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Effects of stimulation of the satiety and feeding centers on gastric, cecal and rectal motility in the rat.*

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Abstract

The effects of electrical stimulation of the satiety and feeding centers (SC, FC) on gastric, cecal and rectal motility were studied in rats anesthetized with urethane. Each center produced excitatory, inhibitory and biphasic responses in these organs. Cecal and rectal responses to stimulation of SC or FC were usually the opposite of the gastric response; for example, the gastric response was excitatory, whereas cecal and rectal responses were inhibitory. Gastric and cecal excitatory responses were abolished by vagotomy and the rectal response by severance of parasympathetic branches of the pudendal plexus (PSB). Gastric and ceca inhibitory responses were fairly depressed by vagotomy and abolished by successive splanchnicotomy, while the rectal inhibitory response was abolished by severance of inferior mesenteric nerves (IMN) and PSB. It was concluded that the satiety and feeding centers modulate not only gastric motility but also cecal and rectal motility, and that the excitatory response is conveyed through vagus nerves to the stomach and cecum and through PSB to the rectum. The inhibitory response is mediated mainly through vagus nerves, partially through splanchnic nerves to the stomach and cecum, and through IMN and PSB to the rectum. The characteristics of efferent terminal neurons eliciting excitatory and inhibitory responses were studied pharmacologically.

KEYWORDS: satiety center, feeding center, gastrointestinal motility, autonomic nerves

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**A CEREBELLAR ATAXIC RAT PRODUCED BY KAINIC ACID
AND CHANGES IN CONCENTRATION AND TURNOVER
RATES OF CATECHOLAMINES IN DISCRETE
BRAIN REGIONS**

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Abstract. We made an animal model of cerebellar ataxia by injections of kainic acid into the cerebellar hemispheres on both sides of male rats. The histological and behavioral changes were observed at 4 weeks following the injections. The concentrations of catecholamines and the disappearance rates of α -MPT-induced catecholamines were measured in discrete regions of the brain of sham-operated and kainic acid-lesioned rats. A lowered dopamine disappearance rate was seen in the accumbens nucleus of the lesioned rats, but no change in norepinephrine. These findings suggest that the decrease in dopamine turnover in the accumbens nucleus is involved in the development of ataxic behavior.

Key words : cerebellum, ataxia, kainic acid, norepinephrine, dopamine.

Neurological mutant mice, most of which show cerebellar ataxia, have been reported in recent years (1). They have been considered as animal models of human hereditary degenerative diseases of the nervous system. There have been many reports concerning abnormal brain metabolism of norepinephrine (NE) in several strains of these mice (2-4). We made an animal model of cerebellar ataxia by injections of kainic acid in the rat cerebellar hemispheres on both sides (5, 6). The present paper reports neuronal degeneration, changes in concentration, and the turnover rate of catecholamines in the brain of kainic acid-induced ataxic rats.

Wistar strain male rats weighing 200 g were anesthetized with sodium pentobarbital and immobilized in a stereotaxic apparatus. Under direct visualization, 2.5 μ g kainic acid (obtained from Sigma Chemical Co.) in 1 μ l of saline was injected under stereotaxic guidance 2 mm deep into each cerebellar hemisphere, particularly into the cortex of the posterior lobus (5, 6). Control rats were sham-operated. In the first set of experiments, 4 weeks after the injection, the animals were deeply anesthetized, and killed by aortic perfusion with buffered formaldehyde. The brains were removed, transferred to phosphate buffer containing 30 % sucrose, then stored in the same fluid. Frozen sections were cut transversely at 50 μ m thickness and stained with cresyl violet. In the sec-

ond set of experiments, kainic acid-induced ataxic rats (4 weeks postoperatively) and sham-operated rats were decapitated for the measurement of endogenous catecholamine concentration and for the determination of the α -MPT-induced catecholamine disappearance rate in discrete regions of the brain. The latter groups of rats were decapitated 4 h after they had received DL- α -methyl ρ -tyrosine methylester hydrochloride (α -MPT) (300 mg/kg i.p.), an inhibitor of the enzyme tyrosine hydroxylase. After decapitation, brains were quickly removed and frozen on powdered dry ice. Serial transverse sections of 400 μ m thickness were made with a cryostat at a temperature of -10°C . At the level of the lesion, each thick section was stained with cresyl violet and examined under a microscope. The locus coeruleus, cerebellum, substantia nigra, median eminence, arcuate nucleus, accumbens nucleus, caudate nucleus, septal nucleus, and cerebral cortex were removed with small punches according to the method of Palkovits (7). The concentrations of NE and dopamine (DA) were determined using a modification of the radioenzyme assay for catecholamines (8).

