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EVALUATION OF CENTRAL ADRENERGIC RECEPTOR SIGNAL TRANSMISSIONS AFTER AN ANTIDEPRESSANT ADMINISTRATION TO THE RAT

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Abstract—The effects of several antidepressants, amitrityline, citalopram, desipramine, fluoxetine, maprotiline, mianserin, nialamide, nomifensine, tranylcypromine and viloxazine, on the accumulation of cyclic AMP and inositol monophosphates were studied in rat cerebral cortical slices. The two enzymatic systems were stimulated either by adrenergic agonists or by forskolin. Cyclic AMP and inositol monophosphates (IPs) formed were determined by a double label method. *In vitro* all drugs, except inhibitors of monoamine oxidase, nialamide and tranylcypromine, inhibited α_1-agonist-mediated production but did not modify the cyclic AMP accumulation. Otherwise, chronic desipramine but not citalopram administration decreased the accumulation of cyclic AMP (−39%) elicited by β-adrenoceptor agonists; no change was observed in inositol phosphate metabolism after administration of these two drugs. These data support previous investigations showing a decrease in cyclic AMP production after chronic treatment with norepinephrine uptake blockers but do not confirm the hypothesis of a modification of α_1-adrenoceptor-stimulated inositol phosphate metabolism.

For a long time, common, central biochemical effects of drugs acting on various forms of depression have been searched for but have yet to be discovered. With respect to their acute actions, some antidepressants were found to promote an increase in norepinephrine (NE‡), serotonin or both in the synaptic clefts. The relevant mechanisms were either a reuptake inhibition of the corresponding amine or a monoamine oxidase inhibition [1]. However, it was quickly shown that these biochemical modifications were not relevant in terms of therapeutic action as they appeared immediately while antidepressant clinical effectiveness requires several weeks of treatment.

The first biochemical modification which appeared to be common to most of these drugs and time-related to their pharmacological effectiveness was a decrease in the response to NE of the cyclic AMP-generating system in the rat brain [2]. In most cases, this was accompanied by an apparent decrease in the number of β-adrenoceptors [3–5]. Moreover, several animal behavioural experiments have suggested that chronic antidepressant administrations induced an increase in the responses mediated by α_1-adrenoceptors [6–8]. These data supported an enhancement of the density of these receptors [9, 10] although some other data did not confirm this [11]. It is also established that the activation of α_1-adrenoceptors is coupled to the hydrolysis of inositol phospholipids [12, 13]. As some of these antidepressants have also a high affinity for α_1 binding sites [14], it might be expected that they alter the hydrolysis of inositol phospholipids. The goal of this study was therefore to check whether several antidepressants might induce common biochemical effects on inositol phosphate (IP) metabolism and on the cyclic AMP generating system. These two parameters were evaluated before and after antidepressant administrations using specific agonists: 6-fluoronorepinephrine (6-FNE) for α_1-adrenoceptors, isoproterenol for β-adrenoceptors and NE for both.

These experiments were done *in vitro* on rat brain cortical slices after either a direct contact with the antidepressants or a chronic treatment of the animals. The selected antidepressants were representative of the various mechanisms observed in this class of drugs after a single administration.

MATERIALS AND METHODS

myo-[2-^{3}H]Inositol (20 Ci/mmol) and [U-^{14}C]-adenine (271 mCi/mmol) were obtained from Amersham (Les Ulis, France). NE, isoproterenol, forskolin and desipramine were purchased from the Sigma Chemical Co. (St Louis, MO, U.S.A.); 6-FNE, nialamide and tranylcypromine from Research Biomedicals Inc. (Illkirch, France); propranolol from Imperial Chemical Industries (Cergy, France); and prazosin from Pfizer (Orsay, France). The other antidepressant drugs were kindly provided by the companies indicated: amitriptyline (Roche, Neuilly-Sur-Seine, France), citalopram (H. Lundbeck, Copenhagen, Denmark), mianserin (Organon, Riom, France), nomifensine (Hoechst, L'Aigle, France), fluoxetine (Eli-Lilly, Surrey, U.K.), maprotiline (Ciba-Geigy, Rueil-Malmaison, France) and viloxazine (Imperial Chemical Industries). Cation exchange resin (AG50W-X4, hydrogen form, 200–400 mesh) and anion exchange resin (AG1-X8,

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‡ Abbreviations: 6-FNE, 6-fluoronorepinephrine; IP, inositol phosphate; IP_1, D-*myo*-inositol 1-phosphate; NE, norepinephrine.

formate form, 200–400 mesh) were obtained from Bio-Rad (Richmond, CA, U.S.A.), and neutral alumina gel (WN3) from Sigma.

