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Angiotensin II Increases MAO Activity in Rat Central Nervous System

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The effects of angiotensin II (ANG II) and bilateral nephrectomy on monoamine oxidase (MAO) activity were studied in rat hypothalamus and medulla oblongata. ANG II increased MAO activity in both central nervous system (CNS) regions. The fall of circulating ANG II caused by 48 h bilateral nephrectomy decreased the activity of the enzyme in the mentioned areas. The results showed that ANG II stimulates catecholamine metabolism in the CNS.

Key words: Angiotensin II, MAO, Nephrectomy, Norepinephrine.

Angiotensin II (ANG II) interacts with catecholamines (CA) in several organs and tissues modifying its metabolism (5, 21, 22). An inverse relationship between circulating ANG II levels and norepinephrine (NE) content in the central nervous system (CNS) has been reported (4, 5). Indirect hypertensive effects of ANG II are mediated by the enhancement of sympathetic function (10, 22). ANG II-NE interaction is present at presynaptic nerve ending level (3, 4). It inhibits NE uptake and increases NE synthesis and release from central and peripheral catecholaminergic stores (4, 59). ANG II altered the NE/NE metabolites ratio into cytoplasmatic as well as into vesicular NE stores of the CNS (8). The fall of circulating ANG II caused by bilateral nephrectomy, decreased NE metabolites in hipothalamus and medulla oblongata reaching similar metabolite levels in these regions as in pargyline treated animals. On the other hand, ANG II reversed those effects (9). Since MAO metabolites neuronal NE, these results provided evidence that ANG II could modify and regulate MAO activity. From this point of view these exper-

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iments were planned to study the effects of ANG II and bilateral nephrectomy on MAO activity in different areas of the CNS.

Materials and Methods

Research was carried out in male Wistar rats of about 180-250 g body weight. The experiments were performed in hypothalamus and medulla oblongata of the CNS.

Animals were divided into the following groups: a) control (sham operated), b) injected with ANG II, c) bilaterally nephrectomized.

Under ether anesthesia, the group c animals were previously nephrectomized 48 h before the experiments were carried out. After 48 h of bilateral nephrectomy, circulating ANG II falls to the lowest levels (4). All the groups were anesthetized with urethane (1 g/kg, i.p.). ANG II (Sigma), (2.5 µg dissolved in 40 µl of saline), was injected into the right cerebral ventricle. Groups b and c were injected with saline. After 30 min, the rats were sacrificed by decapitation, between 2 and 3 h p.m., in order to avoid circadian changes, hypothalamus and medulla oblongata were removed, dissected, weighed and then homogeneized. Concentrations of proteins in tissues were measured by spectrophotometric U.V. technique. MAO activity was determined by the fluorometric method of WEISSBACH *et al.* (28). This technique is based on kynuramine oxidation by MAO to aldehide and the further conversion to the fluorescent compound 4-hydroxiquinoleine. Results are expressed as pM of hydroxiquinoleine formed in 30 min/g of protein^{-1}. Analysis of variance followed by orthogonal comparisons was used for the analysis of results.

Results

Table I shows that ANG II increased MAO activity in hypothalamus and medulla oblongata. Bilateral nephrectomy decreased the activity of the enzyme in both organs (compared with control and with ANG II). In hypothalamus, MAO activity was a 230.4 % higher in the ANG II treated groups than in the nephrectomized one. In medulla oblongata, this difference, between the mentioned groups was only a 48.8 %.

Table I. *Effects of angiotensin II (ANG II) and bilateral nephrectomy (Nephr.) on MAO activity in rat hypothalamus and medulla oblongata. Results are expressed in pM of 4-hydroxiquinoleine per 30 min per g of protein^{-1}.* Number of cases in parenthesis.

	Hypothalamus	Medulla oblongata
Control	1.08 ± 0.08 (9)	0.97 ± 0.05 (10)
ANG II	2.61 ± 0.08 (8)	1.22 ± 0.06 (9)*
Nephr.	0.79 ± 0.10 (7)**	0.82 ± 0.05 (9)**

* $p < 0.05$ compared with control, ** $p < 0.05$ compared with angiotensin II.

