changes in μ, δ and κ opioid receptors. This finding provides neurochemical support to other data showing the lack of tolerance and dependence liability following repeated administration of this enkephalinase inhibitor.

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P.fr.238

RB 38 B, a selective neutral endopeptidase inhibitor, induced reversal of escape deficits caused by inescapable shocks pretreatment in rats

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The presence of opioid peptides in human brain and the observed euphorogenic and anxiolytic properties of opiates sugest that defectively operating opioid system may be involved in the pathogenesis of various mental illness (Berger and Nemeroff, 1987). This hypothesis is supported by the well known desinhibitory potency of laudannum tincture in humans, the clinically observed antidepressant effects of opiates and the involvement of endogenous enkephalins in behavioural reinforcement. Numerous pharmacological studies with enkephalinase inhibitors have shown that these compounds afford protections to endogenous opioids and thereby mimic a large number of opioid effects. Besides analgesia, enkephalinase inhibitors elicit a variety of opioid-like effects, for instance, they display naloxone-reversible antidepressant effect properties in some models of experimental depression (Ben Natan et al., 1984). The aim of the present study was to investigate if RB 38 B, a selective neutral endopeptidase inhibitor (Xie et al., in press), is able or not to induce a reversal of escape deficits caused by inescapable shock pretreatment.

Previously to Learned Helplessnes induction and in order to find a subanalgesic dose of RB 38 B, we have tested the drug on the tail electric stimulation test, an experimental pain model. Rats were implanted with two electrodes into the base of its tail. The nociceptive stimuli were delivered to the animals from an electronic stimulator via the electrodes. Trains of 0.5 s. of square pulses were used with the following characteristics: 125 Hz, 1.6 ms. duration and increasing voltage. The first one was 0.25 V being the cut off 70 V. The response to electic shocks was evaluated using a scale incorporating 3 parameters. 1st) the tail withdrawal, 2nd) vocalization and 3rd) vocalization after electric stimulus. Control and experimental animals were ICV treated with saline or RB 38 B respectively. The doses of RB 38 B injected were 50 and 100 mcg/rat. At the dose of 100 mcg, RB 38 B showed a significant increases in the threshold for the 3rd parameter ($U = 2$; $p < 0.05$). However at the dose of 50 mcg RB 38 B did not show any difference compared to the control ($U = 13.5$; n.s.).

In view of these results we have studied the effect of RB 38 B (50 mcg) on the Learned Helplessness paradigm (LH), an experimental model of depression in rats. All the animals received a pretreatment of 60 inescapable shocks (1 mA during 15 s. every 60 ± 20 s.). 48 hr. later an avoidance and escape session were performed in a two-ways shuttle

Table 1

Means of escape failures after LH induction.

Drug	1st session X ± s.e.m	2nd session X ± s.e.m	3rd session X ± s.e.m
saline	11.4 ± 1.89	10.5 ± 2.51	7.5 ± 2.81
RB 38 B	4.7 ± 0.81 *	2.3 ± 0.48 *	2.2 ± 0.90

* $p < 0.05$ vs. saline

box (FR 2 schedule) for 3 consecutive days in the morning and the number of escape failures was recorded. 6, 24, 32 hr after the inescapable shocks session and 15 min before the avoidance and escape test, control and experimental animals were injected ICV with saline and RB 38 B (50 mcg/rat/day) respectivily. Results showed that control rats exhibited significantly more escape failures than the RB 38 B treated animals.

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P.fr.239

Metabolism of enkephalins in rat brain after chronic administration of neuroleptics

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The aim of this paper was to study the effect of chronic administration of chlorpromazine (CPZ) or thioridazine (TDZ) in doses of 2 or 6 mg/kg or haloperidol (HAL) in doses of 0.25 or 1 mg/kg i.p. on the level of leu- and met-enkephalin in striatum. Neuroleptics (NL) were injected 1, 2 or 3 months. The level of enkephalins (ENK) was measured 24 h after last dose of NL or 8 days after drug withdrawal using radioimmunoassay. In some groups of animals treated by NL, dopamine agonist apomorphine (AP) was injected 30 min before decapitation of rats. In animals treated 1 month by HAL the release of ENK into perfusion fluid taken from lateral brain ventricle and the release of neuropeptides from striatal slices in vitro were measured. The dose and time-dependent increase of striatal ENK level was observed after chronic administration of CPZ, TDZ or HAL. Eight days after withdrawal of chronically administered all examined NL the evident decline of the level of ENK in striatum was seen. AP pretreatment significantly decreased ENK level elevated by chronic injections of NL. In perfusion fluid obtained from lateral ventricle of brain of animals treated 1 month with HAL a dose-dependent increase of ENK levels was observed, and was augmented by potassium ions. In other rats treated by the same way with HAL the evident increase of ENK release from striatal slices was observed.

It is concluded that: chronic administration of classical, cataleptogenic neuroleptics blocking of dopaminergic neurons elicits specific changes in the striatal neurons synthesizing and releasing ENK. Central enkephalins take part in the mechanism of action of chronically administered neuroleptics. Our results support the hypothesis that activation of dopaminergic neurons inhibits tonically the synthesis of enkephalins in striatum.

P.fr.240

Haloperidol, chlorpromazine and apomorphine alter central regional neuropeptidase activity

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Haloperidol has been shown to stimulate the *de novo* synthesis and release of neurotensin and pro-opiomelanocortin (POMC) peptides in specific regions of the rat brain. Several studies have reported increased levels of POMC mRNA, stimulation of trypsin-like and alpha-amidating enzyme and the formation of alpha-MSH and β-endorphin