Stimulation of cyclic AMP and IP formation. Male Wistar rats (180–250 g) were decapitated and their brains rapidly removed. Brain slices were prepared by cross-chopping using a McIlwain tissue chopper set at 0.25 mm. The slices were pre-incubated in Krebs–Ringer bicarbonate buffer with gassing with 95% O_2/5% CO_2 for 30 min at 37°. Aliquots (50 μL) of packed slices were then dispersed among glass tubes containing 0.5 mM 3-isobutyl-1-methyl-xanthine, 5 mM lithium chloride, 0.54 μCi [^{14}C]-adenine/mL (final concentration 2 μM), 8 μCi [^{3}H]-inositol/mL (final concentration 0.4 μM) Krebs–Ringer bicarbonate buffer. Then, agonist alone or with an antidepressant was added. The tubes (250 μL) were gassed for 30 sec, capped and incubated in a shaking water bath for 45 min at 37°. When antagonists were used, they were added prior to agonist addition. The reaction was stopped by the addition of 940 μL of methanol/chloroform (2:1), 310 μL of chloroform and 310 μL of distilled water. The tubes were then centrifuged (2000 rpm; Jouan CR 412) at 4° for 10 min. Supernatant (750 μL) was diluted with 1 mL of 10 mM Tris–HCl buffer, pH 8.5 (total volume 1.75 mL), and applied to columns containing 1 mL Dowex AG50W-X4. [^{14}C]-Cyclic AMP and [^{3}H]IPs were eluted and isolated according to Morin *et al.* [15] with minor modifications. Dowex AG50W-X4 resin was rinsed with 1.5 mL of distilled water. Then, 4 mL of distilled water were run through the columns to remove [^{14}C]-cyclic AMP. The eluant obtained was applied to alumina columns and [^{14}C]cyclic AMP was purified by 0.1 M imidazole, pH 7.3 (2 mL followed by 6 mL). One millilitre of the last fraction was counted to determine the amount of [^{14}C]cyclic AMP formed. Otherwise, [^{3}H]IPs were isolated from the two first eluant fractions (1.75 + 1.5 mL) diluted with 2.5 mL of 10 mM Tris–HCl buffer, pH 8.5 (total volume 5.75 mL), and loaded onto Dowex AG1-X8. The elution was carried out as described previously by Morin *et al.* [15].

Animals treatment. In the chronic drug experiments, rats were anesthetized with chloral hydrate (400 mg/kg, i.p.) and implanted s.c. in the dorsal region with osmotic minipumps (model 2001, Alza Corp., Palo Alto, CA, U.S.A.). These minipumps delivered continuously saline, desipramine (16 mg/kg per day) or citalopram (1 mg/kg per day) for eight consecutive days directly into the right jugular vein. Animals were housed individually and maintained in a 12 hr light/dark cycle with free access to food and water. They were killed by decapitation 24 hr after the end of the infusion. Whole brains were rapidly removed and prepared as described previously.

RESULTS

Effects of adrenergic agonists and forskolin

Cyclic AMP accumulation was increased to about 2000% of control by 100 μM forskolin and to 940% by 100 μM NE (Fig. 1). Isoproterenol- and 6-FNE-induced increases accounted for approximately 70% and 7% of the NE response, respectively (Table 1).

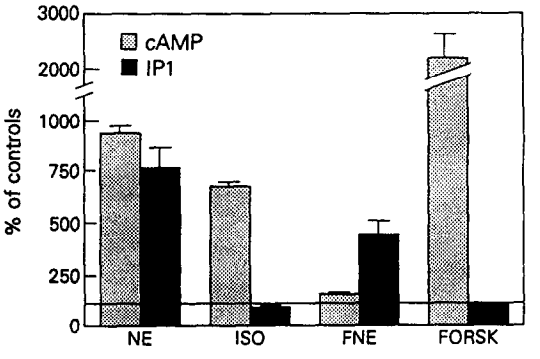

Fig. 1. Effects of NE, isoproterenol (ISO), 6-FNE (FNE) and forskolin (FORSK) on basal cyclic AMP formation and IP metabolism in rat cerebral cortical slices. Concentrations of agonists used were: NE, 6-FNE and forskolin, 100 μM; isoproterenol, 1 μM. Experimental conditions were as described in Materials and Methods. Values are expressed as percentages of basal response without agonists (100%). Basal values were 0.567 ± 0.062 and 0.055 ± 0.008 pmol/mg protein/45 min for cyclic AMP and IP_1 formations, respectively. Data are means ± SEM values from five experiments, each done in triplicate.

