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Effects of amantadine on circulating neurotransmitters in healthy subjects

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Abstract Considering that glutamatergic axons innervate the C1(Ad) medullary nuclei, which are responsible for the excitation of the peripheral adrenal glands, we decided to investigate catecholamines (noradrenaline, adrenaline and dopamine) plus indolamines (plasma serotonin and platelet serotonin) at the blood level, before and after a small oral dose of amantadine, a selective NMDA antagonist. We found that the drug provoked a selective enhancement of noradrenaline plus a minimization of adrenaline, dopamine, plasma serotonin and platelet serotonin circulating levels. Significant enhancement of diastolic blood pressure plus reduction of systolic blood pressure and heart rate paralleled the circulating parameter changes. The above findings allow us to postulate that the drug was able to enhance the peripheral neural sympathetic activity. Minimization of both adrenal sympathetic and parasympathetic activities was also registered after the amantadine challenge. The above findings supported the postulation that this drug should be a powerful therapeutic tool for treating diseases affected by adrenal sympathetic hyperactivity.

Keywords Adrenal sympathetic activity · Neural sympathetic activity · Amantadine · Rostral ventrolateral medullary C1(Ad) nuclei · A5(NA) pontomedullary nucleus · NMDA glutamatergic antagonist · Neural sympathetic activity · Adrenal sympathetic activity · Serotonin · Adrenaline · Noradrenaline · Catecholamines

Introduction

Adrenal glands secrete adrenaline (Ad) (80%) + noradrenaline (NA) and dopamine (DA) (20%), approximately. Sympathetic nerves release NA (80–90%) plus DA. Both branches of the peripheral sympathetic activity may act in association or dissociation (Young et al. 1984), in accordance with the physiological and/or pathophysiological circumstances. At the central nervous system level, the C1(Ad) rostral ventral lateral (RVL) medullary nuclei and the A5(NA) pontomedullary nucleus are responsible for these two branches of the peripheral autonomic nervous system (ANS), respectively (Bazil and Gordon 1993; Byrum and Guyenet 1987; Guyenet 1984; Li et al. 1992; Loewy and Haxhiu 1993; Morrison et al. 1991; Strack et al. 1989; Woodruff et al. 1986). Both CNS structures interchange inhibitory axons. Adrenaline released from C1-axons inhibits A5(NA) neurons by acting at alpha-2 post-synaptic receptors, whereas NA released from A5(NA) axons inhibits the adrenergic nuclei by acting at alpha-2

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inhibitory receptors located at these latter (Li et al. 1992; Strack et al. 1989; Woodruff et al. 1986).

Amantadine, a glutamate (NMDA) antagonist is considered as an anti-Parkinson agent because it might attenuate the glutamatergic + acetylcholinergic over the dopaminergic predominance at the striatal level (Bibbiani et al. 2005). However, considering that glutamate axons innervate and excite the RVL medullary nuclei, responsible for the adrenal sympathetic activity, by acting at NMDA receptors (Bazil and Gordon 1993; Hand et al. 1997; Morrison et al. 1991), we decided to asses circulating neurotransmitters before and after an oral dose of the drug. With respect to this, we should inform that we have measured those parameters in some 20,000 normal and diseased subjects. Noradrenaline (NA), adrenaline (Ad), dopamine (DA), platelet serotonin (p5-HT), plasma serotonin (f5-HT) and plasma tryptophan have been assessed during supine-resting state and after many types of physiological and pharmacological challenges. The above parameters have been investigated also in a great deal of psychiatric and somatic diseases during both relapses and remission periods (Lechin et al. 1996; Lechin and van der Dijs 2006a, b). Finally, although we have investigated the effects of amantadine on circulating neurotransmitters throughout the oral glucose challenge (Lechin et al. 2009), we decided to assess the above parameters without the sugar administration.

