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Interaction of Taurine and Related Compounds With GABAergic Neurones in the Nucleus Raphe Dorsalis

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LILJEQUIST, R. *Interactions of taurine and related compounds with GABAergic neurones in the nucleus raphe dorsalis.* PHARMACOL BIOCHEM BEHAV **44**(1) 107–112, 1993.—The effects of $GABA_A$ (muscimol) and $GABA_B$ (baclofen) receptor agonists on spontaneous motor activity and food consumption of rats were compared to those produced by taurine and related compounds (3-aminopropanesulphonic acid, 5-aminovaleric acid, and guanidinoethanesulphonic acid). Local application of muscimol into the nucleus raphe dorsalis caused a dose-dependent increase in spontaneous motor activity. Muscimol-stimulated motor activity was blocked by picrotoxin. High doses relative to muscimol of 3-aminopropanesulphonic acid, guanidinoethanesulphonic acid, and 5-aminovaleric acid also attenuated the action of muscimol. Taurine by itself was ineffective on locomotion but enhanced the effect of a small dose of muscimol. Baclofen also stimulated activity but to a lesser extent than muscimol. Baclofen's stimulatory action on motor activity was partially blocked by 5-aminovaleric acid, whereas 3-aminopropanesulphonic acid was without effect. Muscimol and baclofen both increased food consumption of rats. Picrotoxin blocked this effect of muscimol, whereas the action of baclofen was blocked by 5-aminovaleric acid. Muscimol, taurine, and guanidinoethanesulphonic acid all reduced 5-hydroxytryptamine (5-HT) concentration in the hypothalamus. In radioligand binding studies, guanidinoethanesulphonic acid at micromolar concentrations displaced [^{3}H]GABA from $GABA_A$ receptors. It is concluded that taurine may have a slight direct effect on GABA receptors but is more likely to act as an indirect neuromodulator of GABAergic neurotransmission in the brain.

Taurine Muscimol 3-Aminopropanesulphonic acid 5-Aminovaleric acid Guanidinoethanesulphonic acid 5-Hydroxytryptamine Locomotory activity Food consumption

THERE is evidence to suggest that taurine, a sulphonic amino acid, may act as an inhibitory neurotransmitter or neuromodulator in the CNS. Although the mode of action of taurine still remains to be elucidated, it has been shown that taurine affects the metabolism of transmitters such as 5-hydroxytryptamine (5-HT) (31), dopamine (7), and GABA (15). Recognition sites for [^{3}H]taurine have been demonstrated in different brain areas of rats (12,14).

Taurine has a pharmacological profile similar in many aspects to the major inhibitory neurotransmitter in the brain, GABA. Both taurine and GABA have muscle-relaxant and anticonvulsant properties. Further, both have similar effects on the regulation of body temperature (32). The underlying mechanism and the neuroanatomic location of this interaction is not known. However, it has been reported that taurine interacts with both $GABA_A$ and $GABA_B$ receptors (13,34).

Data from autoradiographic studies show evidence that the nucleus raphe dorsalis contains GABA (1,6,33). A physiological role for GABA in this brain area is suggested by the fact that injections of GABA receptor agonists into the raphe nucleus increase motor activity and food consumption of rats in a dose-dependent manner (3,16,26,28,29). This effect is accompanied by a decrease in 5-HT concentration in the striatum and hypothalamus (26). These results are in agreement with the suggestion that the behavioral activation follows from the inhibitory effect of GABAergic stimulation on the serotonergic neurones (29).

The aim of the current study was to examine the actions of taurine and related agents on spontaneous motor activity and food consumption in rats and compare the behavioral effects of taurine with those of GABAergic agonists in the same experimental situation. Thus, we compared the effects of taurine, 3-aminopropanesulphonic acid (homotaurine; a $GABA_A$ receptor agonist), 5-aminovaleric acid [a weak $GABA_B$ antagonist; (21)], and guanidinoethanesulphonic acid (GES) [a taurine and glutamate uptake inhibitor; (10,22,25)] with the effects of muscimol and baclofen on motor activity, food consumption, and 5-HT concentration. The possible action of GES on GABAergic receptors is not known and therefore we measured the ability of GES to displace GABA from its receptors.

