produces an increase in SLA whilst the putative inhibitor carfecillin shows lower activity in vitro and has no effect on SLA in mice.

The active metabolite of acetorphan, thiorphan, is a good competitive inhibitor of enkephalinase from the particulate fraction of mouse brain striata. Using a method based on that of Hudgin et al (1981), IC_{50} values obtained for thiorphan and carfecillin were found to be 10.6 ± 1.9 nM and 207 ± 57 nM respectively.

Intraperitoneal administration of acetorphan in ICI-GBI mice produced a dose related increase in SLA at doses of 50-150 mg kg^{-1}; this effect was more rapid in onset when the drug was administered intracerebroventricularly at doses of 3-50 µg $animal^{-1}$. Similarly, the synthetic analogue D-ala^2-D-leu^5enkephalin (DADL), alone, produced a significant increase in SLA compared to vehicle treated controls at doses of 0.1µg $animal^{-1}$, and a 1hr pretreatment with acetorphan caused a significant (27.4%; $p < 0.05$) increase in the DADL response. Furthermore, this effect was abolished by naltrexone (0.1mg kg^{-1} ip) which itself showed no significant effect on SLA at this dose. However, the penicillin, carfecillin, showed no effect on SLA at doses of 50-250 µg/animal (icv). Similarly, the response to DADL was not significantly affected by pretreatment with carfecillin.

Carfecillin is some 20 fold less active in vitro against enkephalinase compared to the active metabolite of acetorphan and we therefore suggest that for this reason, carfecillin does not significantly affect SLA. This is analagous with the finding that the maximal locomotor activity elicited by acetorphan is in turn less marked than that triggered by morphine or other opioid agonists (Rethy et al 1971). Furthermore, enkephalin releasing neurones do not exert marked tonic control on systems involved in modulation of SLA, which is why the opioid antagonist naltrexone has no effect on SLA itself, and, this is also reflected by the fact that the effects of acetorphan are more marked when combined with the synthetic opioid analogue DADL.

We can therefore conclude that the effects produced by acetorphan are opioid mediated and that although carfecillin is active against enkephalinase in vitro, we propose that there is insufficient increase in enkephalinergic tone to effect locomotor activity due to its low enkephalinase inhibitory activity.

Furthermore, it has been proposed that locomotor hyperactivity induced by enkephalinase inhibitors such as acetorphan may result not only from protection of local enkephalins but may also be linked with mesolimbic dopaminergic neurones (Michael-Titus et al 1987).

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