Materials and methods

Experimental design

Levels of plasma noradrenaline (NA), adrenaline (Ad), dopamine (DA), free-serotonin (f5-HT), tryptophan, and platelet serotonin (p5-HT) as well as systolic blood pressure, diastolic blood pressure, and heart rate were measured before (0 min) and after (60, 90 and 120 min) the oral administration of 100 mg of amantadine in 35 healthy volunteers. Platelet aggregation was measured before and after 120 min of the drug administration. We performed similar measurements 2 weeks before, in the same volunteers after administration of placebo. The group of volunteers comprised 19 men and 16 women, whose ages ranged from 26 to 62 years (mean ± SE = 43.5 ± 4.8). Informed consent was obtained in writing from all volunteers, and the procedure was approved by the ethical committee of FUNDAIME. All volunteers were within 10% of ideal body weight, none had any physical or psychiatric illness. Exclusion criteria included pregnancy, lactation, smoking, and alcohol abuse. Volunteers were recumbent during all procedures. A heparinized venous catheter was inserted into a forearm vein at least 30 min before beginning the test. We used cold, plastic syringes to collect blood samples at the times specified above. Amantadine (100 mg) was administered orally after the first blood sample (0 min) was obtained. Blood samples were obtained for measuring plasma neurotransmitters and platelet aggregation. Blood for measuring plasma neurotransmitters was transferred to plastic tubes, each containing 1 ml of an anti-oxidant solution (20 mg of EDTA plus 10 mg of sodium metabisulphite per ml). The tubes were carefully inverted several times and placed on ice until centrifugation. To obtain platelet-rich plasma (PRP), the tubes were centrifuged at 600 rpm at 4°C for 15 min. Two milliliters of PRP was stored at −70°C until needed for determination of p5-HT levels. The remaining blood was centrifuged again at 7,000 rpm, and two aliquots of the supernatant, which was platelet-poor plasma (PPP), were stored at −70°C until needed for determination of catecholamines and f5-HT levels. Blood samples for platelet aggregation were processed immediately. A physician in constant attendance noted any symptoms reported by the subjects and monitored heart rate and blood pressure.

Analytical assays

Neurochemistry

Plasma catecholamine and serotonin samples were measured in duplicate, and all determinations were made at the same time. We used reverse-phase, ion-pair high performance liquid chromatography with electrochemical detection for the detection of monoamines. Optimization of chromatographic conditions and attainment of adequate quantification parameters allowed us to maximize sensitivity and reproducibility (Lechin et al. 1998).

Reagents and standards

Noradrenaline, adrenaline, dopamine, serotonin creatinine sulphate, dihydroxybenzylamine, sodium octyl sulphate, dibutylamine, acid-washed aluminium oxide, Na_2HPO_4, citric acid and EDTA were purchased from Sigma-Aldrich (St. Louis, MO, USA). Microfilters were purchased from Whatman GmbH (Germany) through Merck S.A (Caracas, Venezuela). Acetonitrile and 2-propanol were obtained from Merck, S.A. (Caracas, Venezuela). Glass-distilled water was de-ionized and filtered through a Milli-Q reagent grade water system (Millipore, Bedford, MA, USA). Solvents were filtered through a 0.2-μm Millipore filter and were vacuum de-aerated. Standard solutions (1 mmo1/l) were prepared in 0.1 mo1/l perchloric acid and diluted to the desired concentration.

Equipment

Liquid chromatography was performed using Waters 515 HPLC pump (Waters Corporation, Milford, MA, USA) equipped with a Rheodyne valve injector 7125i, which was fitted with a 50 µl sample loop (Rheodyne; Berodine, Berkeley, CA, USA). A 15 cm × 4.6 mm inner diameter Discovery C18 column packed with octadecylsilane 5 µm particles was preceded by a column prefilter of 2 µm porosity, both from Supelco/Sigma-Aldrich (Sigma-Aldrich, St. Louis, MO, USA). The detection system was a Waters 460 Electrochemical Detector (Waters Corporation, Milford, MA, USA). The potential of the working electrode (glassy carbon) was set at +0.61 V versus the Ag–AgCl reference electrode for the detection of catecholamines and 0.70 V versus the Ag–AgCl for the detection of indolamines. The chromatograms were registered and quantified with the Empower software from Waters Corp. The results were corrected for the volume of EDTA added.

