Pharmacology Biochemistry & Behavior, Vol. 39, pp. 437–442. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/91 $3.00 + .00

Behavioral and Neurochemical Modifications Caused by Chronic Alpha-Methylparatyrosine Administration

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Received 3 August 1990

MOLINENGO, L., P. GHI, L. OGGERO AND M. ORSETTI. *Behavioral and neurochemical modifications caused by chronic alpha-methylparatyrosine administration.* PHARMACOL BIOCHEM BEHAV **39**(2) 437–442, 1991.—The chronic administration of alpha-methylparatyrosine (AMT) caused a reduction of the noradrenaline levels in the hippocampus (at 150 and 300 mg/kg/day) and in the subcortex (at 30, 150 and 300 mg/kg/day). The acetylcholine levels were reduced in the hippocampus and in the olfactory brain at all the tested doses of AMT. An increase of the B_{max} of muscarinic and α_1-adrenoceptors was observed at 30 mg/kg/day of AMT; only in the subcortex AMT caused no modification of the density of muscarinic receptors. The degree of increase of the receptors density at 30 mg/kg/day was reduced at the higher doses of AMT. AMT 30 mg/kg/day caused a reduction of the errors in the staircase maze after 20 days of interruption of the daily training. These results might suggest a correlation between the behavioral effect and the increase of density, not only of the adrenoceptors, but also of the muscarinic receptors. It is proposed that the behavioral effects caused by chronic AMT are the consequence of complex neurochemical interactions.

α-Methyl-p-tyrosine ACh levels NA levels Muscarinic receptors α_1-Adrenoceptors Forgetting
Chronic administration Cortex Hippocampus Olfactory brain Subcortex

A large body of literature suggests that catecholaminergic systems play an important role in regulating memory function in animals [see (16,23) for reviews]. According to Squire and Davis (25), brain noradrenaline (NA) seems not to play an essential role in the formation of memory. However, there is evidence that NA may play a role in memory retention (11,15).

Altman and Quatermain (1) observed that catecholamine stimulating agents alleviated the memory deficit caused by anisomycin. Pharmacological agents which stimulate the monoamine system improve memory retrieval (24), and transplantation of NA neurons improved retention and retrieval in aged rats (8).

In the studies reviewed above, the improvement of memory retention was obtained with procedures which stimulate the catecholaminergic systems of the CNS and it may be supposed that a reduction of the activity of central monoamine systems might cause the opposite effect. To verify the validity of this supposition we studied how the inhibition of catecholamine biosynthesis caused by a chronic administration of α-methyl-p-tyrosine (AMT) (31) modified the memory retention of an operant conditioned reflex. In addition, the level of NA and the density of α_1-adrenoceptors were evaluated in experimental situations similar to those used in behavioral experiments to see if there was any correlation between the neurochemical and behavioral modifications caused by the chronic administration of AMT.

It may be noted that interference between aminergic and cholinergic systems (3, 4, 29, 30) may play a role in the modifications of behavior caused by the chronic AMT administration. Therefore, the levels of acetylcholine (ACh) and the density of muscarinic receptors were also evaluated in the same experimental situations. Neurochemical measures were made in tissue from the cortex, hippocampus, olfactory brain and subcortex.

METHOD

Subjects

Male albino rats (Morini, Wistar derived strain) of 150–200 g were used. They were housed 5 per cage and fed ad lib with a standard rodent diet, except when otherwise stated. They had free access to tap water.

Sections of the CNS Examined

The following sections were selected to evaluate ACh and NA levels and the density of muscarinic and α_1-adrenergic receptors: 1) frontal and parietal cortex (cortex); 2) olfactory bulbs with the cortex piriformis and the tuberculum olfactorium (olfactory system); 3) the hippocampus; 4) the remaining brain (subcortex) after cerebellum, pons, medulla oblongata and the residual parts of the cerebral cortex have been removed and discarded.

The Staircase Maze

The staircase maze, described in a previous research (6,7), was used. A staircase of 13 steps with a corridor 17 cm long in the vertical wall, was employed. Thirty-two rats were used.

