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Norepinephrine metabolism in neuron: dissociation between 3,4-dihydroxyphenylglycol and 3,4-dihydroxymandelic acid pathways

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KEY WORDS norepinephrine; metabolism; mono-amine oxidase; desipramine; deprenyl; clorgyline

ABSTRACT

AIM: To investigate the pre-synaptic metabolism of norepinephrine (NE), judged by variations in plasma concentration of 3,4-dihydroxyphenylglycol (DHPG) and 3,4-dihydroxymandelic acid (DOMA). **METHODS**: Pithed and electrically stimulated (2.5 Hz) rats were given intravenous infusion of exogenous NE (6 nmol·kg^{-1}·min^{-1}). Plasma NE, DHPG, DOMA, and the activities of mono-amine oxidases (MAO) were measured with the radio-enzymatic assay. **RESULTS**: Exogenous NE induces an about 100-fold increase in plasma NE concentration while blood pressure remained within normal limits. A 12-fold increase in plasma DHPG and 1.2-fold increase for DOMA were observed. When NE transportation across the pre-synaptic membrane was inhibited by desipramine (2 mg/kg, iv), a great reduction in plasma DHPG concentration (about 25 % of control) was observed while DOMA remained unchanged. When MAO-A activity was inhibited to 25 % of control by clorgyline (2 mg/kg, iv) and MAO-B to 30 % by deprenyl, the plasma DHPG and DOMA concentrations were reduced to 15 % and 70 % of controls, and to 26 % and 76 % of controls, respectively. When clorgyline and deprenyl were combined, plasma DHPG was vanished (less than 2 % of control) while plasma DOMA remained in the same range (72 % of control). **CONCLUSION**: The metabolizing system of NE in pre-synapse, associating with the pre-synaptic reuptake plus oxidative deamination on the external membrane of mitochodria, is predominant for the reduction to DHPG.

INTRODUCTION

Nerve terminals are unique sites in economy of the sympathetic system: the rate of release of norepinephrine (NE) can be largely increased and as much as 90 % of released NE can be reuptaken through the pre-synaptic membrane[1,2]. Thus, this is an efficient mechanism to clear NE in synaptic cleft. Trendelenburg[3] has proposed a "metabolizing system" that combines the transport of NE through the pre-synaptic membrane with oxidative deamination under the control of mono-amine oxidase (MAO) located at the surface of mitochodria.

NE reuptake by pre-synaptic membrane was deaminated oxidatively that lead to produce the 3,4-dihydroxyphenyl aldehyde known to be unstable, which was metabolized immediately by reduction (aldehyde reductase) to 3,4-dihydroxyphenylglycol (DHPG) or by oxidation (aldehyde dehydrogenase) to 3,4-dihydroxymandelic acid (DOMA)[4,5]. Those two compounds can pass through the membrane and into the blood circulation. Hence, any change of neuronal reuptake of NE should be followed by a change in plasma concentrations of DHPG and DOMA. It is clear for DHPG but not for DOMA[6-8]. In a previous study, we have shown statistically significant correlations between plasma NE and plasma DHPG or DOMA concentrations in healthy volunteers and in rats given clonidine[9]. We also confirmed that pithing of the rat with electric stimulation represented an appropriate experimental set-up: electric stimulation restores plasma NE to its normal level associated with an apparent physiological equilibration between pre- and post-synaptic phenomena[10].

In this experimental frame, we studied the change of plasma DHPG and DOMA after NE reuptake, mono-amine oxidases (MAO)-A, and MAO-B was inhibited.

MATERIALS AND METHODS

General procedures Experiments were performed in male Wistar rats (Grade Ⅲ, Certificate № 005),

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12 to 14 weeks old (326.0 g ± 1.5 g). Anesthesia, general operations, pithing and electric stimulation (2.5 Hz) were carried out according to Dong *et al*[10].

Intravenous infusion of exogenous NE It was shown that stimulation of spinal roots of sympathetic fibres increased blood pressure but did not restore it up to normal range in pithed rats[10]. This suggests that synaptic concentration of NE in post-synaptic receptors is likely insufficient, thus NE was intravenously infused at 6 nmol·kg^{-1}·min^{-1}. In three groups of rat (anesthetized, pithed, and pithed plus 2.5 Hz stimulation), NE [(−)-norepinephrine bitartrate diluted in NaCl 0.9 %] was intravenously infused at a rate of 6 nmol·kg^{-1}·min^{-1}. Blood samples (2 mL in each time) were obtained from the femoral artery in anesthetized and pithed rats before and after 30 min, 60 min, and 90 min infusion of NE and in pithed plus 2.5 Hz stimulation rats they were collected before infusion of NE, after 2.5 Hz stimulation, and at 30 min, 60 min, and 90 min after infusion of NE. After collection of each sample, an identical volume of blood from another normal anesthetized rats was injected according to a previously described technique[10]. The mean arterial pressure (MAP) and the heart rate (HR) were recorded during the experiment.