METHOD

Animals and Drug Injections

Male Wistar rats (weight 230–250 g) were used. Rats were anesthetized with ethyl ether and the drugs to be tested (1 μl

volume) injected into the nucleus raphe dorsalis (coordinates (26) 6.4 mm caudal, lateral 0, and 10.2 mm to ventral from the point of 1 mm to lambda) using stereotaxic apparatus (SEZH-3, Moscow, USSR, with minor modifications). Drugs were injected during 1 min and the needle was left in place for an additional minute. The antagonist was applied first. Controls were injected with the drug vehicle (distilled water). The pH of the drugs was adjusted to 7.2.

Lidocaine HCl was injected into the tissues surrounding the point of injection to inhibit pain effects on the parameters measured. Ether inhalation was discontinued during the operation so animals were awake a few minutes after drug injection (mean 2.7 min, range 1–5 min in the saline group). The behavioral measurements were started 15 min after drug injection. The activity was measured for 90 min, after which rats were killed by decapitation. Striata and hypothalamus were rapidly dissected out for biochemical analyses. The number of rats were 8–13 in each group. Some brains were saved for histological examination of the site of injection: one microliter of methylene blue was injected into the nucleus raphe dorsalis under ether anesthesia. After fixation in formalin, the brain areas containing the raphe nucleus were sectioned with a Lancer (Cambden Instuments, Loughborough, UK) Vibratome and brain slices (100 μm thick) were stained with cresyl violet. The site of drug injection in remaining animals was examined under a light microscope immediately after dissection of the hypothalamus.

Locomotor Activity

Locomotor activity was measured using an Animex (LKB-FARAD, LTD., Stockholm, Sweden) activity meter. Animals were placed individually in Plexiglas standard housing cages and the activity was measured for 15–105 min. Food consumption was measured at the same time. Pellets of standard laboratory food were weighed both before being placed on the bottom of the cages and again after the experiment.

Biochemical Determinations

5-HT concentrations in the striata and hypothalamus were measured spectrophotofluorometrically (2).

Receptor Binding

GES displacement of $GABA_A$ and $GABA_B$ binding was studied according to method described by Bowery et al. (4), with slight modifications, using crude synaptic membrane fractions from rat cortex. Frozen cortices were homogenized in 15 vol 0.32 M sucrose. The homogenate was centrifuged for 10 min at 1,000 × g. The supernatant (S1) was centrifuged for 10 min at 20,000 × g, the pellet suspended in distilled water, and centrifuged for 20 min at 8,000 × g. The washing was repeated twice with distilled water and the pellet frozen to −20°C. On the day of assay, the membranes were washed by resuspension and recentrifugation twice in 50 mM Tris-HCl buffer (pH 7.4) containing 2 mM $CaCl_2$. Binding assays were performed in this buffer, in addition containing 1 nM [^{3}H]GABA, 40 mM isoguvacine HCl to block the effect on $GABA_A$ binding sites, and 1 mM baclofen to block the $GABA_B$ binding sites. Fifty nanomoles of GABA was used to determine the nonspecific binding. After incubating 15 min at room temperature, the reaction was terminated by centrifugation and bound radioactivity counted by liquid scintillation spectrometry.

Drugs

The following drugs were used: muscimol and GABA (Sigma Chemical Co., St. Louis, MO), [^{3}H]GABA (New England Nuclear Corp., Newton, MA), baclofen HCl (Lioresal^R, kindly provided by CIBA-GEIGY, Basel, Switzerland), picrotoxin and taurine (Fluka Chemical Corp., Ronkonkoma, NY), 3-aminopropanesulphonic acid (Aldrich Chemical Co., Milwaukee, WI), 5-aminovaleric acid (Janssen Pharmaceutica, Beerse, Belgium), and guanidinoethanesulphonic acid (synthesized by Prof. J. J. Halmekoski, Dept. of Pharmacy, University of Helsinki).

