The Doctoral Program

ION CHANNELS AND TRANSPORTERS AS MOLECULAR DRUG TARGETS („MolTag“)

is pleased to invite you to the following lecture

“Functional and structural studies on positive allosteric modulators of α7 nicotinic receptors”

by Prof.Dr. Hugo R. ARIAS

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on: Wednesday, June 7th, 05:00 pm (17:00)

at: UZA 2, Althanstr. 14, 1090 Vienna, Seminarroom 2D 313

Abstract: Positive allosteric modulators (PAMs) enhance the efficacy of agonists without directly acting on orthosteric, but allosteric, binding sites. We previously characterized the pharmacological activity of three novel PAMs [PAM-2 (3-furan-2-yl-N-p-tolyl-acrylamide), -3 (3-furan-2-yl-N-o-tolyl-acrylamide), and -4 (3-furan-2-yl-N-phenyl-acrylamide)] with high selectivity for the α7 nicotinic acetylcholine receptor (AChR) (Arias et al., 2011, Biochemistry 50, 5263; Arias et al., 2016, Int. J. Biochem. Cell Biol. 76, 19). Since these compounds reactivate desensitized α7 AChRs, they were initially classified as type II PAMs (Targowska-Duda et al., 2014; Neurosci. Lett. 569, 126). This classification is supported by macroscopic current studies where the profile of PAM-2 and -4 resemble that of PNU-120596, a type II PAM. However, subsequent single-channel results indicated that the profile of PAM-2 resembles that of 5-hydroxyindole (5-HI) and NS-1738, type I PAMs (Andersen et al., 2016, Neuropharmacology 107, 189). Additional functional studies suggest that PAM-2 enhances peak currents in α7 AChRs but delays the desensitization of α7β2 AChRs. The observed activity of PAM-2 on hippocampal α7* AChRs also supports this dual activity.

The results showing that PAM-2 affects neither the 5-HT_{3A} receptor nor the α7/5-HT_{3A} chimera suggest that the active site for PAM-2 is located neither at the extracellular domain nor at the junctional domain comprising the pre-M1 and M2-M3 loop (Andersen et al., 2016). The results showing that the quintuple α7 mutant (i.e., S223T/A226S/M254L/I281M/V288F) is sensitive neither to PAM-2 nor PNU-120596, but to 5-HI and NS-1738, support the view that the active site of PAM-2 overlaps the PNU-120596 intrasubunit pocket. Additional docking studies suggest that PAM-2 binds to an intersubunit locus using the α7β2 model. In other words, it seems that the potentiating effect of PAM-2 is elicited by interaction with the intrasubunit pocket, whereas the decreased desensitization effect is elicited by binding to the intersubunit locus.

Passive avoidance test results indicated that PAM-2 enhances memory acquisition (1 mg/kg) and memory consolidation (0.5-2 mg/kg), in an α7-selective manner, and that an inactive dose of DMXBA, a selective α7 agonist, enhances the activity elicited by an inactive dose (0.1 mg/kg) of PAM-2, suggesting synergistic interaction (Targowska-Duda et al., 2016; Behav. Brain Res. 302, 142). Using the set-shifting task test, it was also demonstrated that PAM-2 enhances cognitive flexibility in an α7-selective manner, and increases the activity observed for selective α7-agonists (Potasiewicz et al., 2015, Br. J. Pharmacol. 172, 5123). Forced swimming tests indicated that PAM-2 has antidepressant-like activity (Targowska-Duda et al., 2014; Arias et al., 2015, Neurochem. Int. 87, 110).

Biochemical studies indicated that the chronic treatment (21 days) with PAM-2 up-regulates α7 AChRs and increases Erk1/2 phosphorylation in the hippocampus but not in the cortex (Targowska-Duda et al., 2016). In addition, PAM-2 enhances nicotine-induced release of dopamine and GABA, and 5-HT, but not ACh, in the nucleus accumbens. These results suggest that PAM-2 provokes a myriad of neurochemical effects that can be translated into the observed behavioral outcomes.

In conclusion, novel α7 PAMs might be used for the development of therapies for cognitive impairment and depression-related diseases.

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