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## МАТЕРИАЛЫ КОНФЕРЕНЦИИ И ШКОЛЫ

# LOW-MOLECULAR-WEIGHT ANTAGONISTS OF THE THYROID STIMULATING HORMONE RECEPTOR AND THEIR EFFECT ON THE SYNTHESIS OF THYROID HORMONES IN THE IN VITRO AND IN VIVO

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There are currently no effective drugs for inhibiting thyroid stimulating hormone (TSH) receptors in Graves disease and TSH-dependent tumors. To reduce the level of TSH, thyroid hormones are used, which, according to the negative feedback mechanism, reduce the production of TSH, but they cause dysfunctions of the cardiovascular, endocrine and bone systems. A promising approach for inhibiting TSH receptors is the development of low-molecular-weight antagonists of an allosteric site localized in their transmembrane channel, the most promising of which are thieno[2,3-*d*]pyrimidines. We synthesized compound TP48 (5-amino-N-(tert-butyl)-4-(4-iodophenyl)-2-(methylthio)thieno[2,3-*d*]pyrimidine-6-carboxamide) and its analog TP52, and studied their effect on TSH-dependent synthesis of thyroid hormones in the *in vitro* and *in vivo*. Using FRTL-5 thyrocyte culture, it was shown that TP48 and TP52 suppress TSH-stimulated expression of the *Nis* gene encoding the $Na^+/I^-$-cotransporter and the *Dio2* encoding D2-deiodinase. At the same time, a decrease in the production of thyroid hormones and a weakening of $Ser^{133}$ phosphorylation of the factor CREB involved in the synthesis of thyroxine were also found. The TP52 was more active than TP48. Treatment of male Wistar rats with thyroliberin increased the levels of all forms of thyroid hormones, enhanced the expression of *Tg*, *TPO* and *Dio2* genes encoding thyroglobulin, thyroperoxidase and D2-deiodinase, and reduced the expression of the *Tshr* encoding TSH receptor in the thyroid gland of rats. Pretreatment with TP48 and TP52 reduced the stimulation of thyroxin production and the expression of the *Tg* and *Dio2* genes. The TP48 and TP52 had a little effect on the basal levels of thyroid hormones and the expression of genes encoding thyroidogenic proteins in the thyroid gland, indicating the intrinsic activity of neutral antagonists. Thus, new thieno [2,3-*d*]pyrimidines with the activity of neutral antagonists of TSH receptor have been developed, which can be used to restoration of thyroid function in hyperthyroidism.

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