Statistics

Data from the locomotor activity and food consumption experiments were analyzed using a two-way analysis of variance (ANOVA), with the factors of drug effect and activity at 30, 60, and 105 min. Individual groups were compared using the Bonferroni test (18). The 5-HT concentrations were compared using Student's t-test.

RESULTS

Locomotor Activity

Muscimol, a rather specific $GABA_A$ receptor agonist, caused a dose-dependent increase in motor activity ($F = 39.7$, $p < 0.001$, for drug effect and $F = 33.5$, $p < 0.001$, for differences in the activity at 30, 60, and 105 min using a two-way ANOVA. In individual group comparisons, a dose of 50 ng muscimol caused an effect significantly different from that of the saline group at any time of recording, but 25 ng muscimol affected only the last measurement (Table 1). The action of 50 ng muscimol was almost completely antagonized by 50 ng picrotoxin, which by itself was without effect on locomotor activity.

Taurine at doses of 0.15 and 0.30 mg did not alter motor activity. However, when taurine was administered together with 25 ng muscimol this combined treatment slightly enhanced the muscimol effects 30 and 60 min after drug injection.

Administration of 3-aminopropanesulphonic acid [a taurine homolog reported to have $GABA_A$ receptor agonist properties; (4,8,9)], 5-aminovaleric acid, and guanidinoethanesulphonic acid [a taurine and glutamate uptake inhibitor; (10,22,25)] did not change the activity when given alone.

3-Aminopropanesulphonic acid (300 ng) antagonized the action of 50 ng muscimol. 5-Aminovaleric acid (100 ng) antagonized the action of 25 ng muscimol. Six-hundred nanograms of guanidinoethanesulphonic acid also counteracted the stimulation caused by 50 ng muscimol.

One-hundred nanograms of baclofen [a $GABA_B$ receptor agonist; (9)] caused a stimulation of locomotor activity at 105 min.

3-Aminopropanesulphonic acid (300 ng) with baclofen (100 ng) produced a greater stimulation than baclofen alone. 5-Aminovaleric acid (500 ng) slightly counteracted the baclofen (100 ng)-induced stimulation but caused small, nonspecific movements such as head twitches.

Food Intake

Food intake was increased after 25 ng muscimol, 50 ng muscimol, and 25 ng muscimol given together with 0.15 mg taurine (Fig. 1). The baclofen-produced increase in food consumption was completely antagonized by 500 ng 5-aminovaleric acid.

TABLE 1

LOCOMOTORY ACTIVITY AS CUMULATIVE COUNTS (MEAN ± SD) AT 30, 60, AND 105 min AFTER DRUG INJECTION INTO THE NUCLEUS RAPHE DORSALIS (n = 8-13 IN EVERY GROUP)

	30 min	60 min	105 min
Saline	226 ± 210	599 ± 393	1,046 ± 575
Pic 50 ng	167 ± 352	520 ± 352	792 ± 378
Mus 25	406 ± 356	1,292 ± 926	2,784 ± 1,527*
Mus 50 ng	1,440 ± 592†	4,574 ± 1,481†	7,805 ± 2,590†
Mus 50 ng‡ Pic 50 ng	300 ± 200	563 ± 300	1,122 ± 401
Tau 0.15 mg	202 ± 107	361 ± 171	762 ± 312
Tau 0.30 mg	296 ± 170	791 ± 540	1,410 ± 1,321
Mus 25 ng‡ Tau 0.15 mg	936 ± 308§	2,473 ± 781¶	3,777 ± 1,353
APS 300	183 ± 102	441 ± 260	794 ± 531
Mus 50 ng‡ APS 300 ng	495 ± 431#	1,169 ± 1,056#	1,878 ± 971#
GES 600 ng	259 ± 143	438 ± 263	670 ± 516
Mus 50 ng‡ GES 600 ng	312 ± 225#	653 ± 450#	1,239 ± 997#
AVA 100 ng	189 ± 144	566 ± 346	797 ± 538
Mus 25 ng‡ AVA 100	226 ± 181	851 ± 456	1,166 ± 4,401¶
Bac 100	411 ± 388	1,326 ± 1,002	2,659 ± 868**
Bac 100 ng+ APS 300 ng	666 ± 362	1,747 ± 378†	3,507 ± 1,005†
Bac 100 ng + AVA 100 ng	493 ± 358	1,245 ± 576	2,136 ± 812
Bac 100 ng + AVA 500 ng	499 ± 216	1,136 ± 569	1,811 ± 896††