Isoproternol (1 μM) and forskolin (100 μM) did not induce any change in IP metabolism, but NE or 6-FNE (100 μM) increased D-*myo*-inositol 1-phosphate (IP_1) accumulation (Fig. 1). NE caused an 800% increase (Fig. 1) and the 6-FNE response accounted for 60% of the NE response (Table 1). Propranolol (10 μM) antagonized completely the production of cyclic AMP induced by isoproterenol, antagonized partially that elicited by NE but did not modify 6-FNE and forskolin-induced increases (Table 1). The accumulation of IP_1 elicited by these latter compounds did not change in the presence of propranolol (Table 1).

Prazosin (1 μM) entirely inhibited IP_1 production elicited by NE or 6-FNE. It also decreased the cyclic AMP response to NE (−25%) and entirely abolished the response to 6-FNE.

Effects of adrenergic agonists and forskolin in the presence of antidepressants

Antidepressants alone were without effect on cyclic AMP and IP_1 accumulations but some of them significantly decreased the responses induced by NE or 6-FNE, whereas isoproterenol and forskolin responses were unchanged.

Figure 2 shows a decrease in IP_1 formation induced by NE (b) or 6-FNE (c) in the presence of mianserin, amitriptyline, nomifensine, citalopram, desipramine or maprotiline (100 μM). No significant change was seen with nialamide, tranylcypromine, fluoxetine or viloxazine.

Increasing concentrations of these drugs have different effects on NE stimulation (Fig. 2a). Except amitriptyline and to a lesser extent mianserin and nomifensine (IC_{50} = 3, 11 and 29 μM, respectively), the antidepressants studied did not significantly

Table 1. Inhibition of cyclic AMP and IP_1 accumulations induced by NE, isoproterenol, 6-FNE or forskolin in the absence or presence of propranolol and prazosin

	Stimulation (%)					
	[^{14}C]cAMP			[^{3}H]IP_1		
	Alone	+Pz	+Pp	Alone	+Pz	+Pp
NE	100 ± 9	75 ± 6*	18 ± 2†	100 ± 11	3 ± 2†	100 ± 8
Isoproterenol	70 ± 11	65 ± 8	2 ± 1†	2 ± 1	0 ± 1	1 ± 1
6-FNE	7 ± 3	0 ± 1*	8 ± 2	60 ± 9	1 ± 1†	56 ± 5
Forskolin	256 ± 37	251 ± 32	260 ± 28	2 ± 1	3 ± 2	1 ± 1

The concentration of NE, 6-FNE and forskolin was 100 μM, that of isoproterenol 1 μM. Antagonists, propranolol (Pp; 10 μM) and prazosin (Pz; 1 μM), were added 10 min before the agonist. These antagonists alone did not modify basal values which were 0.540 ± 0.037 and 0.044 ± 0.003 pmol/mg protein/45 min for cyclic AMP and IP_1 formations, respectively.

Data are expressed as percentages ± SEM of NE response (NE alone = 100% which represented 4.950 ± 0.225 and 0.341 ± 0.016 pmol/mg protein/45 min for cyclic AMP and IP_1 accumulations, respectively).

Values are from three separate experiments, each carried out in triplicate.

Significantly different from agonist stimulation without antagonist by Student's *t*-test or Mann–Whitney test (*$P < 0.05$, †$P < 0.0001$).

modify IP metabolism at concentrations lower than 100 μM. Likewise, dose–response curves (Fig. 3a) indicate that at least a 100 μM antidepressant concentration was necessary to inhibit NE-elicited cyclic AMP accumulation whatever the drug tested (Fig. 3b). This inhibition was only observed with mianserin, amitriptyline, maprotiline and desipramine and was more pronounced with 6-FNE (Fig. 3c).

Effects of adrenergic agonists and forskolin after chronic administration of desipramine or citalopram

Neither chronic desipramine administration (16 mg/kg/day for 8 days) nor citalopram (1 mg/kg/day for 8 days) modified the IP_1 accumulation induced by the α_1-agonists (Figs 4 and 5). Cyclic AMP accumulation elicited by 100 μM NE or 1 μM isoproterenol was decreased (−39%) after desipramine (Fig. 4) but not after citalopram administration (Fig. 5). In the same way, no significant change was seen with 6-FNE and forskolin after chronic antidepressant administration.

