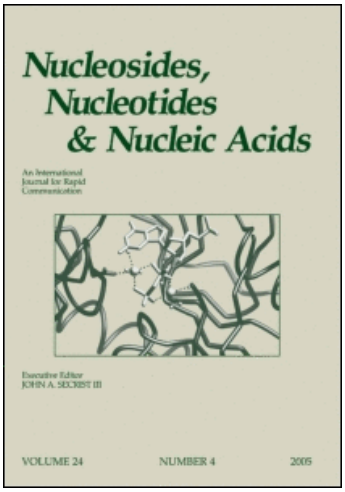

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AMPPCP ACTS VIA P_1 AND NOT P_2 RECEPTORS IN SOME ISOLATED SMOOTH MUSCLE PREPARATIONS

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Abstract

Isolated tissue studies using the P_1-purinoceptor antagonist 8-SPT show that AMPPCP acts entirely via P_1 receptors in the rat duodenum and by P_1 and P_{2Y} receptors in the guinea-pig taenia caeci.

Adenosine and adenosine 5'-triphosphate (ATP) have direct pharmacological effects on many isolated smooth muscle preparations, interacting with P_1- and P_2-purinoceptors respectively. ATP is also rapidly degraded, eventually to adenosine, by ectonucleotidases present on smooth muscle. P_2-purinoceptors have been subdivided into P_{2X} (mediating contraction) and P_{2Y} (usually mediating relaxation), largely on the basis of agonist potencies: 2-methylthioATP (MeSATP) is more potent than ATP on P_{2Y} but equipotent on P_{2X} receptors, whereas the slowly degradable analogues α,β-methyleneATP (AMPCPP) and β,γ-methylene ATP (AMPPCP) are more potent than ATP on P_{2X} but less potent on P_{2Y} receptors[1].

Recent experiments using the rat colon muscularis mucosae, which possesses P_1- and P_{2Y}-like purinoceptors, both of which, unusually, mediate contraction, have shown that the effects of AMPPCP, like those of adenosine, were powerfully inhibited by the P_1 antagonist 8-(p-sulphophenyl)theophylline (8-SPT), whereas those of ATP and AMPCPP were unaffected[2]. This unexpected finding suggested that AMPPCP acts via P_1 receptors in this tissue, rather than weakly via P_{2Y} receptors. We have therefore investigated whether its effects in two other tissues, the guinea-pig taenia caeci and the rat duodenum, both of which relax in response to adenosine and ATP, are mediated via P_1 or P_{2Y} receptors. Unlike ATP, AMPPCP is not significantly degraded to adenosine in either tissue during 20 minutes incubation.

Tissues were suspended in organ baths containing Krebs' solution (35°C), aerated with 95% O_2 - 5% CO_2 and placed under a resting tension of 1g, and responses

were recorded isometrically. Concentration-response curves to agonists were obtained non-cumulatively and tissues were preincubated with 8-SPT for 30 min. before concentration-response curves to the agonists were repeated, with the antagonist being added again after each washout. Relaxations were measured following precontraction of the tissues with carbachol.

In the rat duodenum the relaxant effects of ATP, AMPCPP and MeSATP were not affected by 8-SPT (100μM), whereas the effects of adenosine and AMPPCP (up to 100μM) were abolished. Lower concentrations of 8-SPT (5-50μM) also abolished responses to AMPPCP in this tissue and a parallel shift was observed only at 2μM 8-SPT. At 1μM, 8-SPT did not affect the dose-response curve to AMPPCP. Adenosine was paradoxically less affected by the antagonist, with parallel shifts being observed with concentrations of 8-SPT between 10 and 50μM, and little or no antagonism being observed at lower concentrations. 8-SPT, at concentrations of 20 and 2μM produced similar shifts in the dose-response curves to adenosine and AMPPCP respectively, dose ratios of approximately 5 being estimated. The data were not consistent with a Schild plot of unit slope and thus no estimate of pA_2 could be made using either agonist.

In the guinea-pig taenia caeci 8-SPT (50 and 100μM) again inhibited the relaxant effects of adenosine but not those of ATP, AMPCPP or MeSATP. Responses to AMPPCP were also inhibited, but not to the same extent as those of adenosine, as 8-SPT (100μM) produced a dose-ratio of close to 2 for AMPPCP but a dose-ratio of close to 7 for adenosine.

These results and our previous work on the rat colon[2] show that AMPPCP has unexpected direct actions on P_1-purinoceptors in smooth muscle, although it is commonly regarded as a P_2 agonist selective for P_{2X}-purinoceptors. This effect is all the more surprising as the structurally closely related analogue AMPCPP, like ATP itself and MeSATP, appears to be free from this P_1 agonist activity. In the taenia caeci AMPPCP was not inhibited by 8-SPT to the same extent as adenosine, suggesting that in this tissue it does have a significant P_{2Y} effect. However, in the duodenum AMPPCP was inhibited by 8-SPT even more powerfully than was adenosine itself, and did not appear to have any P_{2Y} purinoceptor activity at concentrations up to 100μM. The dose ratios observed for 8-SPT against the two agonists were, however, not consistent with a simple competitive antagonism at a homogeneous receptor population, although in other tissues competitive antagonism has been observed[3].

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