Catecholamines assay

The assay was performed by extraction of the catecholamines onto 20 mg of alumina followed by their elution with 200 µl of 1.0 mol/l $HClO_4$ using Regenerated Cellulose microfilters 0.2 µm pore size (Whatman GmbH). The instrument was calibrated with standard plasma: after incubation with acid-washed aluminium oxide, a plasma pool of free catecholamines was processed similar to plasma samples, but 20 µl of a standard solution of noradrenaline, adrenaline and dopamine (50, 25 and 25 ng/ml, respectively) was added to the plasma pool. Both the standard plasma and the sample plasma were supplemented with 20 µl of internal standard (100 ng/ml of dihydroxybenzylamine). The mobile phase was KH_2PO_4 6.8045 g/l, EDTA 0.100 g/l and di-*N*-butylamine 100 µl/l. Sodium octyl sulphate was added as ion-pair agent in a concentration of 0.6125 g/l with the pH adjusted to 5.6. The sensitivity of this method for noradrenaline, adrenaline and dopamine was 6.4, 5.8 and 2.0 pg/ml, respectively. The intra-assay coefficients of variation were 2.8, 4.0 and 4.0%, respectively. The inter-assay coefficients of variation were 6.7, 4.5 and 4.3%, respectively.

Serotonin assay

After sonication of PRP to disrupt the platelets (Ultrasonic Liquid Processor, model 385; Heat Systems Ultrasonics Inc., Farmingdale, NY, USA), both platelet-rich and platelet-poor plasma were processed in the same way: 200 µl of 3.4 mol/l perchloric acid and 50 µl of 5-hydroxy-tryptophan solution (114.5 µg/ml) as internal standard were added to 1 ml of plasma, vortexed and centrifuged at 10,000 rpm for 15 min at 4°C. The supernatant was filtered through a 0.22 µm membrane (Millipore) and 10 µl was injected into the column. Calibration runs were generated by spiking blank platelet-poor plasma with 50 µl of a solution containing 5-HT (10 µg/ml) and 50 µl of 5-hydroxy-tryptophan (114.5 µg/ml). This standard plasma was processed in the same manner as the samples. The mobile phase was citric acid 3.8424 g/l, sodium acetate 4.1015 g/l, EDTA 0.100 g/l, di-*N*-butylamine 100 µl/l and 30 ml/l of 2-propanol. Sodium octyl sulphate was added as ion-pair agent in a concentration of 4.25 mg/l with a pH of 5.0. The sensitivity of the method for serotonin was 0.1 ng/ml. The intra-assay coefficients of variation for p5-HT and f5-HT were 6.2 and 8.7%, respectively.

Platelet aggregation

Blood was collected with citrate–phosphate dextrose (1:9 v/v) as the anticoagulant. Blood was subsequently centrifuged at 120*g* for 10 min to prepare PRP. Aggregation studies were carried out according to Born's (1962) method, and aggregation was induced by ADP and collagen at final concentrations of 4 µmol/l and 4 µg/ml, respectively. Maximal aggregation, expressed as the percentage of maximal light transmission, was measured.

Statistical methods

Results are presented as the mean ± SEM. Statistical significance was set at $P < 0.05$. Multivariate ANOVA with repeated measurements and correlation coefficients (exploratory factor analysis) were used. Dbase Stats (TM) by Ashton Tate and Statview SE + Graphics by Abacus were used for statistical analyses.

Results

Significant increases of noradrenaline plus decreases of adrenaline and dopamine plasma levels were registered at all post-amantadine periods. Maximal effects for these catecholamines occurred at 90 and 120 min periods (Fig. 1). Hence, significant increases in noradrenaline/adrenaline and noradrenaline/dopamine ratios were also registered at these periods (Fig. 2).

Both f5-HT and p5-HT parameters showed significant decreases throughout the amantadine but not the placebo test. Tryptophan changes were not observed throughout the placebo or the amantadine tests (Fig. 3).

No significant increases of platelet aggregation were registered after the amantadine challenge (120 min).