DISCUSSION

None of the antidepressants studied modified the cyclic AMP accumulation induced by isoproterenol or forskolin after an acute administration. The stimulation rates were close to those of Fowler and O'Donnell [16] and Zini *et al.* [17]. The isoproterenol response was entirely abolished by propranolol which suggested that the cyclic AMP formed is directly linked to β-adrenoceptor stimulation. On the contrary, the forskolin response was not modified by propranolol. This is in accordance with the results of Seamon and Daly [18] who demonstrated that this compound acts directly on the catalytic unit of the enzyme. This confirms that antidepressants do not affect directly the β-adrenoceptor–adenylate cyclase complex. However, some of these drugs (mianserin, amitriptyline, maprotiline, desipramine) at 100 μM could decrease the cyclic AMP accumulation elicited by NE and 6-FNE. The most active drugs were those who showed the strongest antagonistic properties towards α_1-adrenoceptors, i.e. mianserin, amitriptyline, maprotiline and, to a lesser extent, desipramine [14]. The same blocking effect was observed with prazosin suggesting that this accumulation of cyclic AMP was induced by stimulation of α_1-adrenoceptors. Prazosin partially or completely antagonized the cyclic AMP accumulation induced by NE or 6-FNE, respectively.

It should be noted that in the presence of prazosin the stimulations elicited by NE and isoproterenol were equal. Moreover, propranolol did not inhibit the 6-FNE-induced cyclic AMP accumulation.

All these results suggest that *in vitro* antidepressants inhibit a part of the cyclic AMP production which could be related to the stimulation of α_1-adrenoceptors directly linked to adenylate cyclase [19, 20] or to the production of IP_1 which is supposed to indirectly decrease the activity of adenylate cyclase [21].

Indeed, IP_1 production was decreased in the presence of high concentrations of all the antidepressants studied except the monoamine oxidase inhibitor drugs. This is in accordance with other data [22–24]. This inhibition of IP_1 accumulation can be attributed to the α_1-adrenoceptor blocking properties of these drugs as we observed a significant correlation between their ability to inhibit NE-stimulated IP_1 formation and their affinity for α_1-adrenoceptors ($r = 0.85$, $P < 0.01$). Nevertheless, this α_1-antagonist effect is probably only observable with the most active molecules (i.e. amitriptyline, mianserin and nomifensine). IP metabolism remained unchanged after chronic desipramine or citalopram treatment. One could expect an increase in the production of IP compounds because several authors found an increase in the density of α_1-adrenoceptors following

