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Hyperthermia in experimental models of the serotonin syndrome: influence of vigabatrin

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Serotonin syndrome is likely to be observed as a result of an overdose of serotoninergic drugs or interactions with the combined administration of two or more drugs that increase the intrasynaptic concentration of the serotonin (5-hydroxytryptamine). The aim of this study was to establish the effect of vigabatrin, a GABAergic drug, on the hyperthermic reaction in experimental serotonin syndrome in rats. We used experimental models of serotonin syndrome induced by the combined administration on male Wistar rats of: 1) the serotonin precursor 5-hydroxy-L-tryptophan (100 mg/kg b.w., *i.p.*) and the selective MAO-A inhibitor clorgyline (2 mg/kg b.w., *i.p.*); 2) the selective neuronal uptake inhibitor of serotonin fluoxetine (10 mg/kg b.w., *i.p.*) and the selective MAO-A inhibitor clorgyline (2 mg/kg b.w., *i.p.*). The experiments were conducted at ambient temperature of 22 ± 1°C. The body temperature of the animals was measured with thermistor probes (TX-8), and monitored on multichannel recorder Iso-Thermex 16. The thermistor probes were lubricated with vaseline and inserted rectally to a depth of 6 cm. Pretreatment with vigabatrin (300 mg/kg b.w., *i.p.*) decreased significantly the hyperthermia observed in both experimental models of the serotonin syndrome in male Wistar rats. We assume that in addition to direct GABAergic mechanisms, interactions between neurotransmitters or mediator systems are involved in the response to hyperthermia in serotonin syndrome by GABAergic substances.

Keywords: serotonin syndrome; experimental models; hyperthermia; vigabatrin; rats.

INTRODUCTION

Serotonin syndrome may be observed as a result of an overdose of serotonergic drugs or due to the combined administration of two or more drugs that increase the intrasynaptic concentration of serotonin (5-hydroxytryptamine, 5-HT).

Co-administration of selective serotonin reuptake inhibitors (SSRIs) with another serotonin-ergic drug is a more common cause of induction of severe serotonin syndrome [1]. Clinical cases of serotonin syndrome have been reported in the combination of selective serotonin reuptake inhibitors with MAO inhibitors [2-5], opioids[6-8], linezolid [9] and other drugs.

The pharmacological mechanisms that can cause serotonin syndrome are:

- increase in serotonin synthesis (e.g. 5-hydroxytryptophan);
- increase in serotonin release (e.g. amphetamines);
- inhibition of serotonin reuptake (e.g. SSRI, SNRI, TCAs);
- inhibition of serotonin metabolism (e.g. MAOIs, linezolid);
- activation of postsynaptic serotonergic receptors (e.g. buspirone, triptans).

In most common form, serotonin syndrome is characterized by a triad of symptoms – mental status changes (confusion, agitation), neuromuscular abnormalities (clonus, tremor) and autonomic hyperactivity (tachycardia, hyperthermia) [10]. Stimulation of the $5HT_{1A}$ receptors triggers the development of major signs of serotonin syndrome [11]. Increased body temperature is associated with the activation of $5HT_{2A}$-ergic receptors [12]. Hyperthermia is a sign of severe serotonin syndrome and is usually associated with significant mortality [13].

Medication-induced hyperthermia is resistant to the action of classical antipyretics, so their use is not recommended [14]. Administration of salicylates may even cause a worsening of the hyperthermic reaction [15].

Experimental studies demonstrated that administration of GABA or GABA-ergic drugs such as diazepam, sodium valproate, and vigabatrin caused a decrease in body temperature [16-19].

Vigabatrin (gamma-vinyl GABA; γ-vinyl-GABA) is a structural analog of gamma-aminobutyric acid. S-enantiomer is responsible for its pharmacological activity [20]. Vigabatrin enhances the central inhibitory activity of GABA *via* competitive irreversible inhibition of GABA transaminase, the mitochondrial enzyme responsible for catabolism of GABA [21,22].

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Additional mechanisms involved inhibition of glial uptake of GABA [23] and stimulation of GABA release [24]. Vigabatrin is used as antiepileptic drug for treatment of infantile spasms (West syndrome) and refractory complex partial seizures [25,26].

It is essential to mention that the mortality associated with serotonin syndrome is primarily related to the presence of hyperthermia and its inadequate treatment. In this respect, the aim of this study was to investigate the effects of vigabatrin on the hyperthermic response in two different experimental models of rat serotonin syndrome.

EXPERIMENTAL

Experimental animals. The experiments were performed on male Wistar rats (weight range 200-220 g), divided into groups of 6 rats each. Rats received standard granulated rodent food (Top Mix®, Sliven). During the studies, the animals were housed under standardized conditions: free access to water and food, room temperature 22 ± 1 °C, air humidity 55 ± 10%, and light cycle 12 hours light (08:00-20:00)/12 hours dark (20:00-08:00). The experiments were carried out at the same time of the 24-hour cycle (09:00-15:00 h). The drugs were injected into the inguinal area of the experimental animals intraperitoneally with a 23 G needle.