Pic, picrotoxin; Mus, muscimol; Tau, taurine; APS, 3-aminopropanesulphonic acid; GES, guanidinoethanesulphonic acid; AVA, 5-aminovaleric acid; Bac, baclofen.

*$p < 0.05$, **$p < 0.02$, and †$p < 0.001$ in comparison with the saline group.

§$p < 0.05$ and ¶$p < 0.02$ in comparison with the muscimol 25 ng group.

#$p < 0.001$ in comparison with the muscimol 50 ng group.

††$p < 0.05$ compared with the baclofen 100 ng + 3-aminopropanesulphonic acid 300 ng.

5-HT Levels

Administration of 50 ng muscimol, 0.15 mg taurine, and 600 ng guanidinoethanesulphonic acid caused a significant decrease in concentration of 5-HT in the hypothalamus (Table 2), whereas only guanidinoethanesulphonic acid decreased the level of 5-HT in the striatum.

Receptor Binding

GES inhibited [^{3}H]GABA$_A$, but not GABA$_B$ (results not shown), binding in a concentration-dependent manner at micromolar concentrations (Fig. 2).

DISCUSSION

The results of the present study indicate that injection of muscimol and baclofen, agents that stimulate GABA$_A$ and GABA$_B$ receptor subtypes, respectively, into the nucleus raphe dorsalis results in a stimulation of locomotory activity and food consumption. Moreover, muscimol decreased 5-HT concentration in the striatum and hypothalamus. These data are consistent with previously reported results and support the suggestion that serotonergic neurones in this area are under inhibitory GABAergic control. The locomotory stimulation is suggested to follow from suppression of serotonergic activity due to activation of GABAergic neurones (23,24,26,28,29). Taurine when injected alone did not affect locomotor activity or food intake. However, when administered together with a small dose of muscimol it enhanced the muscimol effects on both locomotion and eating. The taurine homolog, 3-aminopropanesulphonic acid, and the taurine uptake blocker, guanidinoethanesulphonic acid, had no effect on the behavior examined, but both drugs inhibited the effects of muscimol. The increase in food intake, but not the locomotory stimulation, induced by baclofen was counteracted by the putative, weak GABA$_B$ receptor blocker, 5-aminovaleric acid.

When taurine was administered in doses of 0.15 and 0.30 mg, high doses compared with those of muscimol, it did not influence the spontaneous motor activity of rats. However, taurine in a dose of 0.15 mg enhanced the effect of 25 ng