The α -MPT-induced NE or DA disappearance rate was expressed as the ratio of the NE or DA concentration at 4 h after α -MPT and the steady-state concentration $\times 100$.

Following focal injection of kainic acid and upon recovery from anesthesia, the rats exhibited marked gait disturbances. Walking was usually interrupted every few steps by lurching. They were not able to walk straight. Tremor was observed at rest or while maintaining posture. Ataxic gait gradually improved from 1 to 7 days after injection, but ataxic gait was still partly present at 4 weeks. However, Snider *et al.* (12) reported that following a single dose (1 μ g in 1 μ l) of kainic acid injected into the cortex of the anterior lobe, rapid and nearly complete recovery occurred. The reason for this discrepancy may be differences in the dose and volume of injections.

Bilateral cerebellar injections produced large lesions with a radius of 2.5-3.5 mm (Fig. 1A). Extensive degeneration was observed in the posterior lobe of

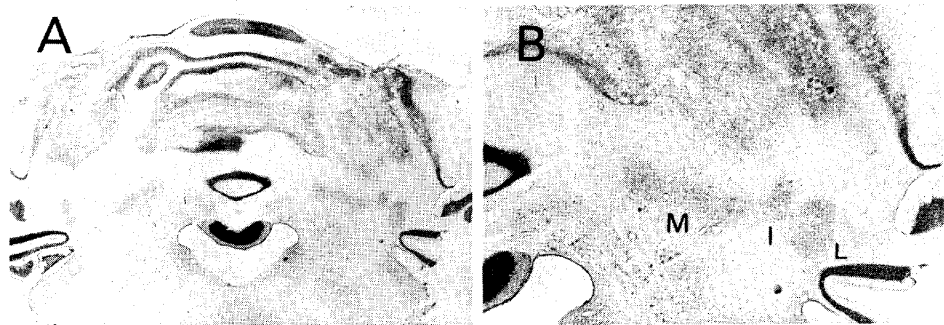


Fig. 1. Photomicrographs of cerebellum in toto (A) and cerebellar nuclei (B) 4 weeks after intracerebellar injection of kainic acid. Transverse sections. I, intermediate nucleus; L, lateral nucleus; M, medial nucleus. A = $\times 3$; B = $\times 15$.

the cerebellum, involving both the vermis and hemisphere. The degeneration was characterized by neuronal loss, severe disruption of cytoarchitecture and gliosis. At the edge of the lesion there were severe losses of Purkinje cells which extended for an additional millimeter. Granule and basket cells were markedly reduced in number. These histological changes are in agreement with the data of Snider *et al.* (6). In addition, degeneration was also observed in the cerebellar nuclei (Fig. 1B). This may be due to a non-specific toxic effect of kainic acid as suggested by Seil *et al.* (9).

In order to elucidate the metabolism of catecholamine in discrete brain regions, we measured NE levels and α -MPT-induced NE disappearance in discrete brain regions of sham-operated and lesioned rats. The results are shown in Table 1. NE concentrations in discrete brain regions of the controls were similar to those reported by Palkovits *et al.* (7). The NE concentrations in the locus coeruleus and the cerebellar cortex in the lesioned rats were almost normal. The α -MPT-induced NE disappearance rate in lesioned rats tended to be lower in the caudate and septal nuclei than that in controls, but the difference was not statistically significant. Our results, however, differ from those found in several strains of ataxic mutant mice in that there is evidence for a metabolic

TABLE 1. NE CONCENTRATIONS AND α -MPT-INDUCED NE DISAPPEARANCE RATES IN DISCRETE REGIONS OF THE BRAIN OF LESIONED (L) AND SHAM-OPERATED RATS (S).