They were kept without food from 6 p.m. to 12 a.m. and were trained every morning to find food pellets (45 mg, Campden Instruments Ltd.) in the corridor corresponding to the 3rd, 6th, 9th, and 12th steps. After 3 months of preliminary training, all rats ran very rapidly onto the staircase and stopped only at the four reinforced steps. Once this training was completed, a trial without reinforcement was performed on the staircase.

In this trial (pretesting trial) the search for food on the 3rd, 6th, 9th and 12th steps was considered a correct response and the search for food on any other steps was considered an error. Then daily training was interrupted for 20 days and a new trial with no reinforcement (testing trial) was performed. Therefore, the experimental scheme was: a) three months of preliminary training, b) pretesting trial, c) no training and AMT administration (15 days), d) no training and no drug administration (5 days) and e) testing trial. Correct responses and errors were counted in the pretesting and in the testing trials. In the first 15 days of the 20-day interval between the two trials without reinforcements, AMT was administered subcutaneously. Control rats received subcutaneously 1 ml of saline solution. As the staircase was composed of 13 steps, the rat had the possibility in each trial of making 4 correct responses (the 3rd, 6th, 9th and 12th steps) and 9 errors.

The ratios (correct responses/total responses) × 100 were calculated from the experimental data obtained in the pretesting and in the testing trials. The percent differences between these two indices were used to evaluate the decay of rat performances consequent to the interruption of the daily training.

TABLE 1

STAIRCASE MAZE TEST: EFFECT OF A CHRONIC ADMINISTRATION (15 DAYS) OF ALPHA-METHYL-P-TYROSINE ON MEMORY DECAY

	% Differences		p
	Mean	S.E.M.	(Dunnett's test)
Controls (8)	16.30	5.17	—
AMT 30 mg/kg/day (8)	−7.50	5.19	>95%
AMT 75 mg/kg/day (8)	28.75	6.35	<95%
AMT 150 mg/kg/day (8)	14.40	5.08	<95%

The number of rats is reported in parentheses. Mean ± S.E.M. of the percent differences between the indexes (correct responses/total responses) × 100 found before and at the end of the period with no daily training.

Determination of ACh Levels

Forty-six rats of the same strain and weight as the rats used in the behavioral test were used. They were killed by microwave irradiation of the head (2450 mHz, 1.5 kW, 3.0 s) at 24 h from the last AMT administration. The skull was opened, the brain was frozen (−30°C). The four sections of the CNS were collected and weighed. The tissue was homogenized in a Polytron at 20,000 rpm for about 3 s in 2.0 ml of boiling McIlvaine's citric disodium phosphate buffer (pH 4.0; 0.014 M). The tissue extracts after homogenization were kept for 30 s in boiling water, then transferred to ice-cold water and diluted with equal volumes of frog-Ringer solution (26) containing eserine hemisulfate (20 μg/ml) and double salt concentration to obtain an isotonic medium (2). The extracts so obtained were centrifuged (1000 × g for 30 min). The supernatant was collected for the bioassay of ACh on the rectus abdominis muscle of the frog (26). The concentrations of ACh are given in μg/g of fresh tissue.

Determination of NA Levels

Twenty-five rats of the same strain and weight as the rats used in the other experiments were killed by decapitation. The four brain areas were dissected. The tissue (80 mg tissue in 300 μl) was ruptured by sonication in ice-cold perchloric acid 0.1 M, containing EDTA 0.1% and sodium metabisulfite 0.05%. The samples were centrifuged at 50,000 × g for 30 min at 4°C. The supernatant was purified on acid-washed alumina according to the method of Ehrenstrom and Johansson (10). The NA concentration in the samples was evaluated according to the method of Keller et al. (18) which utilizes high performance liquid chromatography (HPLC) with electrochemical detection.