Inhibition of the neuronal reuptake of norepinephrine Desipramine (2 mg/kg iv) was used as a tool to inhibit the neuronal reuptake of NE[11]. Its effects on plasma concentrations of NE, DHPG, and DOMA were measured in anesthetized, pithed plus 2.5 Hz stimulation, and pithed plus 2.5 Hz stimulation rats infused with NE. The MAP and HR were measured during the experiments. The blood samples were taken in the end of experiments.

Inhibition of monoamine oxidase activity MAO activity were inhibited by two different compounds: clorgyline known to inhibit MAO-A[12], and deprenyl known to inhibit MAO-B[13]. Two pilot studies were carried out to evaluate the dose-response curves of these two compounds in pithed plus 2.5 Hz stimulation rats infused with NE.

In the first pilot study, the dose-effects of clorgyline for MAO-A in liver of rat as well as plasma concentrations of DHPG and DOMA were measured in 7 groups of pithed plus 2.5 Hz stimulation rats given exogenous NE (6 animals in each group) treated by either NaCl 0.9 % (control) or clorgyline 0.1, 0.5, 1, 2, 5, and 10 mg/kg. Clorgyline was intravenously injected 30 min after completion of the experimental set-up and the arterial blood sample was obtained 60 min later, together with a sample of the liver. As expected, the activity of MAO-A in liver was inhibited in proportion with the dose of clorgyline injected. Up to 2 mg/kg, there was a maximum decrease in plasma DHPG concentration and with no further decrease when dose was increased to 5 or 10 mg/kg. Plasma DOMA concentration was not markedly decreased (Fig 1). Clorgyline 2 mg/kg to induce the maximum effect on neuronal metabolism of NE, regarding to DHPG concentration in plasma, was chosen.

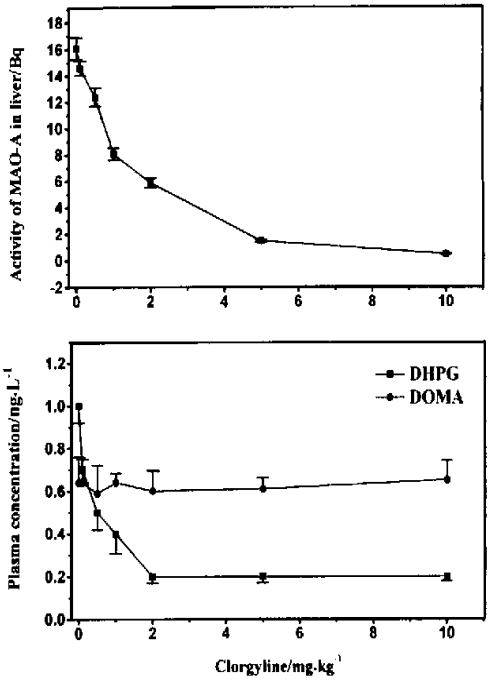

Fig 1. Effects of clorgyline (0.1, 0.5, 1, 2, 5, and 10 mg/kg, iv) on activity of MAO-A in liver (A), and on plasma concentrations of 3, 4-dihydroxyphenylglycol (DHPG) and of 3,4-dihydroxymendalic acid (DOMA) in pithed plus 2.5 Hz stimulation rat given exogenous norepinephrine (B). $n = 6$ rats in each group. $\bar{x} \pm s$.

In the second pilot study, the activity of MAO-B in liver, compared with MAO-A, was measured in rats given intravenous injection of NaCl 0.9 % or deprenyl 1, 2, 5, 10, 20, and 50 mg/kg. The liver samples were obtained 60 min later. Intravenous injection of deprenyl 5 mg/kg induced a 58 % inhibition of MAO-B activity in liver, with a minimal effect on MAO-A (Fig 2), and this dosage was chosen.