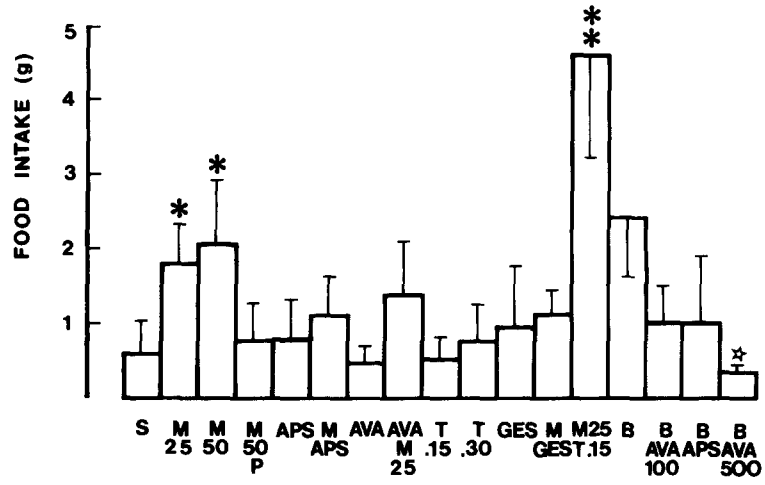

FIG. 1. Food consumption (mean ± SD) 15–105 min after drug injection. S, saline; M, muscimol 25 and 50 ng; P, picrotoxin 50 ng; APS, 3-aminopropanesulphonic acid 300 ng; AVA, 5-aminovaleric acid 100 and 500 ng; T, taurine 0.15 and 0.30 mg; GES, guanidinoethanesulphonic acid 600 ng; B, baclofen 100 ng. Significant differences were $*p < 0.05$ and $**p < 0.02$ compared with the saline group and $\star p < 0.05$ compared with the baclofen group.

muscimol. This dose of muscimol by itself was without effect on locomotor activity 30 and 60 min after drug injection. It should be noted that the taurine and muscimol interaction was of short duration and was significant only at 30 and 60 min after drug administration. This observation may suggest that taurine affects central GABAergic transmission through an indirect action. Moreover, because the interaction of taurine and muscimol was synergistic it is conceivable that they activated different populations of receptor sites. Because the effect of taurine in this situation was probably not a result of a direct GABA receptor stimulation, it may have been due to an increased GABA release. A taurine-produced increase of GABA release has been shown to occur already at lower concentrations than are needed for taurine to activate GABA receptors (13,34).

The stimulatory effects of muscimol on motor activity were antagonized by picrotoxin, which preferentially acts by blocking Cl^- ionophore coupled to central $GABA_A$ receptors. Muscimol, the most selective $GABA_A$ receptor agonist (4,9), was also the most potent agent to induce behavioral stimulation. In this context, it should be noted that muscimol is more potent than GABA itself at stimulating locomotion (unpublished results), a finding in accordance with data showing muscimol to be a more potent activator of $GABA_A$ receptors (4). Using an experimental situation similar to that used in the present study, it has been reported that benzodiazepines activate $GABA_B$ receptors; it may be suggested that the behavioral stimulation observed in the present study is probably a result of activation of $GABA_A$ receptors in the nucleus raphe dorsalis and their inhibitory effect on serotonergic neurones (23,24). On the other hand, baclofen, an agonist at the $GABA_B$ receptors (4), also stimulated locomotion and food

TABLE 2

5-HYDROXYTRYPTAMINE (5-HT) LEVELS IN THE STRIATUM AND HYPOTHALAMUS AFTER DRUG INJECTION INTO THE NUCLEUS RAPHE DORSALIS, APS, 3-AMINOPROPANESULPHONIC ACID; GES, GUANIDINOETHANESULPHONIC ACID

Drugs	5-HT Concentration (mean ± SD; μg/g)	
	Striatum	Hypothalamus
Saline	0.60 ± 0.15	0.81 ± 0.11
Muscimol 25 ng	0.44 ± 0.14	0.72 ± 0.07
Muscimol 50 ng	0.44 ± 0.12	0.72 ± 0.08*
3-Aminopropanesulphonic acid	0.66 ± 0.16	0.82 ± 0.08
Taurine 0.15 mg		0.71 ± 0.07*
Taurine 0.30 mg	0.45 ± 0.11	0.77 ± 0.09
Guanidinoethanesulphonic acid	0.37 ± 0.04†	0.68 ± 0.06*

$*p < 0.05$ and $\dagger p < 0.02$ compared with the saline group.

