Pharmacology Biochemistry & Behavior, Vol. 25, pp. 589–594, 1986. © Ankho International Inc. Printed in the U.S.A. 0091-3057/86 $3.00 + .00

Behavior and Receptor Changes After Kainate Lesioning of Nodular Cerebellum

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Received 7 March 1986

MAITI, A., K. SHAHID SALLES, S. GRASSI AND L. G. ABOOD. *Behavior and receptor changes after kainate lesioning of nodular cerebellum.* PHARMACOL BIOCHEM BEHAV **25**(3) 589–594, 1986.—A study was undertaken on the effects of kainic acid lesioning on the nodulus of the rat cerebellum on behavior and various brain receptors in conscious, freely moving rats. The basis for the study was the observation that barrel rotation and other motor effects induced by intraventricular administration of vasopressin and nicotine could be elicited by their administration into the nodular area of the cerebellum. Histology revealed a marked destruction of Purkinje, stellate, and Golgi cells in the area surrounding the site of kainate administration, with little effect on the granular cells. Immediately after administering 4–12 ng of kainic acid into the nodular cerebellum, rats exhibited circling movements, barrel rotation, and clonic convulsions accompanied by stereotypic head movements, aggressiveness, and gnawing-biting; effects gradually diminishing over 3 days. Receptor binding studies 4–14 days after kainate lesioning revealed a marked increase in ^{3}H-nicotine and ^{3}H-QNB binding in the surrounding cerebellar region, caudate nucleus, and hypothalamus, with no change in ^{3}H-dihydromorphine binding. The findings are consistent with the hypothesis that nicotinic and muscarinic pathways in the vestibular cerebellum, along with its connection to nigrostriatal dopaminergic systems, are involved in the mediation of barrel rotation, ataxia, and other motor disturbances resulting from administration of vasopressin on nicotine intraventricularly.

Vestibular cerebellum Kainic acid Motor behavior Nicotine Receptors

KAINIC acid has been widely used as a selective neuronal lesioning agent in the mammalian cerebellum [11,21], causing severe loss of Purkinje stellate and Golgi neurons with a relative sparing of granule cells, which are thought to be glutaminergic. Stereotaxic injections of kainic acid into various areas of the brain have been extensively studied for the assessment of neurotransmitter function within specific brain areas, including the cerebellum of different species. Fastigial influences on postural tonus have been studied by kainating lesions of the nucleus fastigii unilaterally and bilaterally [12]. The motor effects of localized lesions of the nucleus fastigii and of the intrafastigial infusion of potent GABA receptor agonists and antagonists, such as muscimol, picrotoxin or bicuculline, have also been reported [11]. In a previous study, it was postulated that the cerebellar nodule may, in its role of regulating autonomic activity, be responsive to neurotransmitters and other substances present in the spinal fluid in the fourth ventricles [14].

The present study originated from the observation that the barrel rotation and other motor effects induced by intraventricular administration of vasopressin or nicotine could be elicited by their administration into the nodular area of the cerebellum [1,2]. Although several studies have reported on the motor behavior characteristics of kainate-induced cerebellar lesioned rats, which included severe postural abnormality, circular movements, and barrel rotation, the lesions in the cerebellum were very extensive. In the present study, kainic acid in 1 μl vol. at doses below 12 ng was administered to conscious animals in order to examine the short-term and long-term alterations in behavioral locomotor activity.

METHOD

Sprague-Dawley male rats weighing between 150–180 and 200–300 g were used in two groups. The animals were housed in groups of three per cage in a room with controlled light/dark cycle (12 hr light/24 hr dark) at 23°C and fed ad lib. The rats were anesthetized with chlorpentane (0.3 ml/100 g IP) and secured in a stereotaxic instrument with the level of incisor bar at 5 mm above the level of the intra-aural line. Stainless steel guide cannulae (0.5 mm o.d.) were implanted into the cerebellum with the tip just above the lobule X to avoid injury of the middle cerebellar nuclei. The coordinates at the point of penetration were −12 mm of bregma, 0.1 mm lateral to the midline of the atlas of Paxinos and Watson. After the cannulae were inserted vertically at a depth of 5