The mobile phase composition we used was: 92 ml of a solution containing citric acid 1.0 mM (pH 3.45), Na_2HPO_4 0.1 mM, EDTA 0.1 mM, heptansulfonic acid 1.0 mM (pH 3.45) and 8 ml of acetonitrile. The flow rate was of 0.8 ml/min and the potential was +0.70 V. The obtained peaks were automatically integrated by the data module and the evaluation of the NA concentrations was made using external standards. The concentrations of NA (free base) are given in ng/g of fresh tissue. The instrumentation used was composed by a column μBondapak C18 (Waters Associates, Italy), a pump (Waters 510), an electrochemical detector (Waters 460) and a data module (Waters 740).

Muscarinic Receptor Binding

^{3}H-QNB (39 Ci/mM, Amersham) binding to rat brain membranes was performed according to the method of Yamamura and Snyder (32). Twenty rats of the same strain and weight as the rats used in the other experiments were used. The animals were killed by decapitation and the brains were quickly removed. The four brain areas were dissected out and homogenized in 10 ml of ice-cold 0.32 M sucrose solution using a Potter-Elvehjem teflon-glass homogenizer. The homogenates were then centrifuged at 1000 × g for 20 minutes and the resulting pellets were discarded. Protein concentration in the supernatant fluid was determined according to the method described by Lowry (20) using bovine serum albumin as a standard. Aliquots of supernatant (25–50 μl; 0.2 mg of protein) were incubated in triplicate with increasing concentrations of ^{3}H-QNB (0.05–2.0 nM) for 60 min at 25°C in Na-K phosphate buffer, pH 7.4. Incubations with atropine 1 μM were included to obtain unspecific binding.

The reaction was stopped by addition of 3 ml of ice-cold phosphate buffer followed by filtration under reduced pressure over presoaked Whatman GF/B glass fiber filters. Filters were washed three times with 5 ml of ice-cold buffer. Radioactivity was determined by allowing the dried filters to stand overnight in 5 ml of Beckman Ready-Gel® scintillator followed by liquid scintillation counting (Beckman LS-3801) at 40% efficiency. B_{max} and K_d values were estimated by Scatchard analysis and given in fmol/mg proteins and in pM respectively.

α_1-Adrenoceptors Binding

^{3}H-Prazosin (85 Ci/mM Amersham) binding to rat brain membranes was performed according to the method of Glossman (13). Twenty rats of the same strain and weight as the rats used in the other experiments were killed by decapitation. The different brain areas were quickly removed and homogenized with a Potter-Elvehjem teflon-glass homogenizer in ice-cold 50 mM Tris-HCl and 1 mM EDTA, pH 7.4 buffer.

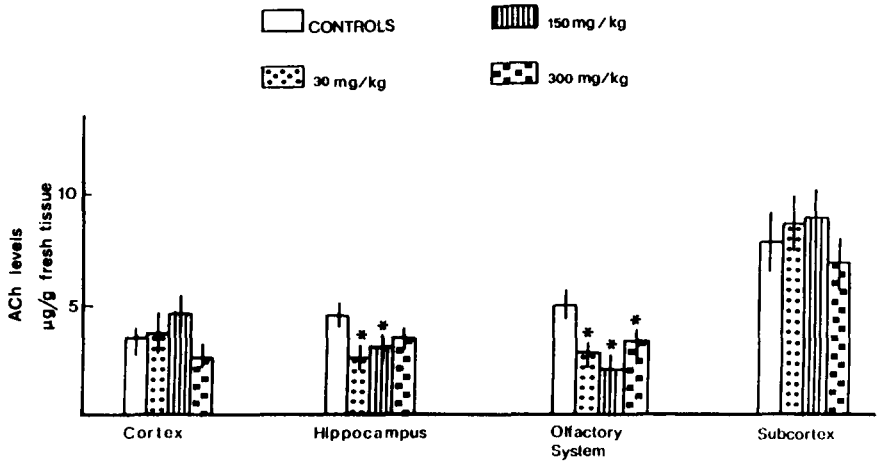

FIG. 1. Acetylcholine levels (µg/g of fresh tissue) found in sections of CNS after chronic administration of AMT 30; 150 and 300 mg/kg/day. Shown are mean values ± S.E.M. of at least 10 rats per point. *The probability of a difference to the controls (Dunnett's test) is over 95%.

