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Enhancing Effect of Taurine on the Rat Caudate Spindle. I: Interaction of Taurine With the Nigro-Striatal Dopamine System

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HASHIMOTO-KITSUKAWA, S., S. OKUYAMA AND H. AIHARA. *Enhancing effect of taurine on the rat caudate spindle. I: Interaction of taurine with the nigro-striatal dopamine system.* PHARMACOL BIOCHEM BEHAV 31(2) 411–416, 1988.—We studied the effects of taurine on the caudate spindle in rats and compared the findings with those of γ-aminobutyric acid (GABA) when these compounds were microinjected into the bilateral striatum. Three μg of taurine was without effect, whereas 10 and 30 μg of taurine enhanced the spindle in a dose-dependent manner. GABA (3–100 μg) had no significant effect. Apomorphine (0.5 mg/kg) and methamphetamine (0.5 mg/kg) given intravenously to pargyline-pretreated rats suppressed the spindle. The suppressing effects of these drugs were reduced by taurine (3 μg) at the dose which, per se, did not affect the spindle. These results suggest that taurine may decrease the activity of striatal dopaminergic neurons and enhance the caudate spindle.

Electroencephalography Striatum Dopamine receptors Taurine Neuroregulators

THE possibility that taurine is an inhibitory neurotransmitter or modulator within the central nervous system has been suggested (5, 13, 18). Taurine is widely but unevenly distributed in brain. High taurine levels are found in the striatum as well as cerebral cortex, hippocampus and cerebellum (27). In addition, taurine may be involved in the transmission of dopamine (DA) neurons. Taurine depressed the motor behavior (1, 6, 11, 17, 29) and affected DA metabolism (1, 2, 11, 33) in mice and rats.

The caudate spindle was elicited in the frontal cortex of rats by electrical stimulation of the striatum (15, 16, 25). Most recently, we reported that the DA system plays an important role in the development of the caudate spindle (12,26). Smaller doses of DA and apomorphine enhanced the spindle, whereas with larger doses, suppression occurred. The preferential DA autoreceptor agonist, (±)-3-(3-hydroxyphenyl)-N-n-propylpiperidine, enhanced the caudate spindle in a dose-dependent manner. These results are consistent with the findings of others that systemic treatment with neuroleptics enhanced the spindle (14, 16, 31, 32) and these enhancing effects were antagonized by apomorphine administered systemically (16). Thus, the caudate spindle should provide a useful model for evaluating effects on the DA system.

The present study was undertaken to investigate the effect of taurine on the caudate spindle and evaluate whether or not taurine interferes with DA neurons. The effect of GABA on the caudate spindle was also examined, because like taurine, this amino acid has an inhibitory effect on the motor behavior and DA metabolism (2,7).

METHOD

Animals

Male Wistar rats, weighing 250–300 g, were used. They were housed in groups of 3/cage in a light (12 hr cycle) and temperature controlled room with ad lib access to food and water.

Caudate Spindle

Animals were anesthetized with ether and immobilized with 2% gallamine triethiodide (0.2 ml/100 g body weight), because general anesthetics, such as sodium pentobarbital, influence the development of the caudate spindle (8). Instead of that, all points of surgical and stereotaxic contact were infiltrated thoroughly with 8% lidocaine and anesthetic lidocaine ointment was supplemented every hour. Then, animals were ventilated artificially, placed in a stereotaxic apparatus (Narishige, SR-6) and subsequently subjected to surgical manipulations. The body temperature was maintained between 37 and 38°C, using a heating pad controlled from a rectal thermistor (Natsume, KN-474).