The International Guiding Principles for Animal Research, as well as the ethical principles in the planning and conduct of experiments according to Ethics Committee for Research at the Medical University - Sofia were strictly adhered to.

Experimental substances. The substances used in the modeling of experimental serotonin syndrome were 5-hydroxy L-tryptophan (Sigma-Aldrich), fluoxetine (Sigma-Aldrich) and clorgyline (Sigma-Aldrich). Vigabatrin (Sigma-Aldrich) was studied. Vigabatrin was intraperitoneally (*i.p.*) administered in a dose of 300 mg/kg body weight before the introduction of serotonin-ergic substances. In the control groups, animals were injected *i.p.* with 0.9% solution of sodium chloride in a volume of 0.2 ml/100 g.

Animal models of serotonin syndrome. In the study we have used experimental models of serotonin syndrome induced by the combined *i.p.* administration on male Wistar rats of: 1) the serotonin precursor 5-hydroxy-L-tryptophan (100 mg/kg b.w.) and the selective MAO-A inhibitor clorgyline (2 mg/kg b.w.) [27]; 2) the selective serotonin reuptake inhibitor fluoxetine (10 mg/kg b.w.) and the selective MAO-A inhibitor clorgyline (2 mg/kg b.w.) [28].

Body temperature monitoring. The experiments were carried out at ambient room temperature of 22 ± 1°C. The body temperature of the animals was recorded using rectal thermistor samples (TX-8) connected to a computer-programmed multichannel device Iso-Thermex 16 (Columbus Instruments, USA). After lubrication with mineral jelly, thermistors were administered rectally at a depth of 6 cm. The body temperature of the rats was recorded before the administration of the serotonin-ergic substances, and then checked at 30-min intervals after their injection.

Data analysis and statistics. The results obtained are presented as mean±SEM, using One way ANOVA (InStat, USA) and graphically using Microsoft Excel software, 2003.

RESULTS AND DISCUSSION

Effects of vigabatrin on the hyperthermic reaction in a model of serotonin syndrome induced by the combined administration of 5-hydroxy-L-tryptophan and clorgyline

Vigabatrin administered *i.p.* in a dose of 300 mg/kg body weight significantly reduced the hyperthermic response, observed at 60 min, in rats with a model of serotonin syndrome induced by 5-hydroxy-L-tryptophan and clorgyline, compared to the group with a model of serotonin syndrome (5-hydroxy-L-tryptophan + clorgyline). In this model, all of the animals have died between 60 and 90 min of recordings (Fig. 1).

Effects of vigabatrin on the hyperthermic reaction in a model of serotonin syndrome induced by the combined administration of fluoxetine and clorgyline

In rats with a model of serotonin syndrome induced by fluoxetine and clorgyline, vigabatrin *i.p.* administered in a dose of 300 mg/kg b.w. caused a significant decrease in hyperthermic response between 150 and 300 min of recordings (Fig. 2).

The results of the present study indicate a decrease in the hyperthermic response observed in two different rat models of serotonin syndrome by pretreatment of vigabatrin.

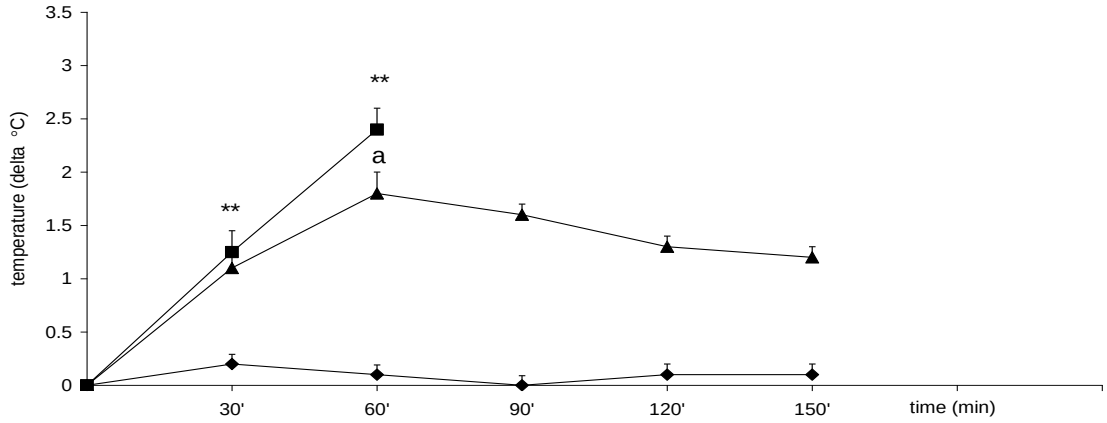

Fig. 1. Effect of vigabatrin on a serotonin syndrome model induced by 5-hydroxy L-tryptophan and clorgyline. Average change in body temperature in rats (temperature Δ°C) after *i.p.* administration of ■ 0.9 % solution of NaCl + 5- hydroxy L-tryptophan 100 mg/kg + clorgyline 2 mg/kg; *i.p.* administration of ▲ vigabatrin 300 mg/kg + 5- hydroxy L-tryptophan 100 mg/kg + clorgyline 2 mg/kg and *i.p* .administration of ◆ 0.9 % solution of NaCl. Statistical significance: compared to NaCl: **P< 0.01; compared to 0.9 % solution of NaCl + 5- hydroxy L-tryptophan 100 mg/kg + clorgyline 2 mg/kg: [a] P< 0.05.