Homogenates were centrifuged at 4°C for 15 min at 48,000 × g. The final pellet was resuspended in ice-cold Tris-HCl buffer (pH 7.4). Protein concentration of resuspended pellets was determined according to the method described by Lowry (20) using bovine serum albumin as standard.

Tubes containing ^{3}H-prazosin (0.5–2.5 nM) and an aliquot of resuspended tissue, corresponding to 1.5 mg of protein, were incubated in triplicate (final volume 250 µl). After 15 min of incubation at 37°C, samples were diluted with 3 ml of ice-cold Tris-HCl buffer and rapidly filtered through presoaked Whatman GF/B filters. The filters were rinsed with three 5 ml washes of ice-cold Tris-HCl buffer. The filters were placed in vials containing 5 ml liquid of scintillation (Beckman Ready-Gel®) and counted in a Beckman LS 3801 liquid scintillation counter (efficiency 40%). Specific binding was defined as the excess over blanks containing 1 µM unlabelled prazosin. The value of B_{max} (fmol/mg protein) and K_d (nM) were estimated by Scatchard analysis.

Pharmacological Treatments

The alpha-methylparatyrosine methylester hydrochloride (Sigma) (AMT) dissolved in saline was injected subcutaneously once every 24 h for 15 days.

In the behavioral test, doses of 30, 75 and 150 mg/kg/day were tested. Higher doses were not used to avoid toxic peripheral effects that may interfere with the rat performance. In the last 5 days of the behavioral test lasting 20 days, the drug ad-

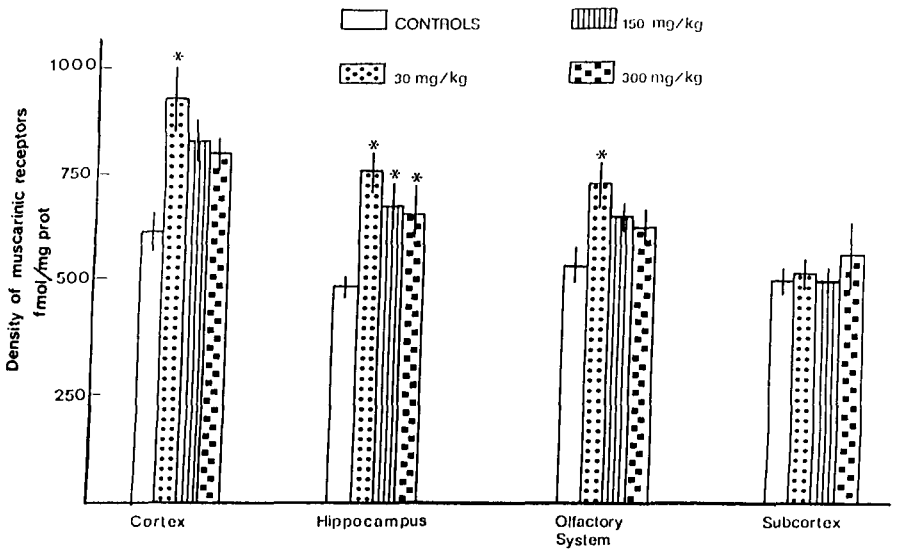

FIG. 2. Density of muscarinic receptors (B_{max} in fmol/mg protein) found in sections of CNS after chronic administration of AMT 30; 150 and 300 mg/kg/day. Shown are mean values ± S.E.M. of at least 4 rats. *The probability of a difference to the controls (Dunnett's test) is over 95%.