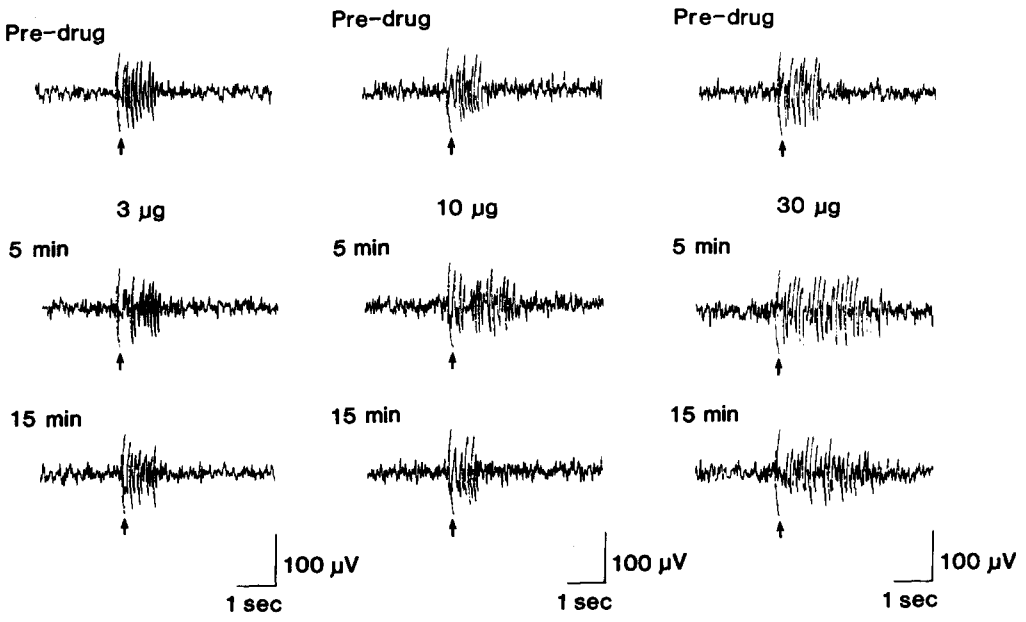

FIG. 1. Effects of bilateral injection of taurine in doses of 3, 10 and 30 μg into the striatum on the caudate spindle in rats. 0 min: immediately after administration of drug. Arrows indicate stimulus artifacts.

TABLE 1

ALTERATION IN DURATION OF THE CAUDATE SPINDLE AFTER TREATMENT WITH TAURINE AND GABA IN RATS

Drugs	Dose (μg/side)	N	Duration (percentage of predrug value) Measured at the Following Times After Administration (min)					
			0	5	15	30	45	60
Vehicle		6	101.6 ±3.5	98.2 ±3.3	104.2 ±3.5	100.3 ±5.1	106.9 ±7.9	101.2 ±7.4
Taurine	3	6	108.7 ±5.0	117.6 ±10.2	110.1 ±8.1	100.9 ±10.2	105.0 ±8.1	95.7 ±6.3
Taurine	10	6	107.8 ±6.8	133.8 ±11.9*	115.8 ±9.8	114.4 ±8.4	114.8 ±8.6	115.8 ±9.0
Taurine	30	6	119.3 ±13.9	139.4 ±10.3*	153.2 ±12.8†	150.5 ±18.3*	135.1 ±10.1	119.8 ±6.2
Vehicle		6	103.4 ±3.9	101.3 ±3.3	105.3 ±3.6	101.0 ±4.5	102.4 ±5.5	99.5 ±6.6
GABA	3	6	94.3 ±6.8	97.8 ±6.7	104.4 ±7.4	100.9 +5.6	102.2 ±6.5	105.6 ±3.5
GABA	10	6	95.0 ±12.9	110.6 ±9.2	117.6 ±10.2	103.6 ±12.5	102.3 ±11.8	98.1 ±11.3
GABA	30	6	95.9 ±12.3	118.4 ±10.2	120.6 ±7.0	120.8 ±11.2	103.2 ±6.5	96.0 ±3.0
GABA	100	6	104.3 ±19.8	108.0 ±18.5	108.7 ±12.3	111.5 ±14.3	103.6 ±16.2	116.4 ±19.7

Alteration in activity (index: duration) of the caudate spindle is shown as a percentage ratio of the predrug values.

N: number of rats. 0 min: immediately after administration of drug.

*$p<0.05$ and †$p<0.01$ vs. vehicle-treated group (Dunnett's test).