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TABLE 1

RUNNING FITS INDUCED BY INTRANODULAR INJECTION OF KAINIC ACID AT VARIOUS DOSES

Doses	No. of Animals used		No. of animals running fits	Latency	Duration
2 ng	2		0	0	0
4 ng	3	increased startle	1	2 min	30 sec
6 ng	3	response and	2*	30 sec	30 sec
8 ng	3	hyperactivity	3	10 sec	30 sec
12 ng	3		3	10 sec	60 sec
20 ng	2		3	Convulsions	

Rats were obtained for a period of 2 hr after administration of kainic acid into the cerebellar nodule.

TABLE 2

ROTATIONAL AND BARREL ROTATION IMMEDIATELY AFTER NODULAR INJECTION OF VARIOUS DOSES OF KAINIC ACID

		Number of rats displaying rotational/circling/barrel			
Doses	N	Turning/ circling	Barrel	Frequency	Duration
4 ng	3	1	0	4-6/min	5 min
6 ng	3	2	0	7-8/min	5 min
8 ng	3	3	1	7-8/min	5-7 min
12 ng	3	3	1	8-10/min	10 min
20 ng	3	1	2	10/min	3 min
50 ng	2	0	2* one death		3 min
Saline	3	0	0	0	0

Rats were observed over a period of 2 hr after administration of kainic acid into the cerebellar nodule.

mm below the bone, they were cemented to the skull with dental acrylic and secured by skull screws. A stainless steel stylet with a protective plastic cap was then inserted to keep the cannulae patent between uses. The rats were used within a period of 4–7 days after surgery.

All injections of kainic acid were made via a 28 gauge internal cannula which projected 1.0 mm beyond the guide cannula in the nodular areas and 3 mm beyond that of the fourth ventricle. The internal cannula was connected to a 10 μl syringe microburet by polyethylene tubing, and injections of various doses of kainic acid in 2 μl were given over a 1-min period, maintaining the internal cannula in position for an additional 3 min.

A number of procedures were devised to assess the postural imbalance in kainate-treated animals 16–24 hr after receiving the neurotoxin.

Tail suspension test. When a rat was held by its tail, it assumed an asymmetric posture in an effort to restore its head to a normal position. The directionality of posturing and the flexion of the forepaws as well as the extension of the hindpaws were noted while the animal remained suspended by the tail for 15 sec.

Tail holding test. With one hand, the rat was gently restrained to prevent lateral deviations of the head while the other hand restrained the tail. A typical response was a fast lateral deviation of the head towards the base of the tail when the tip of the tail was relaxed.

Tail pinch test. When a miniature clip was placed at the tail 3–4 cm from its end, the rat promptly turned in an attempt to remove the clip by biting. The total time spent turning in either direction was recorded over a 15-min period.

Overt activity. Undisturbed in the observation chamber, the animals displayed several behavioral responses: exploration, slow walking with lateral tilting, swaying of the head and neck, ataxic movements, changes in the directionality of movement along with postural asymmetry.

Histology

After completion of behavioral testing, each animal was deeply anesthetized with chloropentane and was intracardially perfused with saline followed by 10% formalin-saline solution. In order to verify cannula placement locations, 50 μM sections were prepared and stained with cresyl violet. India ink was used to determine the site of drug administration.

Receptor Binding Studies

The cerebellum (uvulo-nodular areas and vermal parts), hypothalamus, and caudate nucleus were removed from kainate-induced lesioned and non-injected rats immediately after sacrificing the animal by decapitation. Groups of animals were killed by decapitation 4, 8, and 12 days after the intranodular lesions. After dissection, the tissues were frozen on dry ice, weighed, and homogenized in 0.05 M Tris, pH 7.5. Control rats received a microinjection of 5 μl saline in the nodule; they were killed at the same time as the animals injected intranodularly with kainic acid.

