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EFFECT OF OLANZAPINE ON HYPERTHERMIA IN SEROTONIN SYNDROME MODEL

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ABSTRACT: The serotonin syndrome is a life-threatening adverse drug reaction caused by a significant increase in the concentration of 5-hydroxytryptamine (serotonin) in the central nervous system. The aim of this study was to establish the effects of olanzapine, an antipsychotic drug, on the hyperthermic response in rat experimental serotonin syndrome. In this study, we used an animal model of the serotonin syndrome induced by co-administration of fluoxetine and tranylcypromine. The body temperature of the animals was measured with thermistor probes (TX-8) inserted rectally and monitored on multichannel recorder. Pre-treatment with olanzapine inhibits hyperthermic reaction in an experimental model of the serotonin syndrome and converts a hyperthermic response to serotonergic combination (fluoxetine and tranylcypromine) into a hypothermic response. Our results suggest prevention of the hyperthermia in a serotonin syndrome model with the use of olanzapine and support the hypothesis that the hyperthermic reaction in serotonin syndrome is mediated by activation of central 5-HT2 receptors.

INTRODUCTION: Serotonin syndrome is a life-threatening adverse drug reaction associated with a significant increase of the concentration of 5-hydroxytryptamine (serotonin) in the central nervous system (CNS). This condition can occur with an administration of a single serotonergic medication or with the combined administration of drugs that increase the synaptic serotonin concentration. The following drugs are associated with the development of serotonin syndrome: antidepressants (*e.g.*, SSRIs including fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram; tricyclic antidepressants; serotonin/ norepinephrine reuptake inhibitors, MAO inhibitors), opioid analgesics (*e.g.*, pethidine, tramadol, methadone, fentanyl), antimigraine drugs from the class of triptans (*e.g.*, sumatriptan, zolmitriptan, naratriptan, ergot alkaloids), amphetamines, other medicines and nutritional supplements (*e.g.*, linezolid, buspirone, sibutramine, dextromethorphan, St. John's wort extract, L-tryptophan, 5-hydroxytryptophan).

Potential mechanisms of serotonin syndrome include increased serotonin synthesis (*e.g.*, from 5-hydroxytryptophan), stimulation of serotonin release (*e.g.*, amphetamines), inhibition of serotonin reuptake (*e.g.*, selective serotonin reuptake inhibitors - SSRIs, venlafaxine, tricyclic anti-depressants, opioid analgesics), inhibition of serotonin metabolism (*e.g.*, phenelzine, tranylcypromine, moclobemide, linezolid), and direct

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activation of postsynaptic 5-HT receptors (*e.g.,* buspirone and triptans). Another mechanism (a pharmacokinetic mechanism) for the development of serotonin syndrome is a concomitant administration of SSRIs and cytochrome P450 2D6 or 3A4 inhibitors, *e.g.,* when sertraline and erythromycin are combined [1].

The serotonin syndrome is characterized by mental status changes (*e.g.,* agitation, hypomania, confusion, and anxiety), neuromuscular effects (hyperreflexia, tremor, clonus, muscle rigidity) and vegetative dysfunction (diaphoresis, hyperthermia, tachycardia, mydriasis) [2]. It is believed that serotonin syndrome is caused by the over-stimulation of postsynaptic serotoninergic receptors, mainly of the 5-HT1A receptors (hyperactivity, hyperreflexia, anxiety) and the 5-HT2A receptors (hyperthermia, incoordination, neuromuscular excitement) [3]. In the thermo-regulatory processes, a number of neurotransmitters are included, such as serotonin, noradrenaline, dopamine, acetylcholine, gamma-aminobutyric acid (GABA). The serotonergic neurotransmission plays an important role in the control of mammalian body temperature. Activation of 5-HT1A or 5-HT7 receptors induces a decrease in body temperature in rats and mice [4]. The 5-HT2A receptor agonists induce hyperthermia in rats [5]. It was found that hyperthermia in an animal model of serotonin syndrome induced by clorgyline and 5-hydroxy-L-tryptophan was suppressed by the pre-administration of ritanserin or pipamperone, serotonin 5-HT2A antagonists [6]. The aim of the present study is to investigate the effects of 5-HT2 receptor antagonist olanzapine on the hyperthermic response in an experimental model of serotonin syndrome induced by the combined administration of fluoxetine and tranylcypromine.

MATERIALS AND METHODS:

Animals: The experiments were carried out on male Wistar rats (weight range 200-220 g), divided into groups of 6 rats each. Rats were maintained on a standard 12 h light/dark cycle and were provided free access to food and water. Animal procedures were conducted in accordance with the International Guiding Principles for Biomedical Research involving Animals. For this study, we obtained permission from the Ethics Committee on Animals of the Bulgarian Food Safety Agency and Welfare Directorate of the Bulgarian Food Safety Agency (permit no 189/2017).