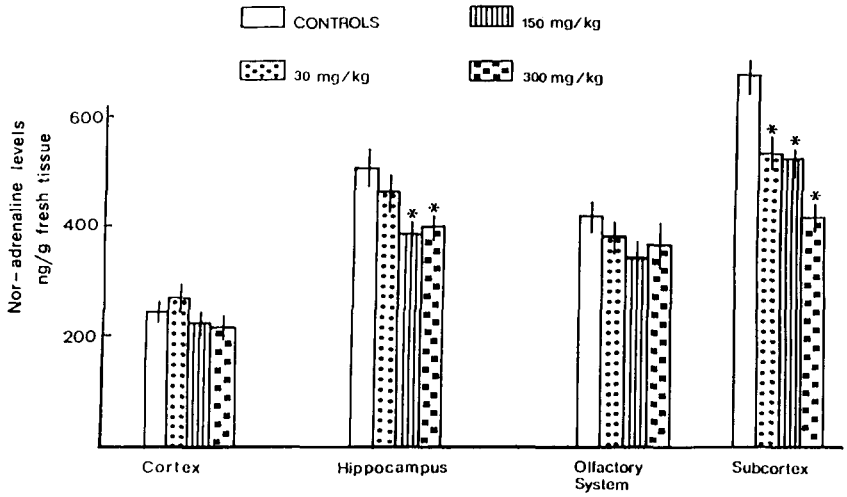

FIG. 3. Noradrenaline levels (ng/g of fresh tissue) found in sections of the CNS after chronic administration of AMT 30; 150 and 300 mg/kg/day. Shown are mean values ± S.E.M. of at least 5 rats per point. *The probability of a difference to the controls (Dunnett's test) is over 95%.

ministration was discontinued to avoid interference of peripheral effects of AMT on rat behavior in the staircase maze. The doses of AMT administered to the rats used for neurochemical measurements were chosen taking into account the results of the behavioral experiments. The selected dosed were 30 and 150 mg/kg/day of AMT. The dose of 300 mg/kg/day was also tested in order to confirm neurochemical modification of limited significance at a higher dosage. In these experiments, rats were killed 24 hours after the last AMT administration.

RESULTS

Staircase Maze

In Table 1 the means and the standard errors of the percent differences between the indexes (correct responses/total responses) × 100 found immediately before and at the end of the interruption of the daily training are given for the controls and for the rats treated with AMT 30, 75 and 150 mg/kg/day for 15 days. The analysis of variance applied to all the experimental data indicates that the modifications caused by the pharmacological treatment are significant, $F(3,28) = 4.77$, $p \approx 0.01$.

The Dunnett's test for the comparison with a control ($p > 95\%$) indicates that only 30 mg/kg/day of AMT caused a significant reduction of the percentages of errors after 20 days of interruption of daily training.

ACh Levels

The levels of ACh (μg/g of fresh tissue) found in the sections of the CNS examined after 15 days of administration of 30, 150 and 300 mg/kg/day of AMT are given in Fig. 1. The levels of ACh found in the controls (cortex 3.59 ± 0.37 μg/g, hippocampus 4.53 ± 0.51 μg/g, olfactory system 5.00 ± 0.33 μg/g, subcortex 7.81 ± 1.17 μg/g) are in the range of the values given by other authors (9,21).

The analysis of variance indicates that the differences between the sections examined are significant, $F(3,177) = 49.22$, $p < 0.001$. The AMT administration caused a significant reduction of the ACh levels, $F(3,177) = 49.22$, $0.05 > p > 0.01$.

Dunnett's test ($p > 95\%$) for the comparison with a control indicates (Fig. 1) that all the tested doses of AMT caused a reduction of the ACh levels in the olfactory system. In the hippocampus the reduction of the ACh levels is significant only at 30 and 150 mg/kg/day of AMT. In the cortex and in the subcortex there is no significant modification of the ACh levels.

Muscarinic Receptors

The B_{max} (fmol/mg prot.) found in the various experimental situations are given in Fig. 2. The values found in the controls ranging from 613 ± 47 fmol/mg of protein (in the cortex) to 480 ± 14 fmol/mg prot. (in the hippocampus) are in the range of the values given by Yamamura and Snyder (32).

