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Noradrenergic Rather Than GABAergic Processes as the Common Mediation of the Antidepressant Profile of GABA Agonists and Imipramine-Like Drugs in Animals

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PONCELET, M , P MARTIN, S DANTI, P SIMON AND P SOUBRIÉ *Noradrenergic rather than GABAergic processes as the common mediation of the antidepressant profile of GABA agonists and imipramine-like drugs in animals* PHARMACOL BIOCHEM BEHAV **28**(3) 321–326, 1987 —The present study was aimed at investigating in rats whether a common mechanism might underlie the reversal of depressive-like behaviors by classical antidepressants and by GABA agonists such as muscimol Blockade of GABA transmission with picrotoxin (1 mg/kg IP) abolished the muscimol (0 5–1 mg/kg)-induced reduction of immobility in the swimming test and the reversal of escape failures in the learned helplessness paradigm Conversely, picrotoxin was found not to reduce the efficacy of imipramine-like drugs in these same animal models The combination of muscimol and tricyclics given at subeffective doses resulted in behavioral changes that can be accounted for by an additive interaction between these two classes of drugs These data confirm the antidepressant-like profile of GABA agonists but suggest that it is unlikely that the primary antidepressant mechanism of conventional antidepressants involves GABA-A receptors In the swimming test, prazosin (2 mg/kg), an alpha adrenoceptor blocker, antagonized the reduction of immobility produced by both muscimol and imipramine-like drugs In the learned helplessness paradigm, penbutolol (0.25–0 5 mg/kg) and, though to a lesser extent prazosin, counter-acted the reversal of escape failures caused by muscimol and imipramine On the basis of these data, it is tempting to speculate that increased transmitter outflow at noradrenergic receptors may be an essential component in the mechanism of action of imipramine-like drugs but also of GABA agonists

GABAergic processes Noradrenergic systems Alpha adrenoceptors Beta adrenoceptors
Antidepressant drugs Swimming-induced immobility Escape failures Learned helplessness Rat

THE therapeutic activity of conventional antidepressant drugs has traditionally been associated with acute and/or adaptive changes in brain monoaminergic transmission and most neurobiological hypotheses on affective disorders have focused on these monoaminergic systems [4] Several lines of evidence, however, suggest that additional brain processes, and more particularly GABA-containing neurones, might be involved in depression and/or recovery from depression.

GABA receptor agonists such as progabide have been reported to show antidepressant activity comparable to that of tricyclic antidepressants [16,25] and CSF-GABA levels have been found to be reduced in depressed patients [2,8] Studies performed on animal models sensitive to antidepressants have revealed an antidepressant-like effect following pharmacological manipulations assumed to enhance GABA transmission. Reduction of the duration of immobility in the swimming test has been observed with AOAA, muscimol and THIP [3]. The peripheral injection of progabide as well as the administration of GABA into the hippocampus or lateral geniculate body has been found to reverse escape deficits in the learned helplessness paradigm [12,22]. In addition, intracerebral injection of bicuculline reportedly triggers helpless behavior in animals [17]

In two animal models of depression: the forced swimming test and the learned helplessness paradigm, this study has a two fold purpose: to confirm that muscimol, a direct GABA agonist, exerts antidepressant-like effects and to investigate whether a common mechanism might be involved in the antidepressant profile of muscimol and imipramine-like drugs. For the latter, we first studied the possibility of a GABAergic mediation of the effects of tricyclics. Finally, the potential involvement of noradrenergic processes in the antidepressant action of imipramine-like drugs and muscimol was investigated.

METHOD

The experiments were carried out on male Wistar A.F. (Centre d'élevage R Janvier, France) or Sprague-Dawley

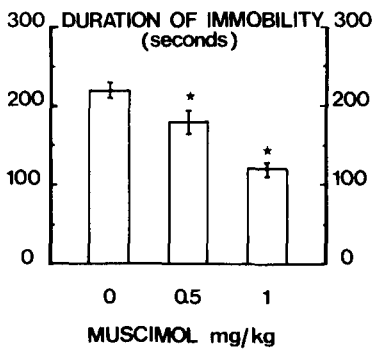

FIG. 1 Muscimol-induced reduction of immobility (mean±SEM) in rats subjected to the forced swimming test The duration of immobility was measured between the 5th and the 10th min after the animal was plunged into the water, 1 hr after receiving muscimol or vehicle N=10 to 12 rats/group *Significantly different from controls at $p<0.05$ (Dunnett's t-test)