Then the effects of MAO inhibition on neuronal metabolism of NE were studied in 4 groups of pithed plus

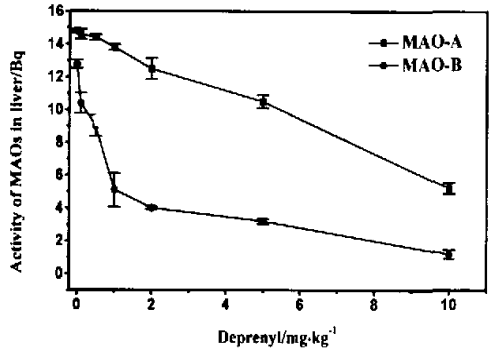

Fig 2. Effects of the deprenyl (1, 2, 5, 10, 20, and 50 mg/kg iv) on activities of MAO-A and MAO-B in liver. $n = 3$ rats in each group. $\bar{x} \pm s$.

2.5 Hz stimulation rats given exogenous NE. NaCl 0.9 %, clorgyline 2 mg/kg, deprenyl 5 mg/kg, and clorgyline 2 mg/kg plus deprenyl 5 mg/kg were given respectively. Treatments were given 30 min after completion of the experimental set-up. Arterial blood sample and liver sample were obtained 60 min later.

Blood samples and biochemical procedures Catecholamines (only NE is reported) and their deaminated metabolites (DHPG and DOMA) were measured according to radio-enzymatic assays previously described[9,14].

MAO activity in liver were measured according to radio-assay described by Da Prada *et al*[15]. Briefly, the liver samples were obtained rapidly, frozen on the dry ice, and stored at − 80 ℃ until measurement of the activity of MAO. After thawing, liver samples were homogenized in 5 volumes of potassium-phosphate buffer 0.1 mol/L, pH 7.4. Each sample was treated in duplicate. The test tubes were kept on ice, 200 μL of water were added, followed by 20 μL of homogenates (4 mg of liver tissue) and 80 μL of MAO substrates: 5-[2-^{14}C]-hydroxytryptamine 5-HT (specific activity: 11.1 GBq/mol, final concentration 200 mmol/L) for MAO-A, or [^{14}C]-phenylethylamine PEA (specific activity: 148 GBq/mol, final concentration 100 mmol/L) for MAO-B. A 10 min incubation at 37 ℃ was followed and the reaction was stopped by addition of 20 μL of HCl 2 mol/L. Deaminated metabolites were extracted by vigorous shaking for 3 min with 5 mL of diethylether. After centrifugation (800 × g), the water-phase was frozen in dry ice and the organic phase was poured into plastic vials containing 1 mL Econofluor to count beta scintillation. In blank tubes, 20 μL of homogenates were replaced by 20 μL of water. MAOs' activities were shown on linear from 2 to 200 mg homogenates. It was (14.74 ± 0.02) Bq for MAO-A and (13.46 ± 0.02) Bq for MAO-B in 4 mg aliquots of liver tissue ($n = 6$). Intra- and inter-assay coefficients of variation were less than 0.5 % ($n = 6$). Thus 4 mg aliquots of liver tissue was chosen.

Drugs B-[Ethyl-1-^{14}C]-Phenylethylamine hydrochloride (1.55 TBq/mol), 5-[2-^{14}C]-hydroxytryptamine binoxalate (2.1 TBq/mol), and Econofluor were obtained from DuPonts. Desipramine, (−)-norepinephrine bitartrate, and clorgyline from Sigma (USA) and deprenyl from RBI (USA).

Statistical analysis Results are expressed as $\bar{x} \pm s$. Statistical differences were tested by either one factor analysis of variance (ANOVA) or t-test. Statistical significance is defined as $P < 0.05$.

RESULTS

Intravenous infusion of NE: effects on blood pressure and plasma concentrations of DHPG and DOMA The intravenous infusion of exogenous NE at 6 nmol·kg^{-1}·min^{-1} induced an about 100-fold increase in plasma NE concentration in three groups of rats (Tab 1). After 30 min, MAP was restored to within normal limits (134 ± 5) mmHg in pithed rats, and approached the same level of anesthetized and pithed plus 2.5 Hz stimulation rats.

Regarding to the deaminated metabolites of NE, a highly significant and apparently time-dependent increase in plasma DHPG concentration was observed in three groups of animals. Plasma DOMA concentrations were also increased but in lower proportion when compared with DHPG (at 60 min: 12-fold increase for DHPG and 1.2-fold increase for DOMA), there was no significant difference in three groups of rats.