Discussion

Previous reports supported the hypothesis that ANG II could modify MAO activity in the CNS (9). The increase of NE/NE metabolite ratio in hypothalamus and medulla oblongata is quite similar in nephrectomized animals as in pargyline (one of the strongest non-hydrazine MAO inhibitor) treated rats. The use pargyline in nephrectomized animals had an additive effect on the mentioned ratio. Besides, pargyline blunted the decrease of this ratio caused by ANG II (9).

In the present paper results showed that ANG II increased MAO activity in hypothalamus and medulla oblongata. On the other hand, decrease of circulating ANG II caused by 48 h bilateral nephrectomy diminished the enzyme activity. Experiments in hypothalamus and medulla oblongata were carried out, because those areas closely related with the control of

cardiocirculatory and sympathetic activity, and in these regions, the highest concentrations of NE and ANG II were found in the CNS (11-13). ANG II and nephrectomy effects were higher in hypothalamus than in medulla oblongata. The cause of the different response in these regions cannot be elucidated with the present data.

Other authors have reported that bilateral nephrectomy did not alter cerebral renin levels (12). Brain and peripheral renin-angiotensin systems are not correlated. Besides, some authors observed an inverse relationship between both systems and indicated that both could interact at the circumventricular area level (12, 23). It has been proved that the modification of cerebral ANG II levels did not alter cerebral catecholamines. Although it has been described a close relationship between cerebral catecholamines and plasmatic ANG II levels (4, 5).

It is well known that circulating ANG II penetrates the haematoencephalic barrier at least in certain circumventricular areas (27) and interacts with NE stores of CNS (20). We have previously reported that an increase of plasmatic ANG II resulted in a decrease of NE levels in hypothalamus and medulla oblongata (6, 8, 26). On the other hand, when plasmatic ANG II was decreased by means of bilateral renal denervation, bilateral nephrectomy, captopril administration or immunization against ANG II, a rise of NE content in the same areas was observed (3, 4, 7, 18). ANG II has been reported to inhibit NE uptake and increase NE release in hypothalamus, while bilateral nephrectomy showed opposite effects since it increased NE uptake and decreased NE release from the mentioned areas (4, 5).

ANG II stimulates sympathetic tone. This action is partially mediated by the enhancement of NE turnover in CNS as in the peripheral nervous system (5, 19). Our experiments suggest another mechanism of interaction: ANG II increased NE metabolism. NE is stored in two neuronal intracellular pools: the cytosolic and the granular or vesicular pools. Both are in a constant equilibrium. The cytosolic pool is exposed to MAO activity. On the other hand, the enzyme cannot catabolize granular store. Pharmacological agents (tiramine, reserpine) that release NE from the granular to the cytosolic pools increased MAO substrate and as a consequence the activity of the enzyme is enhanced (1, 17). As ANG II is known to release NE from the vesicles, this could explain the effect of the peptide on MAO activity.

An increase of MAO activity was observed in hypertension states with high plasmatic renin levels as those produced by arterial renal stenosis (19). This effect was reversed by low sodium diet (2). KRAKOFF *et al.* (16), observed in DOCA-salt hypertension with low plasmatic renin activity, a rise in NE deamined metabolites in myocardium. STURN and SCHEJA (25) also described an increase of catecholamines metabolism in nephrogenic hypertension.

These results can lead to the hypothesis that ANG II-CA interaction in the CNS plays an important role in the development and maintenance of arterial hypertension. Peripheral ANG II penetrates into brain at the circumventricular area level and has binding sites placed in the CNS (21, 22). These regions are considered mediator sites of the effects of circulating ANG II and are also sites for interaction between ANG II and brain CA (14).

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Resumen

Se estudian los efectos de la angiotensina II (ANG II) y de la nefrectomía bilateral sobre la

actividad de la monoaminoxidasa (MAO) en el hipotálamo y en el bulbo raquídeo de la rata. La ANG II incrementa la actividad de la MAO en las dos regiones del sistema nervioso central. La caída de los niveles de ANG II circulante, provocada por la nefrectomía bilateral practicada 48 horas antes, disminuye la actividad de la enzima en las mismas áreas cerebrales. Los resultados muestran que la ANG II aumenta el catabolismo de las catecolaminas en el sistema nervioso central.

Palabras clave: Angiotensina II, MAO, Nefrectomía, Noradrenalina.

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