THE ANTIBIOTIC POLYMYXIN B IS A POTENT ALLOSTERIC MODULATOR OF THE $P2X_7$ RECEPTOR

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The antibiotic polymyxin B (PMB) is known to bind to bacterial lypopolysaccharide (LPS) and neutralize its toxic effects. A previously unknown response of polymyxin B is that the antibiotic greatly amplifies cellular responses mediated by the purinergic receptor of the $P2X_7$ ($P2X_7R$) subtype. We showed that PMB-mediated effects depend on its N-terminal fatty amino acid 6-methylheptanoic/octanoic-diaminobenzoic residue as deletion of this residue abolishes PMB-dependent modulation of ATP triggered responses in HEK293 stably expressing the $P2X_7$ receptor (HEK293-h$P2X_7$) and in natively expressing $P2X_7$ cells. In contrast to PMB, the polymyxin B nonapeptide (PMBN), which is the deacylated amino derivative of PMB lacking the N-terminal fatty amino acid 6-methylheptanoic/octanoic-diaminobenzoic residue, is unable to potentiate a) the ATP-induced Ca^{2+} increase, b) pore formation and consequently ATP-mediated plasma membrane permeabilization, and c) ATP-dependent cytotoxicity also in natively expressing $P2X_7$ cells such as human macrophages. In addition, PMBN is unable to revert the effect of the $P2X_7$ blocker KN-62 and does not induce cell fusion in cells hyper-expressing the receptor. However, PMBN is partially active when the more potent $P2X_7R$ agonist benzoylbenzoyl-ATP (BzATP) is used in place of ATP. In summary, our data show that interaction of PMB with $P2X_7R$ depends on the presence of the highly hydrophobic N-terminal region of this antibiotic. These findings are important for the search of allosteric modulators allowing a fine tuning of the $P2X_7$ receptor with the purpose to promote beneficial and suppress detrimental effects of $P2X_7$ receptor activation.