The procedure for measuring specific ^{3}H-nicotine binding is described elsewhere [2], while ^{3}H-3-quinuclidinyl benzilate (^{3}H-QNB) binding was determined by the procedure of Yamamura *et al.* [23] and ^{3}H-dihydromorphine (^{3}H-DHM) binding by that of Pasternak and Snyder [16]. The radioactive specific activities of ^{3}H-nicotine, ^{3}H-QNB, and ^{3}H-DMH were 78, 80, and 85 Ci/mmole, respectively. All ligands were used at a final concentration of 10^{-9} M in a volume of 0.05 M Tris buffer, pH 7.5, in the presence and absence of 10^{-6} M unlabeled nicotine, QNB, or morphine. Each sample contained 2 mg wet weight tissue in a final volume of 1.2 ml and incubated either in an ice bath (^{3}H-nicotine) or at 30° for 30 min.

RESULTS

Immediate Behavioral Effects of Kainic Acid Injections Into the Nodule of the Cerebellum of the Rat

Marked behavioral effects occurred immediately following the injection of kainic acid into the cerebellar nodule (Table 1). The responses were dose dependent, ranging from mild to moderate and severe reactions in terms of latency and duration.

Running fits. At a dose of 6 ng or more, spontaneous locomotor activity occurred even while the needle was inside the cannula. At 8 ng, the running fit began within 1 min, often followed by circular rotation. At doses of 12 and 20 ng the running fits recurred several times, often followed by mostly tonic and some clonic convulsions. A sudden sound such as clapping of hands often triggered a running fit. No deaths occurred.

TABLE 3

BODY WEIGHT CHANGES AFTER ADMINISTRATION OF KAINIC ACID INTO THE CEREBELLAR NODULE

Groups	No.	(0)	7 day later when KA was given	7th day after KA	14th day After KA
Control	18	150 ± 15	Saline was injected	184 ± 24	195 ± 18
		268 ± 28		312 ± 12	330 ± 25
KA-4 ng	6	150 ± 23	168 ± 20	190 ± 32	235 ± 29
	3	280 ± 12	310 ± 12	350 ± 38	380 ± 34
KA-8 ng	9	152 ± 8	160 ± 5	190 ± 15	210 ± 20
	3	285 ± 9	290 ± 14	310 ± 23	360 ± 30
KA-12 ng	6	155 ± 15	160 ± 6	183 ± 15	195 ± 25

Two groups of rats were used for each set, except for one receiving 12 ng of kainic acid where only the lower weight group was used. Results are expressed as mean ± standard deviation.

Circling movements and barrel rotation. At 8 ng doses, all animals showed some degree of circling movements without any apparent laterality (Table 2). Doses of 20 ng resulted in barrel rotation along the axis of the body with latencies of 30–60 sec and durations under 2 min; however, rotation could be repeatedly elicited by loud sudden noises, such as hand clapping.

A dose of 6 ng kainic acid invariably resulted in irregular myoclonic jerks, occurring within 1 min in the absence of rotation; and at doses of 8 ng, the jerks were recurrent over a period of 10–30 min. In the absence of clonic movements, there occurred within 5 min an extension of the hind limbs and flexion of the forepaws. When quiescent, the rats were generally prostrate or exhibited a scoliosis with the limbs in an extended position. At a dose of 4 ng, the most noteworthy sign was excessive grooming. Nystagmus was noted at all doses and pupillary dilation only at doses of 12 or 20 ng. Increased respiration and hypernea were noted at lower doses of 12 or 20 ng. Increased respiration and hypernea were noted at lower doses even in the absence of running fits. At doses greater than 6 ng after the animals recovered from prostration, which generally lasted 30 min, the animals exhibited motor ataxia and a marked hyperexcitability characterized by salivation, aggressive and stereotypic head movements, gnawing, biting, and excessive grooming, effects which persisted for 1–2 hr.

At doses of kainic acid ranging from 4–12 ng, the animals exhibited dystonia, hyperactivity, and aggressive behavior which persisted for 1–6 days with no residual motor abnormality. Only in those animals which developed barrel rotation and convulsions were persistent motor abnormalities noted. Even after 4 days following kainic acid, all animals exhibited vigorous circling and rotational movements when suspended by their tails.

