SUMMARY

Preliminary studies of the mechanisms and safety of drugs are possible by advanced computational methods. Due to the constantly increasing requirements for drug toxicity assessment, in silico assays are indispensable tools to predict the biological activity of a molecule from the chemical structure.

In the present considerations the focus is centers on two drugs commonly used for Central Nervous System disorders i.e. tiagabine (TGB) and paroxetine (PRX). It has been observed that tachycardia occurs in 1% of patients treated with tiagabine. The newest cardiotoxicity assessment guidelines concentrate on the channels proposed by Comprehensive In Vitro Proarrhythmia Assay (CiPA): KV11.1, NaV1.5-late, CaV1.2, KV4.3, KVLQT1/mink and Kir2.1. Interaction with KV11.1, NaV1.5-late, CaV1.2 plays a critical role in the risk of inducing arrhythmias. Accordingly, at work: KV11.1, NaV1.5, and CaV1.2 Transporter Proteins as Antitarget for Drug Cardiotoxicity collected the essential information about the ion channels involved in the heart. The conducted analysis provided the foundation for molecular docking of the tiagabine molecule to human ion channel models: hKV11.1, hNaV1.5, hCaV1.5. The obtained results were compared with the values received for the reference compounds and then confirmed by in vitro tests. The resulting data are described in the paper titled: Antiepileptic drug tiagabine does not directly target key cardiac ion channels KV11.1, NaV1.5 and CaV1.2. Energy values of R–TGB complexes with models of human ion channels generated by computational chemistry methods indicate that these interactions are probably not the cause of tachycardia induction after TGB therapy.

Molecular modelling studies were also employed in the study of the neurogenic mechanism of action of PRX. For this purpose, the investigated molecule was successfully docked to the sites of active transporters hMATs: hSERT, hNET, hDAT and hGAT1. The results confirmed the interaction of PRX with all transporters studied. However, it was established that the phenomenon of neurogenesis with high probability occurs mainly due to PRX–hSERT interaction as it is the complex with the highest energy value. Additionally, it was observed that PXT interacts with hGATs, which gives an opportunity to search for new PRX derivatives, forming even stronger bond. The data obtained were verified by pharmacological assays on Chinese hamster ovary cells, which confirmed γ–aminobutyric acid reuptake from the synaptic cleft.

keywords: ion channels, tiagabine, paroxetine, neurogenesis, repurposing