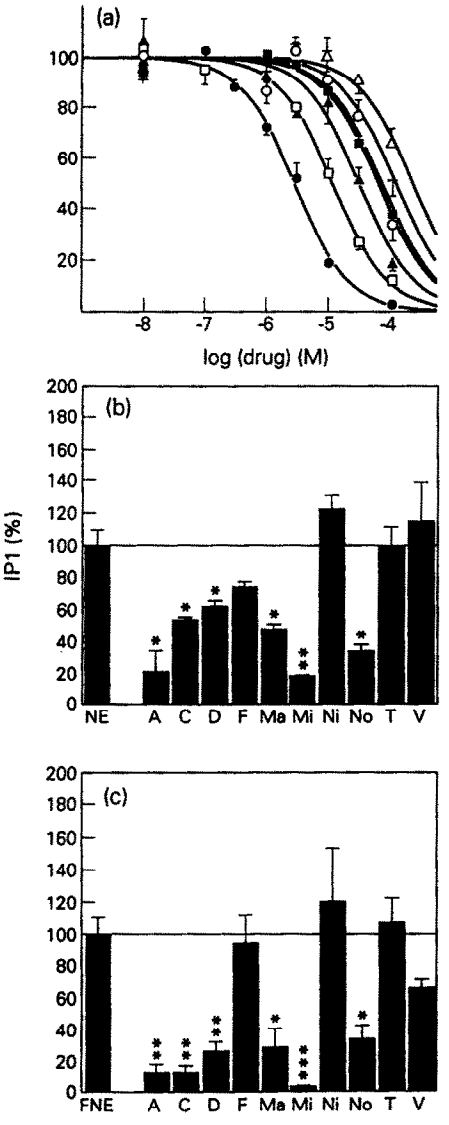

Fig. 2. Stimulation of IP_1 formation by NE (a, b) or 6-FNE (c) (100 μM) alone or in the presence of several antidepressants: amitriptyline (A, ●), citalopram (C, +), desipramine (D, ○), fluoxetine (F, △), maprotiline (Ma, ■), mianserin (Mi, □), nialamide (Ni), nomifensine (No. ▲), tranylcypromine (T) and viloxazine (V). Antidepressants were used at 100 μM (b, c) or at increasing concentrations (a). Data are expressed as percentages of IP_1 response to 100 μM agonist (100%, NE, 0.306 ± 0.027 and 6-FNE, 0.238 ± 0.027 pmol/mg protein/45 min). Each bar represents the mean ± SEM of two to four experiments, each carried out in triplicate. Significantly different from agonist stimulation by Student's t-test (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$).

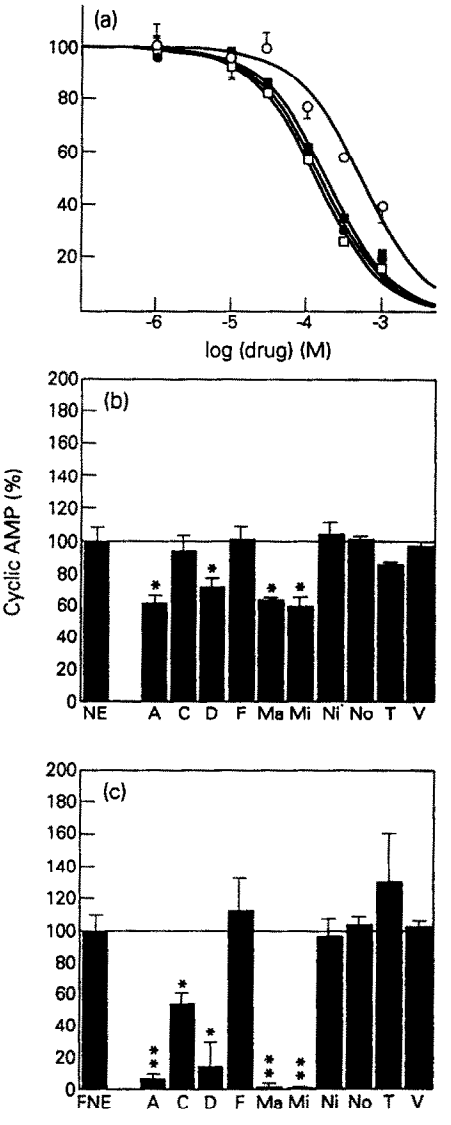

Fig. 3. Stimulation of cyclic AMP accumulation by NE (a, b) or 6-FNE (c) (100 μM) alone or in the presence of several antidepressants. Drugs were used at 100 μM (b, c) or at increasing concentrations (a). For drug abbreviations and symbols see legend to Fig. 2. Data are expressed as percentages of cyclic AMP response to 100 μM agonist (100%, NE, 6.255 ± 0.315 and 6-FNE, 1.107 ± 0.072 pmol/mg protein/45 min). Each bar represents the mean ± SEM of two to four experiments, each done in triplicate. Significantly different from agonist stimulation by Student's t-test (*$P < 0.05$, **$P < 0.01$).

repeated administration with different antidepressants including these two drugs [9, 25]. Our data does not support the hypothesis of an α_1-adrenoceptor upregulation but reinforced the findings of Fowler *et al.* [26] and Li *et al.* [22] who showed that the NE-stimulated inositol phospholipid hydrolysis was not affected by antidepressants. However, we cannot exclude that such an upregulation may occur only with the antidepressants which display high affinities for α_1-adrenoceptors (e.g. amitryptiline, mianserin) but it seems unlikely to be a common mechanism of action of these drugs.

It should also be stated that the duration of the administrations was shorter (1 week) and the dosage of the drug lower, especially for citalopram (1 mg/

