BMC Pharmacology

Meeting abstract

Heterogeneity of release-regulating muscarinic receptors in rat sympathetic neurons: evidence for inhibitory presynaptic M_1 receptors

Helmut Kubista, Kristina Kosenburger, Peter Mahlknecht, Helmut Drobny and Stefan Boehm*

Address: Institute of Pharmacology, Centre of Biomolecular Medicine and Pharmacology, Medical University of Vienna, 1090 Vienna, Austria

Email: Stefan Boehm* - stefan.boehm@meduniwien.ac.at

* Corresponding author

from 14th Scientific Symposium of the Austrian Pharmacological Society (APHAR)
Innsbruck, Austria. 21–22 November 2008

Published: 5 November 2008

BMC Pharmacology 2008, **8**(Suppl 1):A42 doi:10.1186/1471-2210-8-S1-A42

This abstract is available from: http://www.biomedcentral.com/1471-2210/8/S1/A42

Of the 5 known subtypes of mAChRs, M_2, M_3, and M_4 have been reported to act as inhibitory presynaptic receptors in the nervous system, in general, and in sympathetic neurons, in particular. M_1 receptors, in contrast, have rather been viewed as facilitatory presynaptic receptors. In superior cervical ganglion (SCG) neurons, M_1 receptors are well known to inhibit KCNQ channels. Previously, we were able to show that non-presynaptic M_1 receptors in SCG neurons enhance noradrenaline release through an inhibition of KCNQ channels. However, M_1 receptors also mediate an inhibition of voltage-activated Ca^{2+} channels, which represents the predominant mechanism of presynaptic inhibition. Hence, presynaptic M_1 receptors may exert inibitory presynaptic modulation. To test this possibility, we performed experiments on rat superior cervical ganglion neurons. In primary cultures tritium overflow was assayed to investigate the release of [^{3}H]noradrenaline, and the perforated patch-clamp technique was employed to record Ca^{2+} currents. The muscarinic agonist oxotremorine M transiently enhanced ^{3}H outflow and reduced electrically evoked release, once the stimulatory effect had faded. The stimulatory effect was enhanced by pertussis toxin and was abolished by blocking M_1 receptors, by opening KCNQ channels, and by preventing action potential propagation. The inhibitory effect, in contrast, was not altered by preventing action potentials or by opening KCNQ channels, but was reduced by pertussis toxin. The inhibition remaining after pertussis toxin treatment was abolished by blockage of M_1 receptors or inhibition of phospholipase C. When [^{3}H]noradrenaline release was triggered independently of voltage-activated Ca^{2+} channels, oxotremorine M failed to cause any inhibition. The inhibition of Ca^{2+} currents by oxotremorine M was reduced by pertussis toxin and then abolished by the blockage of M_1 receptors. This demonstrates that M_1, in addition to M_2, M_3, and M_4, receptors mediate presynaptic inhibition in sympathetic neurons using phospholipase C to close voltage-activated Ca^{2+} channels. In addition, our results contradict the widely accepted concept that all inhibitory presynaptic receptors restrict transmitter release through a direct inhibition of Ca^{2+} channels via G protein βγ subunits and offer an alternative mechanism.

Acknowledgements

This study was supported by grants P17611 and P19710 from the Austrian Science Fund (FWF).