The analysis of variance indicates that the differences between the sections, $F(3,69) = 19.36$, $p < 0.001$, and between controls and treated groups, $F(3,69) = 16.08$, $p < 0.001$, are significant. Dunnett's test for the comparison with a control ($p > 95\%$) (see Fig. 2) indicates that the increase of B_{max} caused by AMT is significant in the cortex only at 30 mg/kg/day of AMT. In the hippocampus, all the tested doses of AMT caused a significant increase of B_{max}. In the subcortex there is no significant modification of B_{max}. In the olfactory system the modification of the values of B_{max} is significant only at 30 mg/kg/day of AMT and it is no more significant at 150 and 300 mg/kg/day. In some way a reduction of the AMT effect at the higher doses may be noted also in the hippocampus.

No variation of the dissociation constant (K_d) for the radioligand was observed: the maximal variation observed was from 102 ± 14 pM to 90 ± 9 pM. These values are in range of the values given by Yamamura and Snyder (32).

NA Levels

The levels of NA in the sections of CNS examined after the chronic administration of the different doses of AMT are given in Fig. 3. The values found in the controls (cortex 238 ± 7 ng/g, hippocampus 494 ± 29 ng/g, olfactory system 422 ± 17 ng/g, subcortex 689 ± 41 ng/g of fresh tissue) are in the range of the

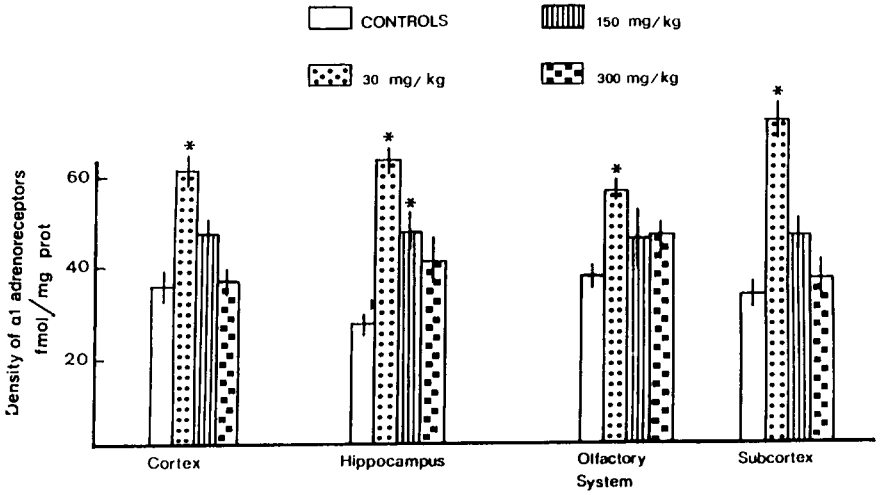

FIG. 4. Density of α_1-adrenoceptors (B_{max} in fmol/mg protein) found in sections of CNS after chronic administration of AMT 30; 150 and 300 mg/kg/day. Shown are mean values ± S.E.M. of at least 4 rats per point. *The probability of a difference to the controls (Dunnett's test) is over 95%.

values given by Ehrenstrom and Johansson (10).

The analysis of variance indicates that the differences between the controls and treated groups, $F(3,84)=10$, $p<0.001$, and the differences between the sections of the CNS, $F(3,84)=75$, $p<0.001$, are significant.

The significance of the differences compared to controls (Dunnett's test $p>95\%$) are given in Fig. 3. The results reveal that the reduction of the levels of NA caused by AMT in the subcortex is apparently correlated to the doses of AMT. In the hippocampus the reduction of the NA levels is significant only at 150 and 300 mg/kg/day of AMT. In the cortex and in the olfactory system there is no significant modification.

α_1-Adrenergic Receptors

The B_{max} (fmol/mg protein) found in the various experimental situations are given in Fig. 4. The values found in the controls (from 36.2 ± 2.0 fmol/mg prot. in the olfactory system to 26.9 ± 1.8 fmol/mg prot. in the hippocampus) are in the range of the values given by Perry et al. (22) for Buffalo strain rats.