Drugs: The substances used in modeling experimental serotonin syndrome are fluoxetine (Sigma-Aldrich) and tranylcypromine (Sigma-Aldrich). In the control group, the animals were injected with 0.9% sodium chloride at a dose of 0.5 ml/kg i.p. In our experiments was administered antagonist of the 5-HT2 receptors olanzapine (Sigma-Aldrich). The used doses in this study (5 mg/kg and 10 mg/kg) were defined by literature data and by our own previously conducted experiments. In experimental rat groups, 5-HT2 receptor antagonist was administered 15 min before serotonergic substances.

Serotonin Syndrome Model: In the present study was used animal model of serotonin syndrome achieved by co-administration of fluoxetine (10 mg/kg, i.p.), and tranylcypromine (3.5 mg/kg, i.p.), previously described by Shioda *et al.,* [7] both serotonergic drugs increased concentration of serotonin *via* inhibition respectively of the 5-hydroxytryptamine (5-HT) reuptake or of mono-amine oxidase (MAO) activity.

Body Temperature Experiments: All experiments started at 10 a.m. and were conducted at an ambient temperature of 24 ± 1 ºC. Body temperature was measured with thermistor probes (TX8) and monitored on multi-channel recorder Iso-Thermex 16 (Columbus Instruments, USA). The thermistor probes were lubricated with vaseline and inserted rectally to a depth of 6 cm. The initial temperature of the animals was determined and then checked at 30 min intervals. The 5-HT2 receptor antagonist was injected 15 min before serotonergic substances.

Data Analysis and Statistics: The results were calculated as Δ values (mean Δ value ± SEM). Transformed data were analyzed with two-way analysis of variance (ANOVA). For statistical significance, a Student's t-test was used. In all cases, values of $P < 0.05$ were considered to be statistically significant.

RESULTS AND DISCUSSION: 1. Change in rat body temperature in a model of serotonin syndrome induced by fluoxetine and tranylcypromine.

The administration of fluoxetine (10 mg/kg, i.p.) and tranylcypromine (3.5 mg/kg, i.p.) induces hyperthermia. Specific changes in the behavior of the animals such as tremors and head shaking are observed 90 min after the administration of the serotonergic substances. The rectal temperature began to increase about 90 min after the injection of serotonergic substances, with a maximum effect at 240 min see **Fig. 1**.

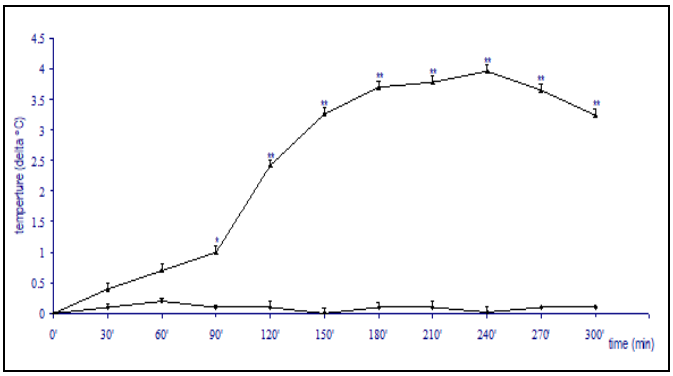

FIG. 1: CHANGE IN BODY TEMPERATURE IN THE SEROTONIN SYNDROME MODEL mean change in rat body temperature (temperature delta °C) after administration of ▲ Fluoxetine 10 mg/kg i.p. + Tranylcypromine 3.5 mg/kg i.p. and ♦ 0.9% NaCl (control). Significant differences: in comparison to control * P <0.05,** P <0.01

2. Effect of olanzapine (10 mg) on hyperthermic response in an experimental model of serotonin syndrome Pre-administration of olanzapine at a dose of 10 mg/kg i.p. on rats with a model of serotonin syndrome inhibits the development of hyperthermia caused by administration of fluoxetine and tranylcypromine see **Fig. 2**.

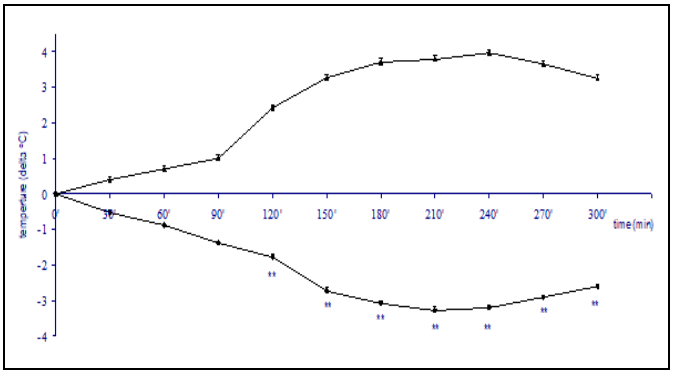

FIG. 2. EFFECT OF OLANZAPINE (10 mg) ON THE HYPERTHERMIC RESPONSE IN A SEROTONIN SYNDROME MODEL. Mean temperature change in rats (temperature delta °C) after administration of ▲ Fluoxetine 10 mg/kg i.p. + Tranylcypromine 3.5 mg/kg i.p. and ● olanzapine 10 mg/kg i.p. + Fluoxetine 10 mg/kg i.p. + Tranylcypromine 3.5 mg/kg i.p. Significant differences: in comparison to Fluoxetine 10 mg/kg i.p. + Tranylcypromine 3.5 mg /kg i.p. ** P <0.01