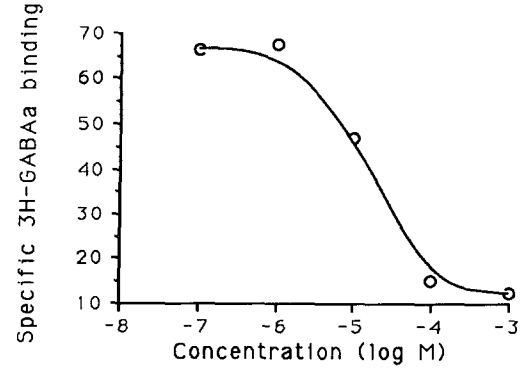

FIG. 2. Inhibition of [^{3}H]GABA binding by guanidinoethanesulphonic acid. Membranes from rat cerebral cortex were incubated in the presence of 1 nM [^{3}H]GABA and different concentrations of guanidinoethanesulphonic acid. Points are means from three different experiments, each done in triplicate.

intake, as shown by the present study and others (26). This effect is, at least in part, mediated via activation of $GABA_A$ receptors because it has been shown that bicuculline, the most selective $GABA_A$ antagonist, at subconvulsive doses antagonizes the effects of 50 ng baclofen (26). Alternatively, in vitro addition of baclofen has been shown to cause GABA release (27), an effect that also might explain the observation that bicuculline in certain situations is able to block the behavioral effects of baclofen.

3-Aminopropanesulphonic acid had no effect by itself on locomotion and food consumption and also failed to decrease 5-HT concentrations. At a dose of 300 ng, it inhibited the effects of 25 ng muscimol completely (16), partly inhibited those of 50 ng muscimol, but had no effect on those of baclofen. 3-Aminopropanesulphonic acid is not a pure agonist at the GABAergic system. It has been suggested that it has antagonistic properties at the $GABA_B$ receptors (8). This partial antagonism might be the reason that it inhibited its own and muscimol effects. The difference in the interaction with muscimol and baclofen probably follows from the relative affinities of 3-aminopropanesulphonic acid to the GABAergic receptors. While 3-aminopropanesulphonic acid has a high affinity to $GABA_A$ receptors, it is a weak inhibitor of [^{3}H]baclofen binding.

5-Aminovaleric acid attenuated the baclofen-induced food intake but not the baclofen-induced locomotory stimulation. It has been shown that 5-aminovaleric acid may act as an antagonist at the $GABA_B$ receptors (4,21). Baclofen effects are also associated with inhibition of monoamine release (4,9). Recently, it has been confirmed by using phaclofen, another $GABA_B$ antagonist, that central $GABA_B$ receptors participate in the regulation of food intake (5).

GES failed to stimulate locomotion and food consumption but clearly depressed 5-HT concentration in the brain areas investigated. GES has been shown to inhibit taurine and glutamate uptake and decrease taurine concentrations in various tissues (10,17,22). It has some actions that are antagonistic to those of taurine, as it produces convulsions whereas taurine suppresses them (20). In contrast to taurine, it was found that in coadministration with muscimol GES antagonized muscimol effects. Radiologand binding studies in vitro showed that GES was able to displace $GABA_A$ binding as effectively as bicuculline, which could explain the antagonism of muscimol effects in this experimental situation.

The GABA antagonist picrotoxin and other agents that inhibited the effects produced by muscimol did not affect by themselves the basal level of spontaneous motor activity. These results agree well with other studies (23,24,30) that show that GABA antagonists do not change the firing rate of raphe cells and 5-HT synthesis in the projecting areas. However, when applied locally into the ventral tegmental area picrotoxin stimulates locomotory activity (19), whereas eating is stimulated following local injection of bicuculline into the hypothalamic "satiety center" (11).

In conclusion, the results suggest that taurine may have a slight GABAmimetic activity but that this effect of taurine is considerably weaker as compared to the effects produced by drugs that directly stimulate central GABA receptors. However, because taurine clearly altered the effects of GABA receptor agonists it may be concluded that it acts as a neuromodulator of central GABAergic activity.

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