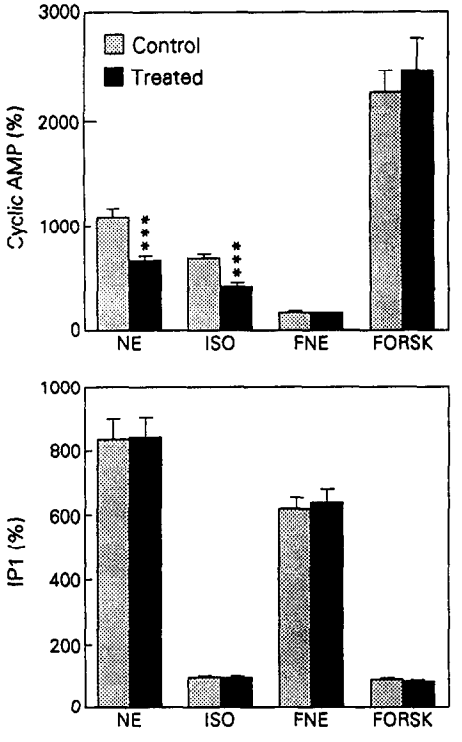

Fig. 4. Effects of chronic administration of desipramine on the responses of cyclic AMP and IP_1 to NE, isoproterenol (ISO), 6-FNE (FNE) and forskolin (FORSK) in slices of cerebral cortex in the rat. Desipramine (16 mg/kg/day) was administered for 8 days using minipumps. NE, 6-FNE and forskolin at 100 μM and 1 μM isoproterenol were used. Data expressed as percentages of basal stimulation (100% represented 0.553 ± 0.122 and 0.042 ± 0.002 pmol/mg protein/45 min for cyclic AMP and IP_1 formations, respectively) are means ± SEM of experiments carried out in quadruplicate with 8–12 animals. Significantly different from saline-treated rats by Mann–Whitney test (***$P < 0.0001$).

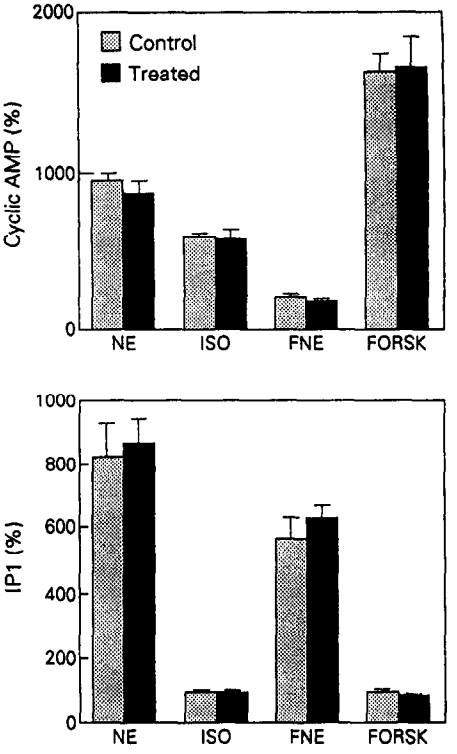

Fig. 5. Effects of chronic administration of citalopram (1 mg/kg/day for 8 days) on the responses of cyclic AMP and IP_1 to 100 μM NE, 6-FNE (FNE), forskolin (FORSK) and 1 μM isoproterenol (ISO) in rat cerebral cortical slices. Data expressed as percentages of basal response (100% represented 0.405 ± 0.023 and 0.042 ± 0.002 pmol/mg protein/45 min for cyclic AMP and IP_1 accumulations, respectively) are means ± SEM of experiments done in quadruplicate with 8–12 animals.

kg/day), than in studies which demonstrated an upregulation of α_1-adrenoceptors. We selected these doses as they were effective in the learned helplessness test [27]: our data show that under these conditions desipramine decreased NE- and isoproterenol-elicited cyclic AMP production as described previously [2, 28, 29]. A direct action of desipramine on the enzyme can be discarded as forskolin-stimulated cyclic AMP accumulation remained unchanged. This decrease is probably linked to the down-regulation of β-adrenoceptors observed by numerous authors [3, 4, 30], as it was similar (−39%) with NE and isoproterenol. Moreover, the production of cyclic AMP induced by 6-FNE which seems to be mediated by α_1-adrenoceptors [20, 31] was not modified. This decrease in cyclic AMP production occurs in the first week of treatment [32, 33] and it was suggested to be one of the common pathways of the antidepressant effect [34, 35]. However, all antidepressants do not modify cyclic AMP accumulation [36, 37]. In this study, chronic citalopram treatment did not, as found by Hyttel *et al.* [38] with a higher dosage. There seems there to be a difficulty in finding a common biochemical modification with either a selective NE or a serotonin uptake blocker but a pharmacological effect resulting from a multiple step process, the ultimate one being common to all the antidepressant drugs, cannot be eliminated. In this hypothesis the decrease in cyclic AMP production could be viewed as the first effect of NE uptake blockers since our data does not support the assumption of a modification of α_1-adrenoceptor-stimulated IP metabolism after chronic antidepressant treatment.

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