Significant and sustained systolic blood pressure and heart rate decreases were registered throughout the

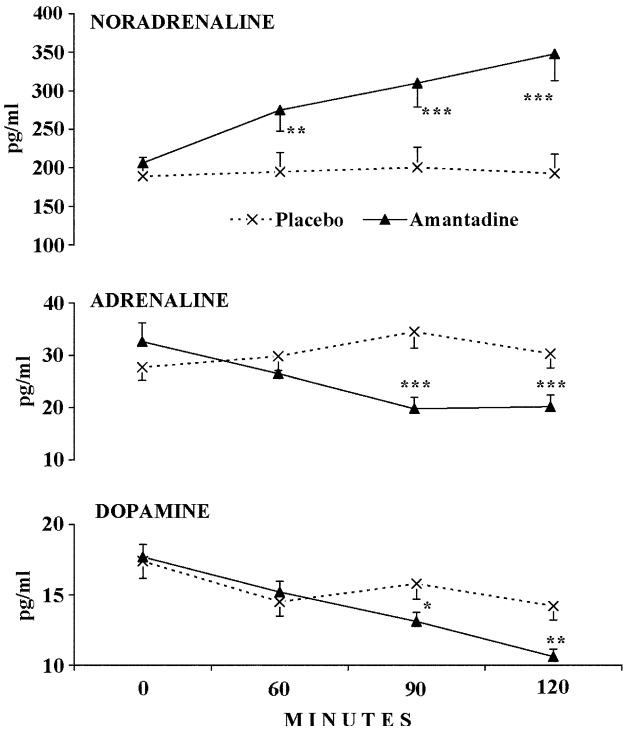

Fig. 1 Noradrenaline, adrenaline and dopamine plasma levels before and after placebo and amantadine test performed 2 weeks apart in 35 healthy volunteers (19 men and 16 women). Results are expressed as mean + SE as the error bars. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ (amantadine versus placebo)

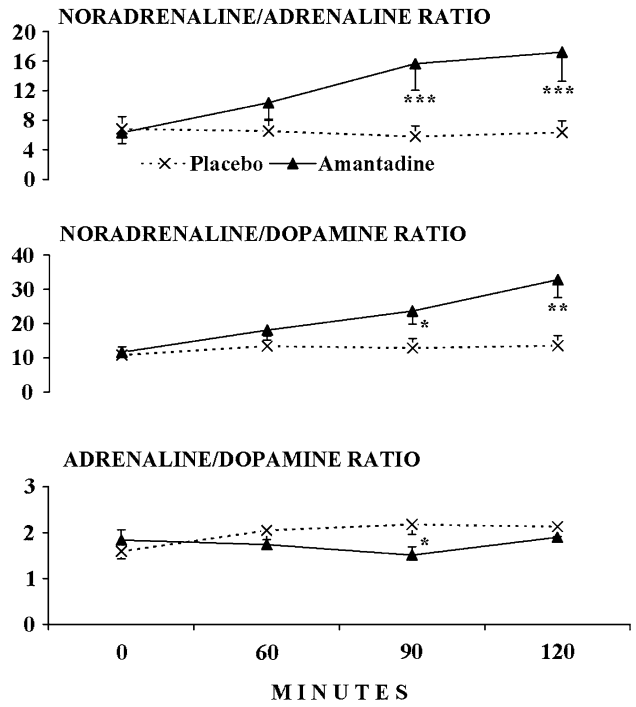

Fig. 2 Amantadine induced a significant rises of the noradrenaline/adrenaline ratio as well as on the noradrenaline/dopamine ratio at the 90 and 120 min periods while a light significant fall was registered at 90 min period on the adrenaline/dopamine ratio after placebo and amantadine tests were performed 2 weeks apart in 35 healthy volunteers (19 men and 16 women). Results are expressed as mean + SE as the error bars. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ (amantadine versus placebo)

amantadine but not the placebo test. Conversely, significant and sustained diastolic blood pressure rises were observed after the amantadine challenge but not after the placebo administration (Fig. 4). Hence, amantadine minimized systolic blood pressure plus heart rate and enhanced diastolic blood pressure.

Significant and progressive negative correlations were found between NA and DA and between NA/Ad ratio and DA throughout the amantadine test. Positive correlations were found between NA/Ad ratio and diastolic blood pressure. Adrenaline versus f5-HT showed significant positive correlation values at post-drug periods (see Table 1).

