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Effect of dizocilpine maleate on monoamines and their metabolites in rat brain[1]

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ABSTRACT Systemic (ip) injection of dizocilpine maleate (DM, 0.1 and 0.5 mg · kg^{-1}) increased the levels of 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid but did not bring about any noticeable change in the dopamine (DA) level in the striatum and limbic area. DM also increased the levels of norepinephrine in the limbic area and 5-hydroxyindoleacetic acid in the hippocampus. Amphetamine increased DA level and reduced DOPAC level in the striatum and limbic area. The behavioral manifestations revealed that DM predominantly evoked circling behavior and ataxia. The results indicate that the mechanism of the behavioral effect of DM may be different from that of amphetamine.

KEY WORDS dizocilpine maleate; dopamine; norepinephrine; 3,4-dihydroxyphenylacetic acid; homovanillic acid; hydroxyindoleacetic acid; high pressure liquid chromatography; limbic system

Dizocilpine (5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine) maleate (DM) is a potent and selective non-competitive *N*-methyl-*D*-aspartate (NMDA) receptor antagonist[1]. The neuroprotective effect of DM has been recently shown in experimentally induced ischemia, kindled seizures, NMDA-induced neurotoxicity, and methamphetamine-induced dopaminergic toxicity[2]. DM has also central sympathomimetic and apparent anxiolytic properties[3]. Systemically administered DM produces locomotor activity in mice and ipsilaterally directed rotational response in rats with a unilateral nigrostriatal lesion induced by 6-hydroxydopamine[3]. In order to investigate the action of DM on the central monoaminergic system, we injected DM ip and meticulously assayed the levels of monoamines and their metabolites in the striatum, limbic area, and hippocampus using high pressure liquid chromatography with electrochemical detection (HPLC-ECD).

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MATERIALS AND METHODS

Behavioral observation Sprague-Dawley rats, ♂, weighing 240 ± *s* 20 g, were used. The locomotor activity, stereotyped behavior and ataxia were observed by a modification of a previously suggested method[4].

Determination of monoamines and their metabolites The rats were decapitated 30 min after the drugs were injected ip for neurochemical assay of monoamines and their metabolites in the striatum, limbic area (olfactory tubercle, nucleus accumbens, and nucleus amygdaloideus) and hippocampus. The 3 brain regions of both hemispheres were dissected out on ice and rapidly frozen with liquid nitrogen. After acid extraction and purification in aluminum oxide absorption procedures, norepinephrine (NE), 5-hydroxyindoleacetic acid (5-HIAA), dopamine (DA) and its metabolites 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA) were assayed by HPLC-ECD as described previously[5].

Chemical reagents DM and (+)-amphetamine were purchased from Merck & Co, USA. Ketamine was made by Jintan Pharmaceutical Manufacturer, Chunzhou,

China. All drugs were dissolved in saline.

Statistics Statistical analysis was made by Dunnett's t test. All values are $\bar{x} \pm s$.

RESULTS

The ip injection of DM 0.1 mg · kg^{-1} predominantly produced circling behavior. At 0.5 mg · kg^{-1}, circling behavior was most prominent accompanied by ataxia. These behavioral changes were quite similar to the effects induced by ip amphetamine 2 mg · kg^{-1}. Similar effects were seen also in ketamine group too.

Neurochemical determination showed that DM increased the levels of DOPAC and HVA in the limbic area and striatum. These effects were apparently dose-dependent. DM also elevated the NE level in the limbic area and 5-HIAA level in the hippocampus. But ketamine showed contradictory effect on the DOPAC and HVA levels in the limbic area and striatum. Amphetamine increased the DA level and reduced the DOPAC level in the striatum and limbic area (Tab 1).

DISCUSSION

Systemically administered DM produces ipsilateral circling in rat with unilateral nigrostriatal lesion produced by 6-hydroxydopamine[3]. Drugs such as haloperidol, clozapine, and prazosin which block catecholamine receptors inhibit the circling. Indirect DA agonists which facilitate DA release are known to induce ipsilateral circling toward the side with the lesion. So, striatal catacholamine release has been supposed to mediate the behavioral effect of DM[3]. Kashihara *et al* measured the striatal extracellular levels of DA and DOPAC after DM injection in freely moving rat. The results indicated that DM decreased the extracellular DA level at the dosages which induced marked hyperlocomotion and / or ataxia. This showed that the behavioral effects of DM are not mediated through DA release in the striatum[6]. In our study, DM increased the levels of DOPAC and HVA in the striatum and limbic area but produced no

Tab 1. Effects of dizocilpine maleate on monoamines and their metabolites in rat brain. $n=5$. $\bar{x} \pm s$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* **saline.**