3. Effect of olanzapine (5 mg) on the hyperthermic response in an experimental model of serotonin syndrome Pre-injection of olanzapine at a dose of 5 mg/kg i.p. on rats with a model of serotonin syndrome inhibits the hyperthermic response induced by fluoxetine and tranylcypromine see **Fig. 3**.

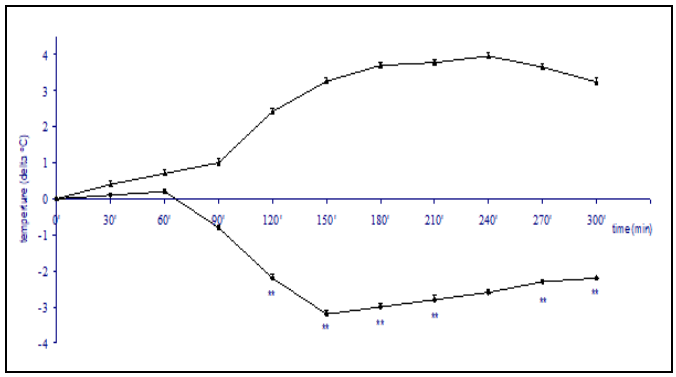

FIG. 3: EFFECT OF OLANZAPINE (5 mg) ON THE HYPERTHERMIC RESPONSE IN A SEROTONIN SYNDROME MODEL. mean temperature change in rats (temperature delta °C) after administration of ▲ Fluoxetine 10 mg/kg i.p. + Tranylcypromine 3.5 mg/kg i.p. and ● olanzapine 5 mg/kg i.p. + Fluoxetine 10 mg/kg i.p. + Tranylcypromine 3.5 mg/kg i.p. Significant differences: in comparison to Fluoxetine 10 mg/kg i.p. + Tranylcypromine 3.5 mg/kg i.p . ** P <0.01.

The atypical antipsychotic drug olanzapine is a thienobenzodiazepine derivative that blocks 5-HT2 receptors to a greater extent than it does dopamine D2 receptors. It also blocks histamine H1, muscarinic M1-M5, and adrenergic α1 and α2 receptors 8. It is effective in treating schizophrenia and acute manic episodes in patients with bipolar disorders. The results of this study indicate that pretreatment with olanzapine at a dose of 5 and 10 mg inhibited the hyperthermic response in an animal serotonin syndrome model. It is assumed that the hyperthermic reaction observed with serotonin syndrome is associated with activation of 5-HT2A receptors [5, 6]. Most atypical anti-pshychotics exert their action primarily through inhibition of serotonin 5-HT2 receptors.

Temperature dysregulation (hyperthermia in neuroleptic malignant syndrome or hypothermia) is a documented side reaction of antipsychotic drugs. Data from various clinical cases summarized by van Marum *et al.*, [9] and Zonnenberg [10, 11] show the development of hypothermia with the use of typical and atypical antipshychotics, especially neuro-leptics with marked 5-HT2-antagonistic activity.

The risk of this side effect increases in the first days after the initiation of therapy or by increasing the neuroleptic dose [9, 12]. Rasnayake *et al.,* [13] describe a case of hypothermia associated with the administration of olanzapine at therapeutic doses in a patient with paranoid schizophrenia. Body *et al.,* [14] reported sublingual use of olanzapine in the treatment of serotonin syndrome.

Atypical neuroleptics clozapine, olanzapine, and risperidone produced dose-dependent hypothermia in rats [15]. The blockade of 5-HT2 receptors from ketanserin or pirenperone induces a decrease in body temperature while blocking of 5-HT1A receptors from pindolol causes an increase in body temperature [16]. Both clinical and experimental studies supported involving of 5-HT2 receptors in the hypothermic action of olanzapine.

CONCLUSION: In summary, pretreatment of rats with olanzapine prevents hyperthermia in a serotonin syndrome model induced by the administration of fluoxetine and tranylcypromine. The present findings assumed that in the mechanism of the hyperthermic reaction observed in serotonin syndrome activation of the central 5-HT2 receptors are involved. In addition, olanzapine converted hyperthermic reaction induced by co-administration of serotonergic drugs (fluoxetine and tranylcypromine) into a hypothermic response, which supports the clinical data on the hypothermic effect of olanzapine.

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CONFLICTS OF INTEREST: The authors declare that they have no conflict of interest.

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