Later Motor Effects of Kainate-Lesioned Animals

At a period to 8 hr after administering kainic acid, such motor deficits as circling, running fits, and barrel rotation had gradually disappeared, but some postural asymmetry of the limbs with extensor hypertonus of the hind limbs and flexion of the forepaws persisted. Also absent was any torticolis or opisthotonus. Except for hyperirritability, slight tremors, and some extensor atonia (flaccidity), locomotion and other bodily movements appeared to be normal. No overt abnormalities were evident 12 hr after kainic acid treatment.

At a period 4–6 hr post kainic acid, the rats were hypersensitive to tail pinching, and the tendency gradually disappeared over 24 hr. At this stage, if the animals were suspended by the tail, they tended to vigorously rotate. During the period 2–3 days post kainic acid, the animals were extremely hyperirritable, pugnacious, difficult to handle, and exhibited marked startle responses with running fits.

Histology After Kainate Lesioning of Nodular Cerebellum

Histological findings after kainate lesioning are described in detail elsewhere [15]. Briefly, the changes consisted of widespread loss of Purkinje and other large neurons in the areas of nodule and uvula, while the granular cells were relatively unaffected.

Body Weight Changes

Measurements of the body weight were determined on all animals during a 3-week period, before and after the intranodular injection of kainic acid or saline. Injection of 0.9% saline and the surgical operation did not significantly affect the body weight (Table 3). On the other hand, the kainate-lesioned animals, especially the group that received 4 ng, showed a slight increase in body weight during 8–16 days after lesioning, as compared with control animals.

After surgery, both the control and experimental group of animals showed daily gains in body weight. During the first 2–3 days after administering kainic acid, there was some weight loss which was followed by daily weight gains at rates slightly greater than in controls. Only those rats who received more than 8 ng kainic acid showed a relatively continuous reduction in body weight during the next 2 weeks.

Effect of Kainate Lesioning on ^{3}H-Nicotine Binding in Various Brain Areas

An increase in ^{3}H-nicotine binding ranging from 27–42% occurred in the remaining nodular area and surrounding cerebellar region 4–8 days following the administration of 4 or 8 ng of kainate into the nodule; while the caudate showed a 51% and the hypothalamus a 20% increase (Table 4). After

TABLE 4

EFFECT OF KAINATE LESIONING ON ^{3}H-NICOTINE BINDING TO VARIOUS REGIONS OF RAT BRAIN

	Nodular area moles/mg×10^{14}		Surrounding Cerebellum moles/mg×10^{14}		Caudate moles/mg×10^{14}		Hypothalamus moles/mg×10^{14}	
	Control	Kainate	Control	Kainate	Control	Kainate	Control	Kainate
4 ng KA 4 days	2.5	3.3 (32%)	2.2	2.8 (27%)	3.3	5.0 (51%)	4.5	5.5 (22%)
8 ng KA 8 days	2.6	3.6 (38%)	2.4	3.4 (42%)	M	M	4.4	5.3 (20%)
8 ng 12 days	2.5	3.5 (40%)	2.2	2.4 (10%)	3.2	6.0 (87%)	4.6	8.0 (74%)
12 ng 8 days	2.3	2.8 (22%)	M	M	3.6	6.8 (89%)	4.5	8.5 (91%)

The results are average of 3–4 separate experiments run in triplicate; the coefficient of variation of each value being no greater than 12%. The days indicated refer to the time after lesioning when measurements were made. Data expressed in moles/mg protein.

TABLE 5

EFFECT OF KAINATE LESIONING OF ^{3}H-DHM BINDING TO VARIOUS REGIONS OF RAT BRAIN

	Nodular area moles/mg×10^{14}		Surrounding Cerebellum moles/mg×10^{14}		Caudate moles/mg×10^{14}		Hypothalamus moles/mg×10^{14}	
	Control	Kainate	Control	Kainate	Control	Kainate	Control	Kainate
4 ng KA 4 days	0.55	0.58 (−10%)	0.45	0.50 (10%)	6.5	8.7 (33%)	5.8	6.0 (5%)
8 ng KA 8 days	0.55	0.60 (−8%)	0.50	0.48 (−4%)	6.2	8.5 (37%)	6.0	6.3 (5%)

The results are an average of 3 separate experiments; the coefficient of variation of each value being less than 12%. Data expressed in moles/mg protein.