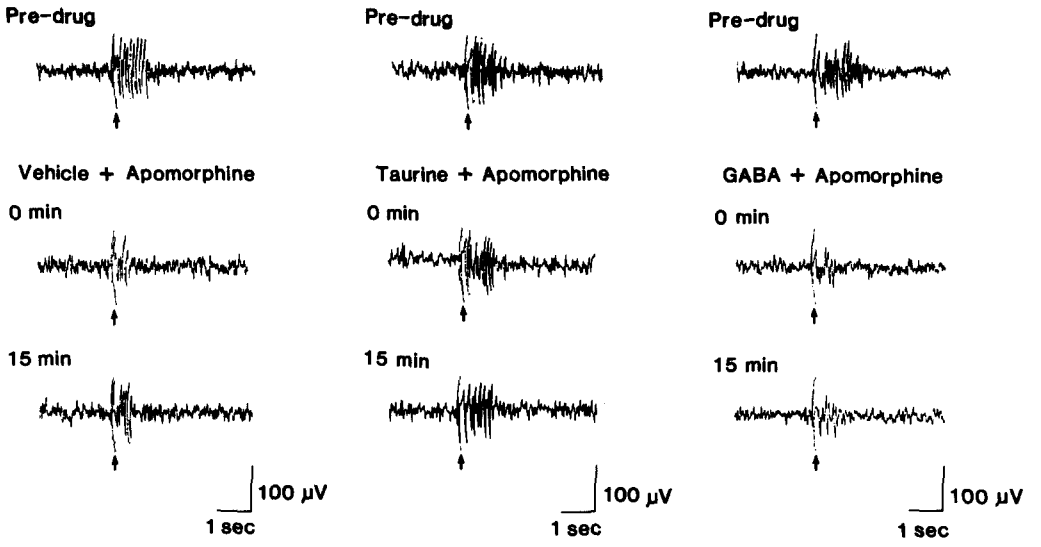

FIG. 2. Effects of taurine (3 μg/side) and GABA (3 μg/side) on suppression of the caudate spindle in pargyline-pretreated rats induced by apomorphine (0.5 mg/kg, IV). 0 min: immediately after administration of apomorphine. Arrows indicate stimulus artifacts.

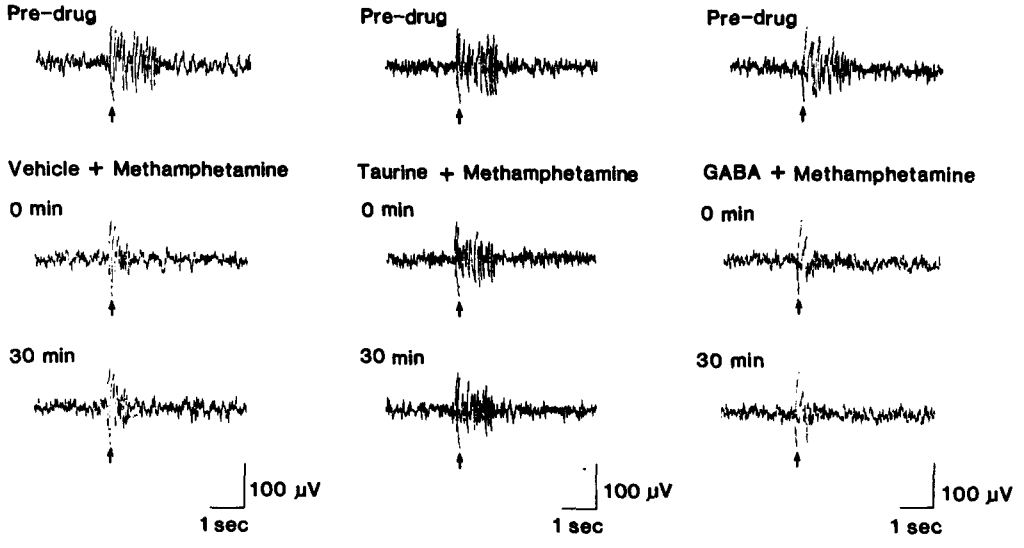

FIG. 3. Effects of taurine (3 μg/side) and GABA (3 μg/side) on suppression of the caudate spindle in pargyline-pretreated rats induced by methamphetamine (0.5 mg/kg, IV). 0 min: immediately after administration of methamphetamine. Arrows indicate stimulus artifacts.

Screw electrodes were inserted through the cranium until their tips arrived at the dura overlying the frontal cortex. A cannula-bipolar electrode (o.d. 0.7 mm and i.d. 0.4 mm) that was capable of both electrical stimulation and injection of drug was implanted into the left striatum. A stainless-steel guide cannula was implanted into the right striatum and was fixed to the skull with small screws and dental cement. The tip of a cannula-bipolar electrode or guide cannula was located at AP, 7.3; ML, 3.0; DV, 3.5 mm; according to the atlas of Albe-Fessard *et al.* (3).