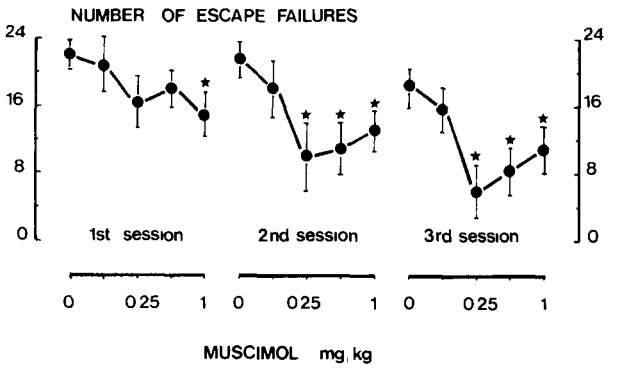

FIG 2 Muscimol-induced reduction of escape failures (mean±SEM) in rats subjected to 3 consecutive daily shuttle-box sessions Data are the number of escape failures out of 30 two-way avoidance trials in animals previously subjected to 60 inescapable foot-shocks Escape failure refers to failure of the rat to change compartments during the electric foot-shock (0 8 mA, 3 sec duration) The indicated doses refer to the daily dose administered from the end of the shock pretreatment onwards N=16 to 20 rats/group *Significantly different from controls at $p<0.05$ (Dunn's t-test)

rats (Charles River, France) weighing 175–200 g at the beginning of the experiments. The animals were housed in groups of 10/cage under standard conditions. room temperature (21±1°C); light/dark cycle (12 hr/12 hr), water and food ad lib

Forced Swimming Test Sprague-Dawley Rats

In the present study, rats were tested and injected once although the procedure which has been used most frequently with rats has involved two sessions in the water and two or more injections of antidepressants before the second session [10,19]. This departure from the usual procedure was aimed at extending the objectives of this study to acute behavioral effects of antidepressants or GABA agonists. As shown by others [3, 10, 26], a single injection of antidepressants or GABA agonists before the second swim could be effective in attenuating despair behavior, and we have previously shown [18] that, in Sprague-Dawley rats, acute or repeated injection of antidepressants reduced immobility at the first swim session provided that immobility was scored between the 5th and the 10th min after the animal was plunged into the water.

The rats were placed individually in Plexiglas cylinders (height 40 cm, diameter 18 cm) containing 15 cm of water at 25°C. Immobility was measured to the nearest second between the 5th and the 10th min after the rats were plunged into the water, a rat being judged to be immobile when it remained floating in the water making only the very small movements necessary to keep its head above water [19].

Antidepressant drugs: muscimol (Sigma), desipramine, imipramine, and clomipramine (Ciba-Geigy) were injected once, 1 hr before testing according to [3] and [18] Potential antagonists. l-penbutolol (Hoechst), prazosin (Pfizer) and picrotoxin (Sigma) were injected 30 min before testing.

Learned Helplessness Training Wistar AF Rats

Inescapable shock pretreatment Electric foot-shocks were delivered in 20×10×10 cm chambers with Plexiglas walls and cover The floors were stainless-steel grids (1.5 cm mesh). A constant current shocker was used to deliver 60 scrambled, randomized inescapable shocks (15 sec duration, 0 8 mA, every min ±15 sec) to the grid floor. Control rats were placed for 1 hr in identical chambers but no shocks were administered Inescapable shock pretreatment was performed in the morning, on day 1

Conditioned avoidance training To evaluate escape deficits, shuttle-box training was initiated 48 hr (day 3) after inescapable shock pretreatment in automated two-way shuttle-boxes (60×21×30 cm) with Plexiglas walls and a floor consisting of stainless-steel rods spaced 1.0 cm apart Each shuttle-box was divided into two equal-size chambers by a stainless-steel partition with a gate providing access to the adjacent compartment through a 7×7 cm space. Animals were placed singly in the shuttle-box, allowed to habituate to the test environment for 5 min (for the first session only) and then subjected to 30 avoidance trials (inter-trial intervals being 30 sec). During the first 3 sec of each trial, a light signal (used as a CS) was presented, allowing the animals to avoid shocks. If a response did not occur within this period, a 0.8 mA shock was applied via the grid floor If no escape response occurred within a 3 sec duration of shock, shock and light CS were terminated The response (avoidance or escape) required of the rat was to cross the gate into the other compartment of the box Shuttle-box sessions were performed for 3 consecutive days (day 3, 4 and 5) in the morning, and the number of escape failures, referred to as absence of crossing response during shock delivery, was recorded Although escape failure is defined as failure to escape within a 30 to 60 sec period in most procedures used for helplessness assessment, the 3 sec duration of shock was selected because the very first seconds following shock onset seem to be critical for detecting escape deficits in animals preexposed to inescapable shocks, especially under a simple FR1 schedule [15,24].