	Saline	Amphetamine 2 mg · kg^{-1}	Ketamine 30 mg · kg^{-1}	Dizocilpine maleate 0.1 mg · kg^{-1}	Dizocilpine maleate 0.5 mg · kg^{-1}
Striatum / ng · g^{-1}					
NE	120 ± 18	130 ± 19*	111 ± 14*	114 ± 17*	109 ± 24*
DA	10 830 ± 869	13 617 ± 1631**	10 570 ± 1439*	10 610 ± 668*	10 819 ± 940*
DOPAC	896 ± 54	652 ± 79***	787 ± 53***	936 ± 87*	1 082 ± 107**
HVA	622 ± 55	659 ± 37*	512 ± 42***	652 ± 47*	688 ± 84*
5-HIAA	366 ± 38	305 ± 59*	320 ± 31*	366 ± 60*	357 ± 67*
Limbic area / ng · g^{-1}					
NE	505 ± 79	616 ± 93*	607 ± 135*	558 ± 70*	666 ± 139**
DA	4 844 ± 614	5 387 ± 412*	5 093 ± 973*	4 275 ± 770*	4 705 ± 819*
DOPAC	458 ± 39	397 ± 31**	601 ± 104***	577 ± 67**	640 ± 101***
HVA	218 ± 12	226 ± 46*	305 ± 49**	266 ± 27***	312 ± 37**
5-HIAA	273 ± 35	269 ± 46*	249 ± 41*	276 ± 19*	292 ± 19*
Hippocampus / ng g^{-1}					
NE	256 ± 36	255 ± 65*	228 ± 16*	237 ± 38*	252 ± 30*
5-HIAA	286 ± 37	335 ± 69*	316 ± 54*	363 ± 57**	418 ± 81***

change in DA level. These effects are obviously different from those of amphetamine. The decrease in striatal DOPAC and HVA following amphetamine administration might be related to the inhibition of DA uptake, causing less to be metabolized to DOPAC and possibly, the inhibition of monoamine oxidase as well[7]. Although we did not measure the extracellular DA level, the increased metabolism of dopaminergic neurons was affirmative. M Carlsson and A Carlsson suggested that the blockade of NMDA receptors resulted in an increased dopaminergic transmission in the striatum[8]. The behavioral changes of DM may be an indirect instead of a direct effect mediated through monoaminergic neuronal activity. The different modes of action on dopaminergic transmission between DM and amphetamine may explain the differences of the effect on central monoamine metabolism.

The neurochemical changes induced by DM are complex. We do not know whether the changes of NE and 5-HIAA level in the limbic area and hippocampus are actually involved in the central sympathomimetic and anxiolytic activity of DM. Also, we do not know why a DM analog ketamine produces contradictory effect on DOPAC and HVA level in the striatum and limbic area. These problems remain to be further investigated.

REFERENCES

1 Wong EHF, Kemp JA, Priestley T, Knight AR, Woodruff GN, Iversen LL. The anticonvulsant MK-801 is a potent *N*-methyl-*D*-aspartate antagonist. *Proc Natl Acad Sci USA* 1986; **83**: 7104-8.

2 Lehmann J. The NMDA receptor. *Drugs Future* 1989; **14**: 1059-71.

3 Clineschmidt BV, Martin GE, Bunting PR, Papp NL. Central sympathomimetic activity of (-)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cyclohepten-5,10-imine (MK-801), a substance with potent anticonvulsant, central sympathomimetic, and apparent anxiolytic properties. *Drug Dev Res* 1982; **2**: 135-45.

4 Sturgeon RD, Fessler RG, Meltzer HY. Behavioral rating scales for assessing phencyclidine-induced locomotor activity, stereotyped behavior and ataxia in rats. *Eur J Pharmacol* 1979; **59**: 169-79.

5 Liu GQ, Algeri S, Garattini S. Depletion of monoamines in the rat by *DL*-tetrahydropalmatine. *Acta Pharm Sin* 1983; **18**: 641-6.

6 Kashihara K, Hamamura T, Okumura K, Otsuki S. Effect of MK-801 on endogenous dopamine release *in vivo*. *Brain Res* 1990; **528**: 80-2.

7 Zetterstrom T, Sharp T, Marsden CA, Ungerstedt U. *In vivo* measurement of dopamine and its metabolites by intracerebral dialysis: changes after *d*-amphetamine. *J Neurochem* 1983; **41**: 1769-73.

8 Carlsson M, Carlsson A. The NMDA antagonist MK-801 causes marked locomotor stimulation in monoamine-depleted mice. *J Neural Transm* 1989; **75**: 221-6.

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地佐西平对大鼠脑内单胺递质及代谢物的影响

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提要 地佐西平 0.1 和 0.5 mg · kg^{-1} ip 增加大鼠纹状体和边缘区内 3,4-二羟苯酰乙酸(DOPAC)和高香草酸的含量, 对多巴胺(DA)含量无明显影响. DM 也增加边缘区去甲肾上腺素水平和海马内 5-羟吲哚乙酸水平. 苯丙胺则增加纹状体和边缘区内 DA 水平, 降低 DOPAC 水平. 结果表明地佐西平的作用机制可能不同于苯丙胺.

关键词 地佐西平; 多巴胺; 去甲肾上腺素; 3,4-二羟苯酰乙酸; 高香草酸; 羟基吲哚乙酸; 高压液相色谱法; 边缘系统 脑, 单胺递质, 代谢物