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Levodopa effect on norepinephrine and dopamine brain levels after portocaval shunt in rats

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Summary. In various brain areas in the rat, after 7 days of portocaval shunt with levodopa administration, we found an increase in norepinephrine and dopamine levels.

The etiology of portal systemic encephalopathy (PSE)[3] is not clear, but many factors have been described[4-6]. The 'false neurotransmitters theory'[7] explains the syndrome by catecholamine (CA) depletion and increase of octopamine found in acute hepatocellular insufficiency[8].

It has been suggested that false neurotransmitters can replace norepinephrine (NE) and dopamine (DA) in hepatic coma, which may explain the arousal effect of levodopa (L-3,4,dihydroxyphenylalanine) in acute hepatic encephalopathy treatment[9,10]. Based on the same mechanism of action, levodopa has been also employed in the treatment of chronic PSE but not always with beneficial results[11,12]. This failure was attributed to the ineffective action of levodopa when employed in later periods of PSE, because in this period the morphologic changes in the CNS are irreversible[11]. For this reason levodopa must be employed in an early state of PSE in which it is possible to reverse the metabolic cerebral changes, especially by increase of CA synthesis.

To investigate this hypothesis we have measured NE and DA levels in CNS of portocaval shunt (PCS) rats in an early state after the operation, and studied the changes produced after levodopa administration.

Material and methods. Male Sprague-Dawley rats weighing 200–250 g were used. PCS was made following the method of Lee and Fisher[13] with modifications[14]. The body weight diminished 10% after 7 days of PCS compared to the control rats. Hepatic weight diminished parallel to the body weight.

CA levels were measured by the fluorimetric method[15] in noradrenergic areas (hypothalamus and amigdala) and dopaminergic areas (olfactory tubercle and striatum nucleus) after 7 days of PCS.

4 groups of animals were used: 1. Control group, 2. PCS group after the 7th post-operatory day, 3. control group after administration of levodopa (100 mg/kg p.o.) coadministered with a levodopa peripheral decarboxylase inhibitor (LPDI), benserazide (N'-[DL-seryl]-N^2-[2,3,4]-trihydroxybencyl hidracine clorhydrate) (25 mg/kg p.o.) and 4. PCS group after the 7th post-operatory day and the administration of levodopa and LPDI, both at the same dose as the former group. The drugs were administered orally and all the rats were decapitated 1 h after the administration. Cerebral areas were dissected as described by Glowinsky and Iversen[16].

Results and discussion. NE levels decreased after 7 days of PCS in noradrenergic areas (45% in hypothalamus, 28% in amygdala). Levodopa plus LPDI produced the elevation of NE levels in the noradrenergic areas studied in PCS rats. These levels approximate to those of the control group (table 1).

Table 1. NE levels in control and PCS rats (7 days of postoperatory) and after levodopa + LPDI administration

NE levels (ng/mg)	Dopaminergic system		Noradrenergic system	
	Olfactory	Striatum	Amygdala	Hypothalamus
Control rats	0.60 ± 0.07 (18)	0.40 ± 0.11 (16)	0.47 ± 0.07 (18)	2.20 ± 0.29 (17)
Control rats + levodopa + LPDI	1.08 ± 0.09 (13)**	0.96 ± 0.11 (13)**	0.81 ± 0.13 (12)**	2.47 ± 0.14 (13)
PCS	0.45 ± 0.11 (16)	0.38 ± 0.03 (17)	0.36 ± 0.08 (17)*	1.20 ± 0.18 (18)**
PCS + levodopa + LPDI	1.19 ± 0.13 (12)**	0.94 ± 0.07 (15)**	0.80 ± 0.087 (15)**	2.39 ± 0.14 (14)

Number of experiments in parenthesis. Statistically significant values compared to control group: * $p < 0.05$; ** $p < 0.001$.

Table 2. DA levels in control and PCS rats (7 days of postoperatory) and after levodopa + LPDI administration

DA levels (ng/mg)	Dopaminergic system		Noradrenergic system	
	Olfactory	Striatum	Amygdala	Hypothalamus
Control rats	2.68 ± 0.12 (18)	4.18 ± 0.50 (16)	0.76 ± 0.08 (17)	0.59 ± 0.04 (17)
Control rats + levodopa + LPDI	7.05 ± 0.39 (9)**	5.90 ± 0.11 (10)**	3.40 ± 0.12 (10)**	4.70 ± 0.14 (10)**
PCS	2.03 ± 0.18 (17)*	3.22 ± 0.48 (18)*	0.98 ± 0.20 (17)	0.90 ± 0.09 (16)*
PCS + levodopa + LPDI	10.09 ± 0.76 (10)**	9.12 ± 0.65 (10)**	7.38 ± 0.32 (9)**	6.79 ± 0.42 (10)**

Number of experiments in parenthesis. Statistically significant values compared to control group: * $p < 0.01$; ** $p < 0.001$.

DA levels diminished in dopaminergic areas after PCS ($p < 0.01$) (table 2). Levodopa + LPDI administration produced a significant increase in DA levels in control and PCS groups ($p < 0.001$) but regional difference patterns were not apparent (table 2). The increase was higher in PCS rats. Statistical comparison of results was made by Student's t-test.

CA levels in the CNS vary early after PCS in rats, which means that hepatic alterations, such as a diminished portal blood flow, induce changes with regard to its metabolism. These changes are reflected in a depletion of CA levels in the olfactory tubercle and striatum nucleus after 7 days of PCS but are reversible by administrating levodopa associated with LPDI.

Zieve et al.[17] showed an improvement in rats with ammonia coma after levodopa, which could be accounted for by the peripheral effect of DA on renal function. However the DA and NE increases in dopaminergic and noradrenergic areas after administration of levodopa plus LPDI in rats after 7 days of PCS may indicate a central action.

The mechanisms of levodopa action in the CNS in this experimental model may be the inhibition of serotonin synthesis[18], the increase of oxygen cerebral consumption[11] and the increase of NE synthesis. All of these mechanisms are secondary to the increase of DA synthesis.

On the basis of these experimental results it is possible to believe that the improvement obtained after levodopa + LPDI administration in the same patients in an earlier state of PSE may be explained by an increase of the CA levels in the CNS.

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The relation between cell proliferation and adenylate cyclase activity in grafts of 3-methylcholanthrene induced mouse uterine cervical tumors

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Summary. In transplanted uterine cervical tumors, induced by 3-methylcholanthrene, a significant negative correlation was obtained between adenylate cyclase activity and cell proliferation.

The role of cyclic adenosine 3′-5′-monophosphate (cAMP) in the control of growth in normal and malignant cells is still a matter of controversy[2-6]. Some of the discrepancies in opinion could be explained by different test cells being used; as a rule, chemical carcinogens or promoters increase the basal level of cAMP while tumorigenic viruses tend to decrease it. The cAMP level is crucial; abnormally high concentrations may arrest cell growth while moderate levels facilitate the growth of some cells. An active adenylate cyclase has been described in solid tumors[7,8] but great variations have been reported in hormone sensitivity, fluoride stimulation and basal activity[9-11].

In an earlier study[12] a trend could be traced for a correlation between adenylate cyclase activity and cell prolifera-