Brain region	Norepinephrine concentration	
	0h conc. (ng/mg protein)	Conc. 4h after α -MPT (% of 0h conc.)
Cerebral cortex	L 8.57 \pm 1.39	26 \pm 3
	S 10.57 \pm 0.77	26 \pm 1
Septum	L 10.49 \pm 1.63	71 \pm 9
	S 10.74 \pm 2.66	49 \pm 14
Caudate nucleus	L 5.98 \pm 0.96	69 \pm 11
	S 6.15 \pm 0.96	47 \pm 4
Accumbens nucleus	L 34.08 \pm 10.64	64 \pm 22
	S 42.41 \pm 8.69	42 \pm 16
Substantia nigra	L 5.02 \pm 0.47	66 \pm 13
	S 8.02 \pm 1.51	71 \pm 18
Arcuate nucleus	L 37.75 \pm 8.11	93 \pm 24
	S 42.68 \pm 15.73	80 \pm 17
Median eminence	L 37.83 \pm 5.37	72 \pm 8
	S 38.43 \pm 7.26	60 \pm 9
Cerebellum	L 7.05 \pm 0.91	39 \pm 9
	S 6.39 \pm 0.13	46 \pm 6
Locus coeruleus	L 9.39 \pm 2.24	62 \pm 10
	S 8.43 \pm 0.88	56 \pm 7

All values given as mean \pm S.E.M. (n=5).

TABLE 2. DA CONCENTRATIONS AND α -MPT-INDUCED DA DISAPPEARANCE RATES IN DISCRETE REGIONS OF THE BRAIN OF LESIONED (L) AND SHAM-OPERATED RATS (S).

Brain region	Dopamine concentration	
	0h conc. (ng/mg protein)	Conc. 4h after α -MPT (% of 0h conc.)
Cerebral cortex	L	3.22 \pm 2.16
	S	4.62 \pm 3.14
Septum	L	19.55 \pm 1.65
	S	9.57 \pm 5.67
Caudate nucleus	L	233.27 \pm 26.08
	S	183.34 \pm 12.61
Accumbens nucleus	L	116.78 \pm 21.34
	S	128.68 \pm 32.71
Substantia nigra	L	12.77 \pm 2.05
	S	16.72 \pm 2.13
Arcuate nucleus	L	19.67 \pm 4.20
	S	12.78 \pm 2.09
Median eminence	L	95.79 \pm 8.06*
	S	63.32 \pm 7.42
Cerebellum	L	ud
	S	ud
Locus coeruleus	L	ud
	S	ud

All values given as mean \pm S.E.M. (n=5). For differences between L- and S-rats : *P<0.05; **P<0.02. ud: undetectable.

error of NE in the brain (2-4).

As shown in Table 2, the DA concentration and α -MPT-induced DA disappearance rate were measured in discrete brain regions. A significantly increased DA concentration was observed in the median eminence of the lesioned rats. The septal, caudate and arcuate nuclei in the lesioned rats tended to have an increased DA concentration, but the difference was not statistically significant. The α -MPT-induced DA disappearance rate of the lesioned rats was significantly decreased in the accumbens nucleus. The α -MPT-induced DA disappearance rate in the median eminence tended to be lower than that of controls, but the difference was not statistically significant. It is of considerable interest that a decrease in the turnover rate of DA was seen in the accumbens nucleus. This nucleus is one of the most significant nerve terminal loci of mesolimbic DA system and is thought to be important in spontaneous motor activity. Consequently, decrease in the DA turnover in the accumbens nucleus may be involved in the development of ataxic behavior. On the other hand, this result supports the opinion of Snider *et al.* (10) that the cerebellum can modify levels and turnover of catecholamines in the brain, possibly via direct ana-

tomic connections as well as by functional interaction with catecholaminergic pathways. The data of the present experiments may be important clinically also. Curzon (11) found that CSF homovanillic acid levels of patients with cerebellar tremor were significantly lower compared to those of controls. Furthermore, Kito *et al.* (12) reported that prolactin responses to thyrotropin releasing hormone injections increased in about half of the cases of spinocerebellar degeneration. They suggest that the activity of dopaminergic neurons in the hypothalamus is impaired in spinocerebellar degeneration in men.

Thus, lesions of the rat cerebellum induced by kainic acid injections may provide a useful animal model for cerebellar ataxia, in which catecholamine levels and the rate of catecholamine turnover can be examined.

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