Drugs were injected daily for 5 consecutive days, from the end of the shock pretreatment session onwards Muscimol and tricyclic drugs were administered twice a day, one half dose in the morning and one half in the afternoon, morning injections being performed at a time corresponding to 30 min before shuttle-box session. Picrotoxin, penbutolol, prazosin were injected in the morning only The schedule of twice daily administration was selected according to previous results [15], and the doses used chosen from results from both the literature and our pilot experiments

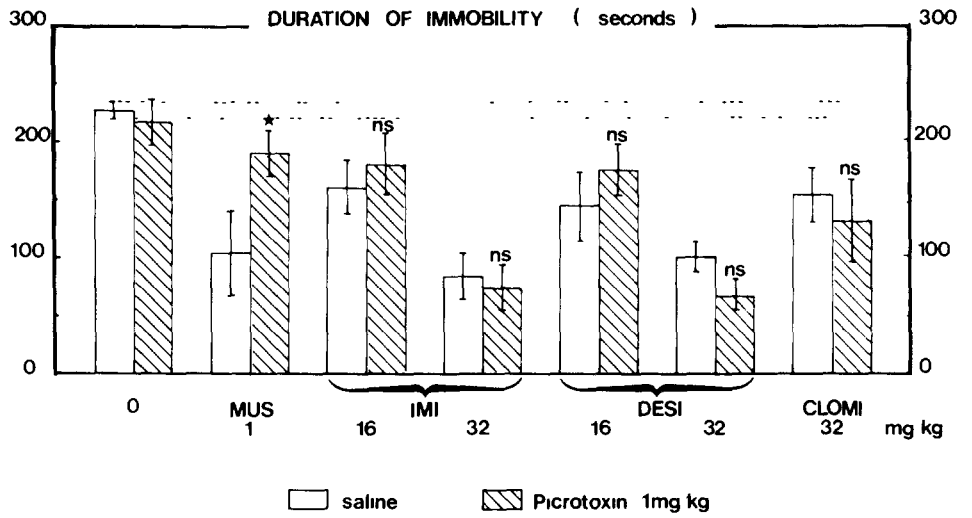

FIG 3 Effects of picrotoxin on muscimol- and antidepressant-induced reduction of immobility (mean±SEM) in rats The duration of immobility was measured between the 5th and the 10th min after the animal was plunged into the water, 1 hr after receiving muscimol (MUS), imipramine (IMI), desipramine (DESI) or clomipramine (CLOMI) Picrotoxin was injected 30 min before testing N=10 to 12 rats/group Performances of the 4 separate groups of saline- or picrotoxin-injected rats associated with each drug tested have been pooled *$p<0$ 05 as compared with animals not treated with picrotoxin (Student's t-test) ns not statistically significant

When we purported to show an antagonism, the doses of antidepressant were high· i e , those required to produce a rapid, complete reversal of escape failures or a substantial reduction in immobility; when synergism was investigated, the doses of antidepressant were moderate, i.e , those sufficient to produce a delayed, partial reversal of escape failures or minimal effect on immobility Drugs were dissolved in distilled water or (penbutolol and prazosin) suspended in acacia gum and injected IP in a volume of 0.5 ml/100 mg of body weight

Statistical analysis was performed by using Student's t-test, Dunnett's or Dunn's t-test after ANOVA

RESULTS

Muscimol reduced both immobility scores in the swimming test (Fig. 1) and escape failures in the shuttle-box paradigm (Fig 2).