Discussion

We demonstrated in the present study that a small dose of oral amantadine triggered abrupt and significant reduction of the adrenaline plasma levels which contrasted the significant rises of plasma noradrenaline. In addition, significant reductions of dopamine plasma values were also registered. Furthermore, maximal decreases of both p5-HT and f5-HT were produced throughout the test.

The enhancement of both the NA/AD plus NA/DA ratios registered after the amantadine challenge is consistent with the postulation of the minimization of the adrenal sympathetic activity plus the enhancement of the neural sympathetic activity. With respect to this, it should be remembered that the A5(NA) pontomedullary nucleus, which interchanges inhibitory axons with the C1(Ad) RVL medullary nuclei (Byrum and Guyenet 1987; Guyenet 1984; Morrison et al. 1991), is responsible for the neural sympathetic activity (Morrison et al. 1991; Woodruff et al. 1986), whereas the latter nuclei excite adrenal glands secretion of catecholamines (Ad + DA and NA) (Strack et al. 1989). These medullary nuclei are crowded by excitatory glutamatergic (NMDA) receptors (Caringi et al. 1998; Drye et al. 1990; Elenkov et al., 2000; Li et al. 1992; Loewy and Haxhiu 1993; Maiorov et al. 1999; Strack et al. 1989).

The significant and abrupt fall of serotonin plasma levels (f5-HT) registered in this study should be attributed to the minimization of circulating adrenaline, triggered by the drug. Thus, 5-HT is retained into the platelet store. This issue is consistent with the significant positive correlations between adrenaline versus f5-HT values, registered throughout the post-amantadine periods. This factor should

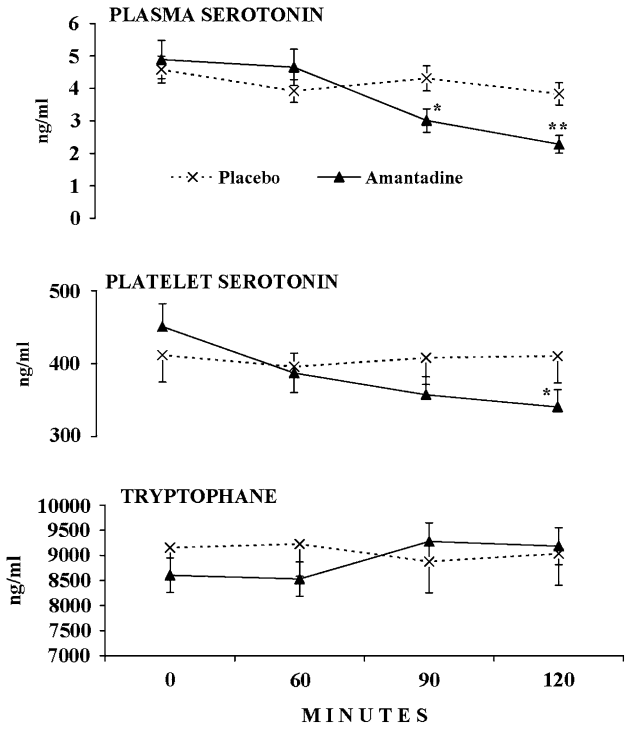

Fig. 3 Plasma serotonin, platelet serotonin and plasma tryptophan circulating levels before and after placebo and amantadine test performed 2 weeks apart in 35 healthy volunteers (19 men and 16 women). Results are expressed as mean + SE as the error bars. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ (amantadine versus placebo)