Inhibition of neuronal reuptake by desipramine Desipramine 2 mg/kg had no effect on MAP in anesthetized rats and in pithed plus 2.5 Hz stimulation rats given exogenous NE (Tab 2). However it restored MAP within its normal range in pithed plus 2.5 Hz stimulation rats.

The plasma NE concentrations were increased in all groups of rats treated with desipramine, the magnitude of the plasma NE response in pithed plus 2.5 Hz stimulation rats was apparently larger than that in anesthetized rats. It could account for the effect that desipramine normalized MAP.

As far as plasma concentrations of deaminated

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Tab 1. Effects of norepinephrine's infusion (6 nmol·kg^{-1}·min^{-1}) on blood pressure and plasma concentrations of DHPG and DOMA in anesthetized, pithed, and pithed plus 2.5 Hz stimulation rats. n = 8 rats in each group. $\bar{x} \pm s$. $^cP < 0.01$ *vs* 0 min. $^fP < 0.01$ *vs* pithing.

Time/min	MAP/mmHg	NE/ng·L^{-1}	DHPG/ng·L^{-1}	DOMA/ng·L^{-1}
Anesthetized rats				
0	151 ± 5	227 ± 32	773 ± 59	701 ± 86
30	146 ± 4	21043 ± 3609^c	6357 ± 285^c	1369 ± 316^c
60	136 ± 4	25229 ± 3401^c	9855 ± 743^c	1610 ± 341^c
90	127 ± 6	31744 ± 6765^c	14065 ± 1034^c	2133 ± 417^c
Pithed rats				
0	59 ± 3	64 ± 8	688 ± 36	980 ± 191
30	134 ± 5^c	20360 ± 2761^c	5275 ± 507^c	1596 ± 284^c
60	124 ± 5^c	23858 ± 2442^c	7264 ± 638^c	1541 ± 252^c
90	121 ± 7^c	27370 ± 2145^c	10684 ± 828^c	1812 ± 277^c
Pithed plus 2.5 Hz stimulation rats				
Pithing	58 ± 2	68 ± 8	628 ± 60	830 ± 119
2.5 Hz stimulation	78 ± 4^f	504 ± 41^f	1063 ± 96^f	1427 ± 178^f
30	144 ± 6^f	19566 ± 2180^f	7497 ± 517^f	1737 ± 256^f
60	131 ± 9^f	26482 ± 2094^f	8330 ± 891^f	1846 ± 242^f
90	127 ± 5^f	32386 ± 2457^f	11436 ± 818^f	1915 ± 190^f

MAP: mean arterial pressure; NE: norepinephrine; DHPG: 3,4-dihydroxyphenyl glycol; DOMA: 3,4-dihydroxymandelic acid

Tab 2. Effects of desipramine (2 mg/kg, iv) on blood pressure and plasma concentrations of NE, DHPG, and DOMA in anesthetized, pithed plus 2.5 Hz stimulation, and pithed plus 2.5 Hz stimulation rats infused with NE (6 nmol·kg^{-1}·min^{-1}) during one hour. n = 8 rats in each group. $\bar{x} \pm s$. $^cP < 0.01$ *vs* control.

	Anesthetized rats		Pithed plus 2.5 Hz rats		Pithed plus 2.5 Hz and NE	
	Control	DIM	Control	DIM	Control	DIM
MAP/mmHg	150 ± 2	151 ± 3	81 ± 7	134 ± 4^c	138 ± 6	134 ± 4
NE/ng·L^{-1}	236 ± 22	392 ± 36^c	579 ± 34	2080 ± 211^c	25376 ± 3125	49443 ± 4691^c
DHPG/ng·L^{-1}	770 ± 28	379 ± 30^c	1364 ± 70	495 ± 23^c	7497 ± 517	1840 ± 31^c
DOMA/ng·L^{-1}	869 ± 32	733 ± 53	1037 ± 99	1077 ± 71	1915 ± 190	2076 ± 175

MAP: mean arterial pressure; NE: norepinephrine; DHPG: 3,4-dihydroxyphenyl glycol; DOMA: 3,4-dihydroxymandelic acid

metabolites of NE are concerned, plasma DHPG were decreased in 3 groups treated with desipramine while plasma DOMA remained unchanged. The decrease in plasma DHPG concentration in pithed plus 2.5 Hz stimulation rats given exogenous NE (about 25 % of control) suggests an efficient inhibitory effects (2 mg/kg iv) on neuronal reuptake. Plasma DOMA was not changed.