At 1 mg/kg, muscimol reproducibly shortened the duration of immobility (Figs. 1, 3, 7), this effect being statistically significant ($p<0$ 01) in each case [Fig 1 $t(3,33)=3.07$, Fig 3 $t(4,45)=3$ 12, Fig 7 $t(4,45)=4$ 15] At 0 5 mg/kg, however, the reduction of the duration of immobility reached significance, $t(3,33)=2$ 54, $p<0.05$, in the initial experiment (Fig. 1) but the same dose produced a non significant effect during the subsequent tricyclic-potentiation experiment (Fig. 5) At higher doses, muscimol did not reduce and even worsen immobility scores probably because of its sedative/incapacitating effects (data not shown)

Analysis of variance performed on the number of escape failures over the 3 shuttle-box sessions (Fig. 2) indicated that daily injection of muscimol significantly [0.25 mg/kg $F(1,178)=9.07$, $p<0.01$; 0.5 mg/kg: $F(1,178)=8$ 04, $p<0.01$ and 1 mg/kg $F(1,178)=7$ 12, $p<0.01$] reduced escape deficits. Except for muscimol 1 mg/kg, $t(5,54)=2.63$, $p<0.05$, a treatment effect was not detectable at the first shuttle-box session (i.e., after 4 injections) but only at the second and third sessions. The fact that the beneficial effect of doses of muscimol higher than 0.25 mg/kg tended to be less marked than that observed at 0.25 mg/kg might be accounted for by the sedative and incapacitating effects of the drug. Administered at 0 25 or 0.5 mg/kg, muscimol exerted no significant effects on shuttle-box behavior in rats not trained for learned helplessness, nor did the drug affect intertrial shuttling in helpless animals (data not shown)

As shown in Fig. 3, picrotoxin 1 mg/kg significantly antagonized, $t(4,45)=2.54$, $p<0.05$, the reduction of immobility scores induced by muscimol 1 mg/kg but not that caused by tricyclic antidepressants such as imipramine 16 or 32 mg/kg, desipramine 16 or 32 mg/kg and clomipramine 32 mg/kg. Likewise, the administration of picrotoxin before each shuttle-box session abolished ($p<0$ 01) the reduction of escape failures observed at the second, $F(1,82)=9.11$, or third, $F(1,82)=10$ 57, shuttle-box session in muscimol (0.5 mg/kg)-treated rats, but did not affect the antidepressant action exerted by imipramine (32 mg/kg/day) or clomipramine (24 mg/kg/day) (Fig 4). When administered alone, picrotoxin 1 mg/kg was devoid of effect on immobility scores (Fig. 3) or on shuttle-box performance of controls (number of escape failures saline 8±2, 6±2, 4±2, picrotoxin 9±2, 5±1, 5±2 at the 1st, 2nd and 3rd shuttle-box sessions, respectively) or of helpless rats (saline. 20.1±1.9; 20 2±2.6; 19 9±2 5, picrotoxin: 20 8±1.9, 20.1±2 7, 20.1±1.4).

When injected at the subeffective dose of 0 5 mg/kg, muscimol did not significantly enhance the efficacy of desipramine ($t=1.6$, ns) and clomipramine ($t=0$ 95, ns), concurrently administered at subeffective doses, in reducing the duration of immobility in the swimming test (Fig 5) Likewise, analysis of variance performed on data obtained from the three shuttle-box sessions (Fig 6) indicated that, globally, the performances of the animals receiving subeffective doses of muscimol + imipramine, or muscimol +

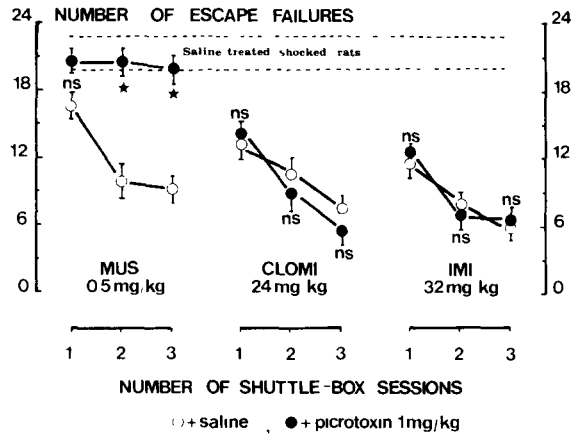

FIG 4 Effects of picrotoxin on muscimol- and antidepressant-induced reversal of escape failures (mean±SEM) in rats trained for learned helplessness Data are the number of escape failures out of 30 two-way avoidance trials at the 1st, 2nd and 3rd shuttle-box session for muscimol (MUS)-, imipramine (IMI)- or clomipramine (CLOMI)-treated animals Picrotoxin was injected once a day (30 min before shuttle-box testing) The indicated doses refer to the daily dose administered from the end of the shock pretreatment onwards N=12 to 16 rats/group The area between the broken lines represents the mean performance of 3 independent groups of saline, shocked rats *$p<0$ 05 as compared with corresponding animals not treated with picrotoxin (Dunn's t-test) ns not statistically significant