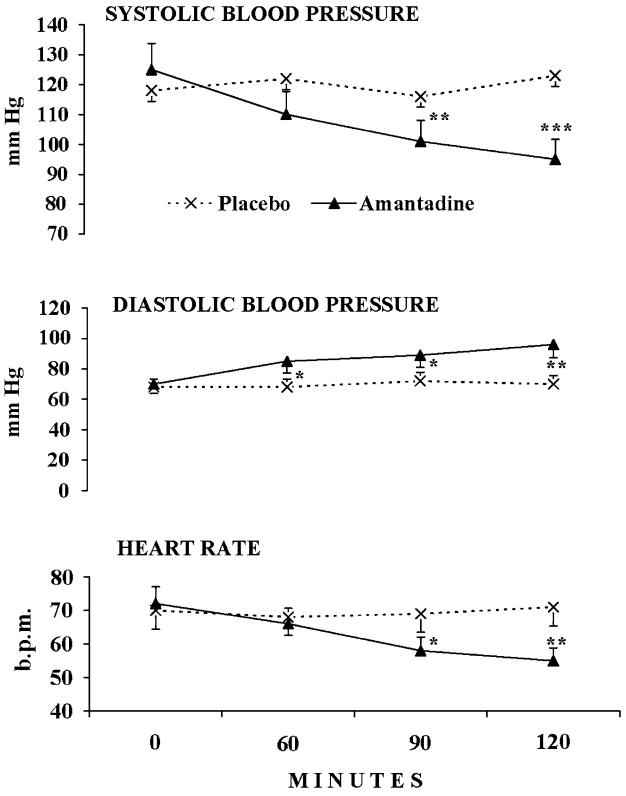

Fig. 4 Cardiovascular parameters registered before and after placebo and amantadine test performed 2 weeks apart in 35 healthy volunteers (19 men and 16 women). Results are expressed as mean + SE as the error bars. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ (amantadine versus placebo)

be added to the reduction of parasympathetic activity triggered by the overwhelming neural sympathetic predominance registered after the amantadine challenge. With respect to this, it should be known that parasympathetic nerves excite enterochromaffin cells which release serotonin to the blood stream (Schwörer et al. 1987; Tobe et al. 1976). In addition, circulating acetylcholine interferes with the uptake of 5-HT by platelets (Rausch et al. 1985). Furthermore, plasma serotonin excites the medullary area postrema (it is located outside of the blood brain barrier) (Reynolds et al. 1989; Wilson and Bonham 1994). This nucleus sends excitatory axons to the C1(Ad) nuclei (Gauthier and Reader 1982; Urbanski and Sapru 1988), thus minimization of this mechanism is responsible for the inhibition of the adrenal sympathetic activity, normally registered during postprandial periods (Lechin 2000; Lechin et al. 1993; 2009). Hence, amantadine would also be able to annul adrenal sympathetic activity throughout the minimization of the area postrema—C1(Ad) axis which depends on the serotonin release by enterochromaffin cells during postprandial parasympathetic period. With respect to the latter, it has been demonstrated that the C1(Ad) nuclei receive excitatory axons from the area postrema (Schwörer et al. 1987; Tobe et al. 1976; Urbanski and Sapru 1988).

Table 1 Significant correlations (r) after oral administration of amantadine 100 mg or placebo in 35 healthy volunteers (19 men and 16 women

	60 min	90 min	120 min
NA versus DA			
Amantadine	−0.43**	−0.67**	−0.81***
Placebo	n.s.	n.s.	n.s.
NA/Ad versus DA			
Amantadine	−0.61**	−0.77***	−0.89***
Placebo	n.s.	n.s.	n.s.
NA/Ad versus DBP			
Amantadine	0.54*	0.65**	0.69**
Placebo	n.s.	n.s.	n.s.
Ad versus f5-HT			
Amantadine	0.58**	0.69**	0.77***
Placebo	n.s	n.s	n.s

NA noradrenaline, *DA* dopamine, *Ad* adrenaline, *DBP* diastolic blood pressure, *n.s.* non-significant

* $P < 0.05$, **$P < 0.01$, ***$P < 0.001$

Summarizing, it should be concluded that amantadine annulled both parasympathetic and adrenal sympathetic activities and favored neural sympathetic predominance. In addition, the neural sympathetic overactivity provoked by amantadine interferes with the parasympathetic drive responsible for the release of intestinal serotonin which redounded in the reduction of both p5-HT and f5-HT circulating levels. With respect to this, we have quoted exhaustive evidence showing the existence of two types of opposite ANS profiles which underlie most diseases: (1) adrenal sympathetic and (2) neural sympathetic (Lechin and van der Dijs 2008, 2009a, b).

According to all the above, we concluded that the administration of an oral dose of amantadine was able to provoke the enhancement of the neural sympathetic branch which minimized both adrenal sympathetic and parasympathetic activities, as reflected by the peripheral autonomic system parameters plus the circulating neurotransmitters profile. The above findings allow the understanding of several therapeutic effects triggered by this drug.

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