Effects of MAO inhibition on plasma DHPG and DOMA concentrations The plasma NE concentrations induced by intravenous infusion of NE were within the same ranges in the 4 groups of rats. MAO-A activity was inhibited by clorgyline (25 % of control), while MAO-B activity remained unaffected (Tab 3). MAO-B activity was evidently inhibited by deprenyl (30 % of control) with no significant effect on MAO-A activity. When clorgyline and deprenyl were injected together, MAO-A and MAO-B activities were further reduced than clorgyline or deprenyl alone (MAO-A: 20 % *vs* 25 % of control, $P < 0.05$; MAO-B: 16 % *vs* 30 % of control, $P < 0.01$). It suggests a small but statistically significant cross-inhibition.

The plasma DHPG concentration was decreased to 15 % of control after clorgyline treatment and to 26 % after deprenyl treatment. A cumulative effect of clorgyline plus deprenyl was observed, since plasma DHPG was almost vanished: (68 ± 12) ng/L, less than 2 % of control. The plasma DOMA concentration was evidently decreased to 70 % of control after clorgyline treatment and 76 % after deprenyl treatment. When

Tab 3. Effects of clorgyline (2 mg/kg, iv) and deprenyl (5 mg/kg, iv) on plasma concentrations of DHPG and DOMA in pithed plus 2.5 Hz stimulation rats infused with NE (6 nmol·kg^{-1}·min^{-1}) during one hour. $n = 6$ rats in each group. $\bar{x} \pm s$. $^bP < 0.05$, $^cP < 0.01$ *vs* control. $^eP < 0.05$, $^fP < 0.01$ *vs* clorgyline. $^iP < 0.01$ *vs* deprenyl.

	Control	Clorgyline	Deprenyl	Clorgyline + Deprenyl
NE/ng·L^{-1}	28156 ± 5128	27931 ± 4847	28333 ± 2802	30483 ± 4967
DHPG/ng·L^{-1}	3791 ± 555	574 ± 92^c	987 ± 137^c	68 ± 12^{cfi}
DOMA/ng·L^{-1}	2497 ± 199	1763 ± 187^b	1894 ± 227^b	1809 ± 105^b
MAO-A activity/Bq	12.8 ± 0.22	3.2 ± 0.3^c	11.9 ± 0.17	2.6 ± 0.5^{cei}
MAO-B activity/Bq	13.8 ± 0.06	13.70 ± 0.08	4.2 ± 0.28^c	2.2 ± 0.4^{cfi}

NE: norepinephrine; DHPG: 3,4-dihydroxyphenyl glycol; DOMA: 3,4-dihydroxy-mandelic acid; MAO-A: monoamine oxydase type A; MAO-B: monoamine oxydase type B.

clorgyline and deprenyl were combined, the plasma DOMA was not further decreased, remaining 72 % of control.

DISCUSSION

The neuronal reuptake of NE is the most efficient pathway to remove NE released in the synaptic cleft. The metabolizing system, proposed by Trendelenburg[3], associates the transport of NE across the pre-synaptic membrane with a MAO dependent-oxidative deamination that takes place on external surface of mitochondria. The oxidative deamination leads to the productions of DHPG and DOMA[5]. In that frame, their plasma concentrations should increase when an experimental maneuver increases the NE concentration in the synaptic cleft, and decrease when NE transporting into the pre-synaptic membrane is inhibited (by desipramine) or when oxidative deamination is inhibited by MAO inhibitors (clorgyline or deprenyl).

Because blood pressure (BP) was not re-established within normal limits during 2.5 Hz electric stimulation[10], an intravenous infusion of exogenous NE was added with three objectives: a) restoring BP within its control limits; b) increasing the synaptic NE level to its upper physiologic limits in order to activate the metabolic system, and c) keeping NE concentration in the synaptic cleft as stable as possible. Exogenous NE were infused at a rate of 6 nmol·kg^{-1}·min^{-1} that restored BP almost in the normal range in pithed and stimulated rats (Tab 1). The plasma NE concentration was about 100-fold higher after an infusion of exogenous NE than before infusion that was expected to counterbalance the synaptic-plasma concentrations' gradient and to maintain the synaptic concentration of NE at its upper physiologic limit.

