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Meeting abstract

Facilitation of transmitter release from rat sympathetic neurons via presynaptic $P2Y_1$ receptors

Giri K Chandaka, Helmut Drobny and Stefan Boehm*

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

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

* Corresponding author

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$P2Y_1$ receptor antagonists are being developed as antithrombotics. In the vasculature, $P2Y_1$ receptors are not only expressed in platelets, but also in the endothelium where they indirectly mediate vasorelaxation. By blockade of these latter effects, $P2Y_1$ antagonists may cause untoward effects. Here, we investigated whether vascular sympathetic axon terminals also possess $P2Y_1$ receptors by determining [^{3}H]noradrenaline release from superior cervical ganglion neurons in cell culture. ADP inhibited electrically evoked release, but this effect was reverted into facilitation when either $P2Y_{12}$ receptors were blocked by cangrelor or their signalling cascade was interrupted by pertussis toxin. The facilitation by ADP was also observed with K^+ stimulation in the presence of tetrodotoxin, was mimicked by 2-methlythio-ATP, and was prevented by suramin, reactive blue 2, and MRS2179. The facilitation by ADP was abolished by the phospholipase C inhibitor U73122, but was not affected by cholera toxin to downregulate G_s proteins, by H-7 to block protein kinases, or by thapsigargin to deplete intracellular Ca^{2+} stores. In patch clamp recordings, activation of $P2Y_1$ receptors led to an inhibition of KCNQ channels, but the KCNQ channel modulators retigabine and XE 991 did not alter electrically evoked noradrenaline release or its facilitation by ADP. These results show that presynaptic $P2Y_1$ receptors mediate facilitation of transmitter release from sympathetic nerve terminals via phospholipase C, and interference with this mechanism by $P2Y_1$ antagonists can be expected to counteract the previously described vasoconstrictive action of these drugs.

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