The caudate spindle was produced by electrical stimulation of the striatum (1 msec, 0.1 Hz, 5 V) and bipolar recordings from the frontal cortex were made. Sixty min later measurements of the caudate spindle were started and after a further 10 min drugs were administered. The intrastriatal microinjection was given through an injection needle (o.d. 0.3 mm and i.d. 0.18 mm) extending 1 mm beyond the tip of the guide cannula. Taurine and GABA were dissolved in saline solution. All injections into the striatum were given bilaterally at a rate of 1 μl/min using a microsyringe. The volume injected was 1 μl. The injection needle was left in position for one additional min.

In experiments to determine the effects of taurine and GABA on suppression of the caudate spindle induced by apomorphine and methamphetamine, intrastriatal injections were given to pargyline-pretreated rats (100 mg/kg, IP, 30

TABLE 2

EFFECTS OF TAURINE (3 μg/SIDE) AND GABA (3 μg/SIDE) ON SUPPRESSION OF THE CAUDATE SPINDLE IN PARGYLINE-PRETREATED RATS INDUCED BY APOMORPHINE (0.5 mg/kg, IV) AND METHAMPHETAMINE (0.5 mg/kg, IV)

Treatment	N	Duration (percentage of predrug value) Measured at the Following Times After Administration (min)					
		0	5	15	30	45	60
Vehicle + Vehicle	5	95.6 ±9.5	98.9 ±10.6	103.6 ±8.1	103.3 ±8.5	104.3 ±8.2	96.8 ±8.5
Vehicle + APO	6	55.7 ±1.6†	66.6 ±7.1*	73.0 ±9.8*	97.7 ±10.3	92.5 ±12.1	79.4 ±14.4
Vehicle + MAP	6	59.7 ±1.9*	60.4 ±5.3†	64.5 ±6.6*	61.2 ±6.8†	57.6 ±9.0*	64.6 ±3.7
Taurine + Vehicle	6	94.8 ±7.9[a]	97.4 ±6.2[a]	102.3 ±9.6[a]	107.9 ±8.4[a]	110.5 ±11.7[a]	101.5 ±6.7[a]
Taurine + APO	8	86.9 ±7.3§	94.1 ±8.0	110.0 ±7.8‡	117.5 ±11.5	113.7 ±6.8	94.8 ±8.1
Taurine + MAP	8	89.7 ±6.4#	87.5 ±5.2#	84.7 ±6.9	84.3 ±5.3¶	90.9 ±5.7#	85.3 ±4.2#
GABA + Vehicle	6	95.4 ±9.2[a]	102.7 ±8.6[a]	105.2 ±5.9[a]	96.3 ±7.0[a]	103.8 ±5.3[a]	101.1 ±7.6[a]
GABA + APO	6	66.1 ±8.3[b]	78.4 ±8.1[b]	97.1 ±7.3[b]	114.5 ±12.8[b]	85.0 ±11.1[b]	82.8 ±6.5[b]
GABA + MAP	6	69.6 ±5.3[c]	69.9 ±2.9[c]	61.2 ±4.9[c]	61.2 ±3.9[c]	67.9 ±4.6[c]	69.2 ±3.7[c]

Alteration in activity (index: duration) of the caudate spindle is shown as a percentage ratio of the predrug values. Rats pretreated with pargyline (100 mg/kg, IP, 30 min) were given taurine, GABA or vehicle 5 min before administration of apomorphine, methamphetamine or vehicle. The caudate spindle was not significantly affected by treatment with pargyline.

APO: apomorphine. MAP: methamphetamine. N: number of rats. 0 min: immediately after administration of apomorphine, methamphetamine or vehicle.

*$p<0.05$ and †$p<0.01$ vs. Vehicle + Vehicle-treated group. [a]Not significantly different from Vehicle + Vehicle-treated group. ‡$p<0.05$ and §$p<0.01$ vs. Vehicle + APO-treated group. [b]Not significantly different from Vehicle + APO-treated group. ¶$p<0.05$ and #$p<0.01$ vs. Vehicle + MAP-treated group. [c]Not significantly different from Vehicle + MAP-treated group (Dunnett's test).

min before) and 5 min later, apomorphine and methamphetamine were given intravenously, in a volume of 2.0 ml/kg body weight. Pargyline, apomorphine and methamphetamine were dissolved in saline solution.

Histology

After the end of experiments, the location of the tips of the electrodes and guide cannulae were confirmed histologically. The animal was anesthetized with pentobarbital sodium and perfused with 10% formalin. Frozen 50 μm thick sections of the whole brain were cut on a freezing microtome (Komatsu, MA-101) and stained with hematoxylin and eosin.

