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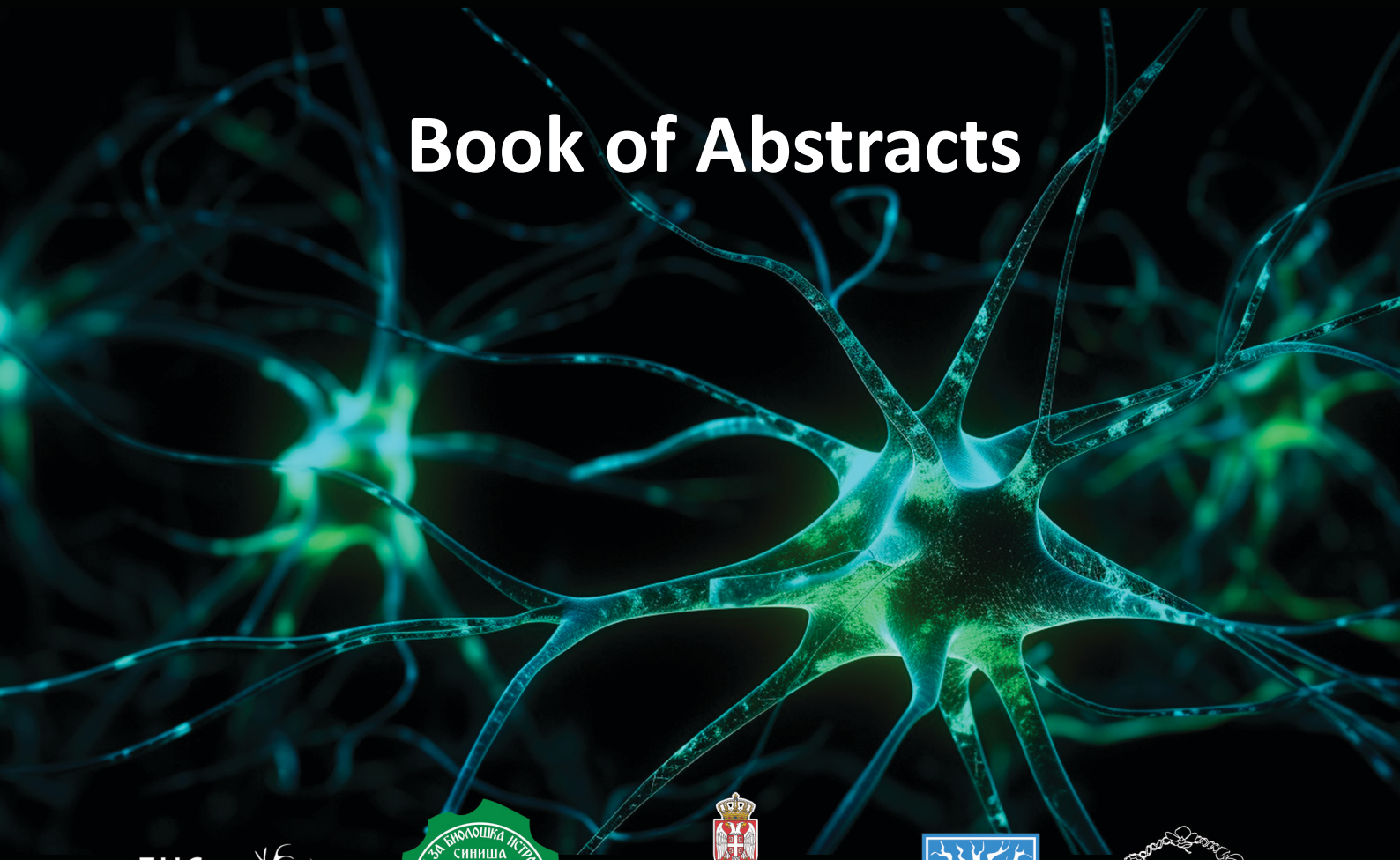

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Long-term alprazolam treatment may cause tolerance development by modulating components of glutamatergic neurotransmission in the hippocampus of male Wistar rats

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The benzodiazepine alprazolam (ALP) is commonly prescribed to treat anxiety, panic, and sleep disorders. However, ALP is often abused for prolonged periods of time, leading to severe side effects such as tolerance, dependence, and withdrawal syndrome. Previous literature data suggest that neuroadaptive changes at synaptic receptors, such as gammaaminobutyric acid receptor type A (GABAAR) and glutamatergic receptors, may be responsible for the occurrence and development of the aforementioned side effects. Therefore, the present study investigated the potential effects of prolonged ALP treatment (*2 mg/kg, ip.*) on the α1-subunit containing GABAAR and components of glutamatergic neurotransmission in the hippocampus of adult male Wistar rats. The study revealed behavioral changes consistent with a possible onset of tolerance and associated changes in the GABAergic and glutamatergic systems. The primary target of ALP, the α1-subunit containing GABAAR, was decreased indicating its potential downregulation by prolonged agonist (ALP) action. Considering studied glutamatergic components, an increase in NMDAR subunits, a decrease in vGlut1, and differential modulation of excitatory amino acid transporters 1 and 2 (EAAT1/2, *in vivo* and *in vitro*) were observed. These changes may all together indicate a compensatory mechanism due to the sustained suppression of glutamatergic neurons by enhanced inhibitory impulses from GABAergic neurons. The data presented provide valuable and, to our knowledge, the first information on components of glutamatergic neurotransmission after prolonged ALP treatment and their potential impact on the development of side effects. However, further research is needed to examine the observed changes in detail.

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