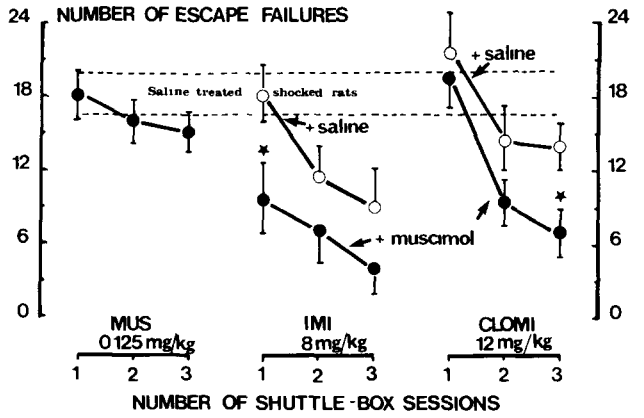

FIG 6 Effects of a subeffective dose of muscimol in combination with tricyclic drugs on escape failures (mean±SEM) in rats trained for learned helplessness Data are the number of escape failures out of 30 two-way avoidance trials at the 1st, 2nd and 3rd shuttle-box session The indicated doses refer to the dose administered daily from the end of the shock pretreatment onwards N=16 to 20 rats/group The area between the broken lines represents the mean performance of 2 independent groups of saline shocked rats Rats treated with muscimol 0 125 mg/kg + imipramine (IMI) or clomipramine (CLOMI) differ significantly from animals given either antidepressant alone at *$p<0.05$ (Dunn's t-test)

clomipramine were not statistically different, $F(1,178)=3$ 92, ns and $F(1,178)=3$ 06, ns, respectively, from those of the rats receiving identical doses of either antidepressant alone Further analysis revealed that differences can be observed between imipramine vs. imipramine + muscimol, first shuttle-box session, Dunn's $t(9,89)=2.57$, $p<0$ 05, or between clomipramine vs. clomipramine + muscimol, third shuttle box session, Dunn's $t(9,89)=2.61$, $p<0$ 05.

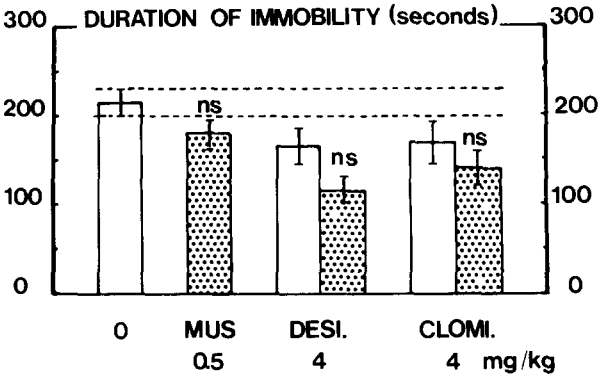

FIG 5 Effects of a subeffective dose of muscimol in combination with tricyclic drugs on the duration of immobility in rats The duration of immobility was measured between the 5th and the 10th min after the animal was plunged into the water, 1 hr after receiving muscimol (MUS), desipramine (DESI) or clomipramine (CLOMI) alone, or either antidepressant in combination with muscimol N=12 to 14 rats/group, ns not statistically significant as compared with corresponding animals not treated with muscimol (Student's t-test)