Statistical Analysis

Results are presented in terms of means±S.E.M. Calculations including statistical analyses were performed on a VAX-8600 computer. All data were analysed by ANOVA, and significant differences between groups were determined using Dunnett's test where ANOVA yielded a significant result (9).

RESULTS

Effects of Bilateral Injections of Taurine and GABA Into the Striatum on the Caudate Spindle

The caudate spindle was not modified by intrastriatal injections of the vehicle.

Figure 1 shows representative experiments on the effects of various doses (3–30 μg) of taurine on the caudate spindle. Three μg of taurine had no effect, but 10 and 30 μg enhanced the caudate spindle dose-dependently. On the other hand, GABA (3–100 μg) did not affect the spindle, even when giving a three-fold larger dose (100 μg) than the highest dose (30 μg) of taurine.

The mean values for the caudate spindle in these experiments are indicated in Table 1.

Effects of Taurine and GABA on Suppression of the Caudate Spindle Induced by Apomorphine and Methamphetamine

Apomorphine and methamphetamine showed a dose-dependent suppression of the caudate spindle at the doses of 0.25 and 0.5 mg/kg. A larger dose (1 mg/kg) of these drugs induced no further suppression (data not shown), hence, in the following experiments, 0.5 mg/kg of apomorphine and methamphetamine were given.

The suppressing effects of apomorphine and methamphetamine were reduced with taurine at the lowest dose (3 μg) which, per se, did not affect the spindle. These effects of taurine were compared to the findings with GABA. GABA did not affect the suppression induced by apomorphine and methamphetamine (Figs. 2 and 3, Table 2).

DISCUSSION

Taurine enhanced the caudate spindle, in a dose-dependent manner, and reduced the suppressing effect of apomorphine and methamphetamine on the caudate spindle. We reported that activation of the nigro-striatal DA system suppressed the caudate spindle, while the inhibition of this system, by stimulating presynaptic DA autoreceptors or blocking postsynaptic DA receptors, enhanced the spindle (12,26). It was also reported that systemic treatment with neuroleptic drugs enhanced the spindle (14, 16, 31, 32) and these enhancing effects were antagonized by apomorphine administered systemically (16). Therefore, the effects of taurine injected into the striatum on the spindle are considered to be mediated through a decrease in the nigro-striatal DA neuronal activity. Taurine was found to depress the motor activity related to DA neuronal activity (1, 6, 11, 17, 29). In addition, taurine elevated the striatal and limbic concentrations of DA (1, 2, 11, 33) and decreased DA metabolites (33). These results and our present data support the possibility that taurine inhibits central DA neurons.

Whether or not taurine affects other neuronal systems involved in the development of the caudate spindle was not excluded. Taurine suppresses the release of acetylcholine (ACH) from the rat superior cervical ganglia and cerebral cortical slices (23). ACH injected into the striatum elicits (19), whereas atropine suppresses the caudate spindle (15). However, taurine showed enhancement of the caudate spindle which is incongruent with its inhibitory effect on the release of ACH. Taurine was also found to affect the release of GABA from rat cerebral cortical (20) and guinea pig cerebellar slices (24), and the enzymes metabolizing GABA (22). But our results indicated that GABA, injected into the striatum, did not demonstrate any effect on the spindle at a wide dose range (3–100 μg). Although taurine has an interaction with ACH or GABA neurons in the various brain regions, the effect of taurine on the caudate spindle may be due to DA neurons.

GABA is known to be an inhibitory neurotransmitter in the central nervous system (10,28) and possesses effects on DA metabolism and motor behavior similar to events seen with taurine (2,7). In the present study, GABA showed no effect on the caudate spindle itself and on the suppressing effects induced by apomorphine and methamphetamine. The effects of GABA on the DA concentration (2), and 4-aminopyridine-stimulated DA release from rat striatal synaptosomes (4) were slight compared with that of taurine. Thus, taurine may have a more important role than GABA in regulating DA transmission.

Lehmann *et al.* (21) suggested that taurine plays a role in the maintenance of homeostasis in the central nervous system during hyperexcitation. In cases of excessive excitation, taurine is released into the extracellular space, inhibits the influx of Ca^{2+} and consequently can protect against excitotoxicity (30). We observed that taurine reduced the suppressing effects induced by apomorphine and methamphetamine at the lowest dose (3 μg) that, per se, did not enhance the caudate spindle. These results indicate that taurine inhibits DA neurons to a greater extent when the DA system is activated.

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