In this experimental set-up, a progressive increase in plasma DHPG concentration was observed, the plasma DOMA concentrations were also significantly increased in 3 different experimental conditions (Tab 1). Thus, the combination of electric stimulation and exogenous infusion of NE at 6 nmol·kg^{-1}·min^{-1} in pithed rats represents an appropriate experimental set-up with control of NE release and an activation of the pre-synaptic metabolizing system. However quantitative differences seem to exist between reductive and oxidative pathways, plasma DHPG was increased by 12 folds while the plasma DOMA only 1.2 folds. The reductive pathway leading to the formation of DHPG was apparently more activated than the oxidative pathway leading to DOMA.

Then, whether inhibition of NE transportation across the pre-synaptic membrane with desipramine could blunt the formations of both DHPG and DOMA were investigated. Desipramine reduced the plasma DHPG concentration in anesthetized as well as in pithed and stimulated rats with or without exogenous NE infusion (Tab 2). Non significant decrease in plasma DOMA were observed in any of three series of experiment. It is unlikely that the inhibitory effect of desipramine at this dose was insufficient. In pithed and 2.5 Hz stimulation rats given exogenous NE (Tab 2), the plasma DHPG was induced to 25 % of control, associated with no change of plasma DOMA. This further showed that DHPG originated essentially from the intraneuronal deamination of NE. Perhaps DOMA has an extraneuronal origin that had been mentioned by Branco *et al*[16], it is needed to be investigated further.

After that, a step was made to investigate the pre-synaptic metabolism of NE with inhibition of MAO activities in pithed plus electrically stimulated rats given

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intravenous infusion of exogenous NE. Clorgyline 2 mg/kg and depranyl 5 mg/kg decreased plasma DHPG and DOMA to almost the same degree: 15 % (DHPG) and 70 % (DOMA) of control after clorgyline treatment *vs* 26 % (DHPG) and 76 % (DOMA) after deprenyl treatment. Thus, no difference was observed between the aldehyde reductase-dependent reductive pathway leading to the production of DHPG and the aldehyde dehydrogenase-dependent oxidative pathway leading to the formation of DOMA.

Combination of clogyline and deprenyl induced a cooperated inhibition of MAO activities (Tab 3). The plasma DHPG nearly disappeared, but DOMA remained unchanged. The differences of transporting kinetics of DHPG and DOMA across the cellular membrane could account for those different responses. The fact that the plasma DOMA was not further decreased when its production rate was likely to be very much reduced by clorgyline and deprenyl was perhaps due to the characteristic of DOMA. DOMA is an acid metabolite, penetrates the cellular membrane with difficulty and retaines in the tissue for a great extent, and its half-life is about 45 – 60 min[17]. On the contrary, DHPG is a glycol metabolite which leaves the neurone easily.

In conclusion, the metabolizing system of NE in pre-synapse, associating with the pre-synaptic reuptake plus oxidative deamination on the external membrane of mitochodria, is predominant for the reduction to DHPG than oxidation to DOMA. This dissociation had also been observed when the metabolizing system was reduced by inhibitor of reuptake: desipramine, and combined inhibition of both MAO-A and MAO-B by clorgyline and deprenyl. DHPG reflects the change of plasma NE and the sympathetic activity better than DOMA.

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神经元内去甲肾上腺素的代谢：3,4－二羟苯乙醇和3,4-二羟苯乙酸两条途径分离

R96 A

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关键词 去甲肾上腺素；代谢；单胺氧化酶；地昔帕明；司立吉林；氯吉林

目的：以血浆3,4-二羟苯乙醇(DHPG)和3,4-二羟苯乙酸(DOMA)的变化为判断指标，研究去甲肾上腺素(NE)在神经元内的代谢. **方法**：大鼠去脊髓并给予2.5 Hz电刺激合并静脉内输入NE (6 nmol·kg^{-1}·min^{-1}). 同位素酶标法测定血浆DHPG和DOMA浓度. **结果**：当静脉内输入NE使血浆NE浓度增加了100倍时，血浆DHPG和DOMA分别增加了12倍和1.2倍. 地昔帕明(2 mg/kg iv)使血浆DHPG浓度降低为对照组的25 %，而DOMA无明显变化. MAO-A抑制剂氯吉林使血浆DHPG和DOMA浓度分别降低为对照组的15 %和70 %，MAO-B抑制剂司立吉林使二者的血浆浓度分别降低为对照组的26 %和76 %. 氯吉林与司立吉林合用使血浆DHPG几乎完全消失，而DOMA无明显变化. **结论**：去甲肾上腺素被突触前膜摄取后，经线粒体外膜上的MAO氧化脱胺，还原产生DHPG为其主要代谢途径.

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