12 days following the administration of 8 ng kainate, the increase in ^{3}H-nicotine binding was 40% in the nodule, 10% in the surrounding area, 87% in the caudate, and 74% in the hypothalamus. At a dose of 12 ng kainate, the increase in both the caudate and hypothalamus was 90%. A Scatchard analysis of ^{3}H-nicotine binding to the nodular and surrounding cerebellum revealed no difference in the Kd (2×10^{-9} M) before and after kainate lesioning (data not shown).

Effect of Kainate Lesioning on ^{3}H-DHM Binding

^{3}H-DHM binding in the nodular area, surrounding cerebellar region, and hypothalamus was unchanged following kainate lesioning; however, opiate binding in the caudate increased 33% and 37% after 4 and 8 ng of kainate, respectively (Table 5).

Effect of Kainate Lesioning on ^{3}H-QNB Binding in Various Brain Areas

An increase in ^{3}H-QNB binding ranging from 93–100% occurred in both the remaining nodular area and surrounding cerebellar region 4–14 days following the administration of 4 ng into the cerebellar nodule; while the caudate showed a 20% and the hypothalamus a 39% increase (Table 6). At doses of 8–12 ng of kainate, the increase occurring 8–12 days later ranged from 136–153% in the nodule and surrounding cerebellar region, while the caudate showed a 23% and the hypothalamus a 60% increase. Comparable increases were seen in the surrounding cerebellum and hypothalamus following the administration of 12 ng kainate, while the ^{3}H-QNB binding in the caudate increased further to 42%.

DISCUSSION

There exists some anatomical and biochemical evidence to indicate that circling or barrel rotation in rodents involves both nigrostriatal and mesolimbic dopaminergic components [5, 20, 22]; however, the barrel rotation resulting from the intraventricular administration of vasopressin, somatostatin and chlorpromazine may also involve muscarinic cholinergic pathways, insofar as carbachol inhibits and atropine enhances the effect [4]. It has been known for over a century that rotation in rats is always associated with postural asymmetry, i.e., the turning behavior in response to unilateral intervention in specific brain regions [10]. Surgical or electrolytic lesions of the posterior cerebellar areas involving

TABLE 6

EFFECT OF KAINATE LESIONING ON ^{3}H-QNB BINDING TO VARIOUS REGIONS OF RAT BRAIN

	Nodular area moles/mg×10^{12}		Surrounding Cerebellum moles/mg×10^{12}		Caudate moles/mg×10^{12}		Hypothalamus moles/mg×10^{12}	
	Control	Kainate	Control	Kainate	Control	Kainate	Control	Kainate
4 ng KA 4 days	0.32	0.62 (93%)	0.52	0.98 (88%)	2.85	3.42 (20%)	3.20	3.30 (39%)
4 ng KA 14 days	0.35	0.72 (105%)	0.55	0.82 (49%)	M	M	M	M
8 ng KA 12 days	0.35	0.84 (140%)	0.56	1.42 (153%)	3.20	3.95 (23%)	2.90	4.70 (62%)
12 ng KA 8 days	M	M	0.58	1.58 (172%)	3.10	4.40 (42%)	2.90	4.84 (67%)

The results are average of 3–4 separate experiments run in triplicate; the coefficient of variation of each value was no more than 10%. Data expressed in moles/mg protein.

the vestibular cerebellum resulted in turning movements with a corkscrew-like distortion of the body axis immediately after recovery from the surgery. Circling behavior produced by unilateral lesions of the central vestibular system has also been demonstrated [19]. The question arose whether any type of rotation and postural asymmetry induced in nonlesioned rats by intraventricular administration of drugs or peptides may be acting on the cerebellar nodule, which is conterminous to the fourth ventricle. The results from the present experiments clearly demonstrate that vasopressin and nicotine administered ICV have a direct action on the nodular areas in inducing such rotational movements and prostration, respectively.