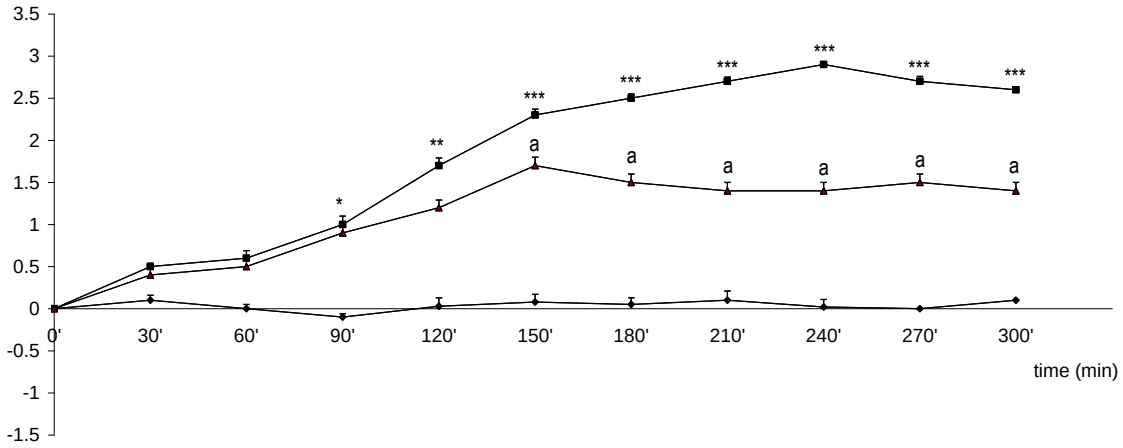

Fig. 2. Effect of vigabatrin on the hyperthermic response in a model of serotonin syndrome induced by fluoxetine and clorgyline. Average change in body temperature in rats (temperature Δ °C) after *i.p.* administration of ■ 0.9 % solution of NaCl + fluoxetine 10 mg/kg + clorgyline 2 mg/kg; *i.p.* administration of ▲ vigabatrin 300 mg/kg i.p. + fluoxetine 10 mg/kg i.p. + clorgyline 2 mg/kg i.p. and *i.p.* administration of ◆ 0.9 % NaCl. Statistical significance: compared to NaCl: *P < 0.05, **P< 0.01, ***P< 0.001; compared to 0.9 % solution of NaCl + fluoxetine 10 mg/kg + clorgyline 2 mg/kg: [a] P< 0.05.

GABA is an essential central inhibitory neurotransmitter that participates in thermoregulation processes. Potentiation of GABA central inhibitory action is achieved by several different mechanisms, including allosteric modulation of GABA receptors (benzodiazepines, barbiturates, Z-drugs), direct $GABA_A$ or $GABA_B$ receptor agonist activity (muscimol, baclofen), increased synthesis of GABA (gabapentin, pregabilin, sodium valproate), suppression of the enzymatic degradation of GABA (vigabatrin, sodium valproate), and inhibition of the neuronal and glial uptake of GABA (tiagabine). Central or systemic administration of diazepam, sodium valproate, and vigabatrin in rats induces dose-dependent decrease in body temperature [17-19, 29]. GABA-induced hypothermia is thought to be mediated by activation of $GABA_A$- and/or activation of $GABA_B$ receptors [30,31].

We assume that in addition to direct GABA-ergic mechanisms, interactions between neurotransmitters or mediator systems are involved in influencing the hyperthermic response of

serotonin syndrome by GABA-ergic substances. Presynaptically localized $GABA_B$ receptors influence the release of noradrenaline, dopamine and 5-hydroxytryptamine [32]. Expression of predominantly $GABA_B$ receptors has been found in most serotonin-ergic and catecholamine-ergic neurons in brainstem nuclei which are involved in the regulation of autonomic functions [33]. The interactions between the GABA-ergic and the serotonin-ergic systems are accomplished by presynaptic heteroreceptor $GABA_B$-inhibition of 5-HT release or by a G-protein coupled interaction between 5-HT_{1A} and $GABA_B$-ergic receptors [34].

Our studies found that vigabatrin effectively attenuated the hyperthermic response in experimental serotonin syndrome in rats. The effects of the investigated GABA-mimetic drug vigabatrin on hyperthermia, associated with serotonin syndrome, support the hypothesis for the interaction between the GABA-ergic and serotonin-ergic systems in thermoregulatory processes.

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