Summary of the dissertation for the PhD degree in pharmaceutical sciences MPharm Łukasz Fijałkowski: *Study of selected 4-aminobutanoic acid analogues complexes with human GABA transporter isoform 1 (hGAT1) in potential mechanism of analgesic effect*

GABA is one of the main inhibitory neurotransmitters in the mammalian brain and spinal cord. The abundant appearance of GABA indicates its importance in the mediation or modulation of the central nervous system (CNS) functions. Upon depolarization of presynaptic neuron membrane the high concentration of GABA is released from the nerve terminals into the synaptic cleft. When released from the presynaptic terminals GABA is subsequently transported out of the synaptic cleft and its vicinity by the plasma membrane GABA transporters (GAT). For many years, anticonvulsant drugs have been used as potential analgesics in various neuropathic pain states. This type of pain is a chronic disease that stems from a primary lesion or dysfunction of the central or peripheral nervous system. It is estimated that approximately 40% of neuropathic patients are resistant to the currently available analgesics. This requires the exploration of novel drug targets to treat neuropathic pain of various origins. Several studies have examined the analgesic activity of GABA uptake inhibitors but there is still insufficient data for the design of new compounds having pain-relieving activity and little is known about their efficacy in neuropathic pain conditions.

To confirm the role of GAT in neuropathic pain the chemical interactions of selected compounds with a model of human GABA transporter 1 (hGAT1) was described using the computational *in silico* methods. To establish the role of hGAT1 in chronic pain, selective hGAT1 inhibitors such as tiagabine and nipecotic acid, were studied by means of *in vivo* experiments with several mouse models of neuropathic pain. It was found that all the investigated drugs could interact with active site of hGAT1. The binding modes of all compounds with hGAT1 were examined in detail.

The data of presented study strongly support the assumption that the antiepileptic and analgesic actions of the studied drugs can be at least in part related to the strength of their chemical interactions with hGAT1. The *in vivo* experiments confirmed the involvement of hGAT1 in regulation of the mechanical nociceptive threshold in neuropathic pain.

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