In addition to the muscarinic and vasopressin receptors, the nodular area of the cerebellum contains receptors for substance P, VIP, cholecystokinin and angiotensin. The close proximity of the nodule to the fourth ventricle raises the issue as to whether vasopressin and other endogenous neuroactive substances in the ventricles can exert an effect upon the nodule. Recently, it was reported that the cerebellar Purkinje neurons can selectively extract small and large molecules from the cerebrospinal fluid with implications for their physiology and pathology [3]. The present findings are consistent with the notion that neuropeptides, such as vasopressin, may be released in spinal fluid from various brain sites and exert an action on Purkinje cells.

The receptor binding studies indicate that kainate lesioning of the cerebellar nodule results in a significant increase in the number of ^{3}H-nicotine and ^{3}H-QNB binding sites in the residual nodular and surrounding cerebellar regions as well as the caudate nucleus and hypothalamus. Insofar as kainic acid destroyed a substantial number of nodular neurons, it would appear that the nicotine and muscarinic cholinergic receptor in the surrounding region were not only spared but actually increased in number. An increase in the density of various neurotransmitter receptors following lesioning of specific brain areas has been described by a number of investigators. Lesioning of the locus ceruleus results in an increase in both cholinergic and adrenergic receptor in the rat cerebral cortex and hippocampus [18]. After partial denervation of the rat hippocampal cortex, there results a compensatory collateral sprouting of hippocampal cholinergic and noradrenergic afferents along with a functional hyperactivity. An upregulation of hippocampal adrenergic receptors and axonal sprouting occurs after septal deafferentiation [9]; while the recovery of spontaneous alternation and hippocampal axonal sprouting occurs following lesioning of the rat entorhinal cortex [17].

Although the Purkinje cells of the nodule undergo virtually complete degeneration within 24 hr after kainic acid, ^{3}H-nicotine and ^{3}H-QNB binding showed an increase. Evidently the contribution of the Purkinje and stellate cells to the binding of either ligand was minimal, and the elevation in receptor densities was attributable to the surrounding granular layer. The granular layer has been shown to be least vulnerable to kainic acid [3,11]. In view of the finding that kainate lesioning of the cerebellar nodule abolished the prostration and seizures elicited by administering nicotine directly into the nodule [15], the sites for nicotine's action appear to reside in the Purkinje or stellate cells of the nodule; however, the possibility cannot be excluded that nicotine may be acting presynaptically. Ultrastructural analysis of kainate lesioning of cerebellar cortex has revealed that synaptic terminals on Purkinje dendritic spines remained tightly attached postsynaptically up to 3 weeks after treatment [3].

It is generally believed that [13] the Purkinje cells have an inhibitory synaptic contact with vestibular as well as intracerebellar nuclei, such as the nucleus fastigii. There are numerous studies indicating that lesions or ablations of the flocculonodular lobe of mammals results in ataxia, oscillations of the extremity, falling, and prostration [6,7]. Similar effects result from destruction of the caudal parts of the nucleus fastigii, while lesions in the rostroventral regions result in disturbances in posture and coordination [11]. The disturbances in equilibrium and eye movements following ablation of the nodulus have been attributed to a release (disinhibition) of the vestibular nuclei from cerebellar inhibition [8].

Another pathway which appears to be involved in the action of nicotine is the vestibulospinal tract linking the extensor muscles of the limbs with the lateral vestibular and, to

a lesser extent, medial vestibular nucleus. Electrical stimulation of the lateral vestibular nucleus (Deiters') results in excitation of extensor and inhibition of flexor motorneurons. The lateral vestibular nucleus receives abundant projections from cortex of the spinal part of the cerebellum as well as the vestibulo-cerebellum and fastigial nucleus.

ACKNOWLEDGEMENTS

The authors are indebted to Diane Piekut for the photomicrography. This research was supported by HHS Grant DA 00464 and a grant from The Council for Tobacco Research.

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