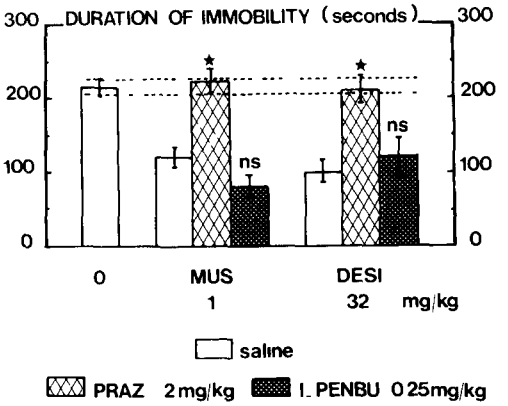

FIG 7 Effects of prazosin and penbutolol on muscimol- and desipramine-induced reduction of immobility in rats The duration of immobility (mean±SEM) was measured between the 5th and the 10th min after the animal was plunged into the water, 1 hr after receiving muscimol (MUS) or desipramine (DESI) Prazosin (PRAZ) or penbutolol (l PENBU) were given 30 min before testing N=12 to 14 rats/group The performance of 3 separate groups of saline-treated rats have been pooled. Rats given prazosin or penbutolol differ from animals given muscimol or desipramine alone at *$p<0$ 05 ns not statistically significant (Dunnett's t-test)

Statistical analysis revealed that blockade of alpha adrenoceptors with prazosin (2 mg/kg) significantly reversed the reduction of immobility provoked by both muscimol, $t(3,33)=3$ 57, $p<0$ 01, as compared with muscimol alone, and desipramine, $t(3,33)=3.86$, $p<0$ 01, as compared with desipramine alone, whereas blockade of beta adrenoceptors with penbutolol did not affect the action of these same compounds (Fig 7) At this dose, prazosin alone did not alter immobility scores (209±12 vs 215±13 sec). In the learned helplessness paradigm, the administration of penbutolol before each shuttle-box session dose-dependently prevented the reduction of escape failures observed at the third

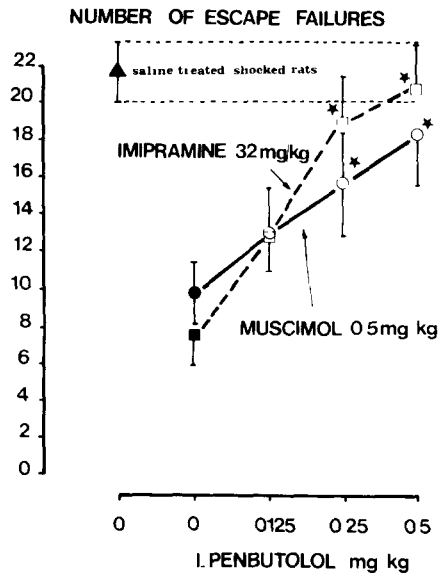

FIG 8 Effects of penbutolol on muscimol- and imipramine-induced reversal of escape failures at the third shuttle-box session, in rats trained for learned helplessness Data are the number of escape failures (mean±SEM) out of 30 two-way avoidance trials The indicated doses refer to the doses administered daily from the end of the shock pretreatment onwards N=16 to 20 rats/group The area between the broken lines represents the performance of 2 independent groups of saline, shocked rats Rats treated with penbutolol (l PENBU) + imipramine (IMI) or + muscimol (MUS) differ significantly from animals given imipramine or muscimol alone at $*p<0$ 05 (Dunn's t-test)

shuttle-box session equally in muscimol- as in imipramine-treated rats (Fig 8), $F(1,158)=12$ 67, $p<0$ 01, as compared with muscimol alone, $F(1,158)=15$ 89, $p<0$ 01, as compared with imipramine alone. Under these same treatment conditions, penbutolol was also found to abolish the attenuation of escape deficits obtained at the second shuttle-box session both in muscimol- or in imipramine-treated animals (data not shown). At a dose (2 mg/kg) reported to reduce the reversal effect of imipramine on escape deficits [15], prazosin attenuated, but did not suppress the antidepressant-like effect of muscimol 0.5 mg/kg (number of escape failures at the third shuttle-box session: muscimol: 7 4±2.6, muscimol + prazosin: 14.8±3 3, $t=2$ 32, $p<0.05$, n=15 rats/group). When administered alone, penbutolol or prazosin were previously found not to alter shuttle-box behavior in controls or in "helpless" rats [15].