The analysis of variance indicates that AMT administration caused a significant modification in the B_{max}, $F(3,65)=52.01$, $p<0.001$. Dunnett's test ($p>95\%$) indicates that there is an increase of the B_{max} in all the examined sections at 30 mg/kg/day of AMT. Only in the hippocampus is the observed increase significant at 150 mg/kg/day also.

No variation of the dissociation constant (K_d) for the radioligand (^{3}H-prazosin) was observed. The values found varied from 0.36 ± 0.08 nM to 0.30 ± 0.05 nM and are in the range of the values given by Perry et al. (22).

DISCUSSION

In the behavioral test, the chronic administration of AMT was discontinued 5 days before the trials at the end of the no-training period. The rats used for the neurochemical measures were killed 24 hours from the last AMT administration. Neurochemical modifications caused by the chronic AMT administration (15 days) may be the condition determining a modification of the spontaneous decay of memory, which was evaluated after AMT administration has been discontinued for 5 days. This 5-day waiting period reduced the interference of peripheral effects of AMT on rat behavior. No weight reduction and certainly no sign of peripheral effects were noted at the moment in the testing trial. The results of the present work indicate that AMT reduced the levels of NA in the hippocampus and in the subcortex.

The NA levels in the cortex and in the olfactory system are unchanged. The reduction of cerebral NA after AMT administration can be considered a well-established fact (12, 18, 19, 27) and there is also evidence that this effect of AMT differs according to the section of CNS examined (27).

There is a discrepancy between our results and the data given by Stein et al. (27) concerning the cortex. This may be due to the chronic administration of AMT in our experiments. This might suggest that, at least in certain structures, some form of tolerance to AMT develops. In the same experimental conditions, AMT caused no modifications of the dissociation constant of the radioligand ^{3}H-prazosin. The density of α_1-adrenoceptors increased at 30 mg/kg/day of AMT in all brain regions (Fig. 4).

It may be supposed that the up-regulation of α_1-receptors is a mechanism to compensate for the reduction of the neurotransmitter. At higher doses of AMT, this effect becomes less evident, presumably as a consequence of toxic actions of high doses of AMT. It may be noted that concomitant with the up-regulation of α_1-receptors, there is a reduction of the percentage of errors in the staircase maze at 30 mg/kg/day of AMT. This effect and the up-regulation of α_1-receptors are reduced, disappearing at higher doses of AMT. The ACh levels are reduced in the hippocampus and in the olfactory system (Fig. 1). In these sections the effect is more evident at 30 mg/kg/day of AMT. No modification of the dissociation constant of the radioligand ^{3}H-QNB was observed and the density of muscarinic receptors increased at 30 mg/kg/day of AMT in the olfactory system, in the cortex and hippocampus. This up-regulation of muscarinic receptors is reduced at higher doses of AMT in the olfactory system.

In the cortex it disappears at 150 and 300 mg/kg/day. To explain the reduction of levels of ACh caused by AMT, it may be noted that Giralt and Garcia-Sevilla (12) reported a reduction of the density of α_2-adrenoceptors after AMT administration. This

down-regulation of α_2-adrenoceptors may enhance (3, 5, 28, 29) the ACh release with a reduction of ACh levels, as we observed. The up-regulation of the muscarinic receptors we observed may be a compensatory mechanism resulting from the reduction of the levels of neurotransmitter (ACh). Therefore, in consequence of rather complex interactions between aminergic and cholinergic systems, the chronic administration of AMT causes very similar modifications in the α_1-adrenergic and in the muscarinic systems.

Considering that Stein et al. (27) reported an increase of 5-HT turnover after AMT administration, there is the possibility that functional modifications of the serotoninergic system may also play a role in the modifications of behavior consequent to the AMT administration. Therefore, it may be suggested that, although the effect of AMT is specific at a biochemical level (inhibition of tyrosine hydroxylase), modifications of the spontaneous decay of memory caused by chronic AMT may be determined by functional modifications of several neurochemical systems.

ACKNOWLEDGEMENT

This work was supported by Ministero della Pubblica Istruzione (60%, 1988).

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