BMC Pharmacology

Meeting abstract

Ionotropic neurotransmitter receptors: activation and allosteric modulation

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from 13th Scientific Symposium of the Austrian Pharmacological Society (APHAR). Joint Meeting with the Austrian Society of Toxicology (ASTOX) and the Hungarian Society for Experimental and Clinical Pharmacology (MFT)
Vienna, Austria. 22–24 November 2007

Published: 14 November 2007

BMC Pharmacology 2007, **7**(Suppl 2):A37 doi:10.1186/1471-2210-7-S2-A37

This abstract is available from: http://www.biomedcentral.com/1471-2210/7/S2/A37

Introduction

GABA and glycine are major inhibitory neurotransmitters. $GABA_A$ and glycine receptors (GlyR) form pentameric chloride channels and belong to the Cys-loop receptor superfamily with 5-HT_3 serotonin and nicotinic receptors. Homology modelling has revealed distinctive binding interactions of antagonists and agonists in the interface of 5-HT_{3A} receptors leading to ligand translocation, closure of the binding cavity and ionophore activation. Allosteric modulation of ionotropic receptors enables the pharmacological fine-tuning of neurotransmission.

Methods

Radioligand binding of [^{3}H]EBOB and [^{3}H]strychnine to native $GABA_A$ and recombinant GlyRs, respectively, and whole-cell patch clamp electrophysiology in cultured rat cerebellar granule cells.

Results

A 17β-alkenyl derivative of the neurosteroid allopregnanolone antagonized the potentiating effects of allopregnanolone selectively on a cerebellar (α6βδ) population of $GABA_A$ receptors with nanomolar potency. Nortropine esters exerted bidirectional allosteric modulation of GlyRs: nor-O-zatosetron had the highest affinity reported for GlyRs. The anaesthetic propofol restored the potency of glycine impaired by a point mutation R271L of GlyR α1 subunits leading to hyperekplexia, an inherited neurological disorder.

Conclusion

Some of these allosteric modulators have nanomolar potencies and serve as promising leads for subunit-selective modulation of ionotropic receptors.

Acknowledgements

Support: OTKA K-62203.