DISCUSSION

In agreement with previous work [3, 12, 22] the present study shows that in rats, stimulation of GABA receptors with muscimol produced an antidepressant-like effect, as suggested by the ability of this drug to reduce the duration of immobility in the forced swimming test and its ability to eliminate escape failures in animals trained for learned helplessness. That these behavioral changes can be prevented by picrotoxin militates in favor of the involvement of GABA-A receptor subtype (receptors linked to chloride ionophore) in muscimol-induced antidepressant-like effects These data are congruent with preclinical and clinical evidence suggesting a connection between depressive state or behaviors and reduced GABAergic transmission, and between enhanced GABAergic function and recovery from depression (see introduction).

These observations prompted us to investigate the possibility that GABAergic processes could be a common neuronal substrate for the antidepressant-like drugs in animals. Although this possibility would conflict with the monoaminergic hypothesis of the mode of action of antidepressants, some reports suggest that tricyclic drugs may interfere with GABAergic processes Imipramine and desipramine were found to increase the in vivo release of endogenous GABA from various rat brain structures [11] In addition, repeated administration of a large variety of antidepressant drugs reportedly modulates (up regulation) GABA binding sites [14]

The present study lends little support in favor of the involvement of GABAergic processes, at least those coupled to GABA-A receptors, in the effect of tricyclic antidepressants in the swimming test and the learned helplessness paradigm The behavioral changes observed in rats under the muscimol + tricyclic drugs combination militate in favor of additive rather than potentiating effects between these two classes of drugs Moreover, and more convincingly, picrotoxin, at doses able to prevent the antidepressant activity of muscimol in both the swimming test and the learned helplessness paradigm, failed to affect that of imipramine-like drugs in these same models This latter observation is at variance with the reported ability of bicuculline to reverse imipramine-induced reduction of escape latency in rats trained for learned helplessness [1] Differences in the parameters taken into account (escape failure vs escape latency) and possible deleterious effects of bicuculline alone on escape latency may partly account for these discrepant findings

The results presented here are more congruent with the reported inability of antidepressants to affect various parameters of GABAergic transmission [13]. Even in Korf and Venema's study [11] purporting to show effects of tricyclics on GABA transmission, the reported increases in release of GABA were observed with rather high concentrations of tricyclics and not specific to these drugs. Moreover, in Lloyds *et al* 's study [14], the GABA binding sites affected by subchronic treatment with antidepressants were the GABA-B and not the GABA-A receptors, whereas these latter receptors are thought to be the ones which are preferentially involved in the antidepressant effect of GABA agonists in animals [3,12]

When considering the numerous neurotransmitter systems that have been demonstrated to be under GABAergic control, diverse neuronal populations may indirectly contribute to the antidepressant-like profile of GABA agonists. In contrast to their inhibitory influence on serotonergic neurons, these drugs reportedly enhance noradrenergic transmission [5, 7, 23] and cause desensitization of beta receptor-coupled adenylate cyclase [27], two effects that are shared by many conventional antidepressant drugs. Our observation that the effects of muscimol on the swimming test and the learned helplessness paradigm were reversed by noradrenergic receptor blockers, perhaps with a test-dependency similar to that observed for imipramine-like drugs ([9, 15, 19, 20] and present study) clearly suggests that facilitation of noradrenergic transmission mediates the antidepressant-like effects of muscimol. Under this hypothesis, the additive effects of muscimol and imipramine-like drugs observed in the learned helplessness paradigm are consistent with the additive effects of these two classes of

drugs on parameters of brain noradrenergic transmission [27].

In the procedural context of the learned helplessness model dealing with repeated drug injections, muscimol-induced adaptive changes in some target cells of the noradrenergic neurons cannot be excluded. Indeed, repeated administrations of recently developed GABAergic agonists have been found to desensitize the beta adrenoceptor-coupled adenylate cyclase [27]. In light of the data reported by Duncan *et al* [6], it is conceivable that such possible GABA-mediated adaptive changes might occur rapidly under inescapable stress and thus contribute to the effects of muscimol in the learned helplessness model.

In conclusion, the present study confirms the antidepressant-like profile of GABA agonists but suggests that it is unlikely that the primary antidepressant mechanism of convential antidepressants involves GABA-A receptors-coupled processes On the other hand, and although the role of additional brain processes cannot be ruled out, it is tempting to speculate that increased transmitter outflow at noradrenergic receptors (alpha or alpha and beta adrenoceptors, depending on the testing procedure used) may be an essential component in the mechanism of action not only of imipramine-like drugs but also of GABA agonists.

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