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Effects of α,β-Unsaturated Sulphones and Phosphonium Salts on Ecto-ATPase Activity and Contractile Responses Mediated via P_{2x}-Purinoceptors

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Abstract—1. In the guinea-pig urinary bladder and vas deferens, several α,β-unsaturated sulphones and phosphonium salts that were tested inhibited ecto-ATPase activity. The sulphones were more active in the bladder but the phosphonium salts were more effective in the vas deferens.

2. These compounds either potentiated or inhibited purinergic contractile responses in the guinea-pig urinary bladder and vas deferens.

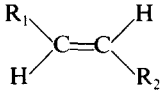
3. α,β-Unsaturated sulphones and phosphonium salts represent a new promising class of compounds, capable of modulating purinergic neurotransmission.

Key Words: Ecto-ATPase, P_{2x}-purinoceptor, α,β-unsaturated sulphones, α,β-unsaturated phosphonium salts

INTRODUCTION

Although the pharmacology of P_2-purinoceptors, at which ATP acts as a principal neurotransmitter, has advanced rapidly during the last decade (see Hoyle, 1992; Burnstock, 1993), it is important to discover potent and specific competitive antagonists of these receptors, as well as inhibitors of ecto-ATPase, an enzyme which is considered to be a transmitter metabolising enzyme. An inhibitor of ATP degradation would be a useful pharmacological tool to discriminate between the effects of ATP and those of its metabolites, as well as to potentiate the effects of ATP. Diverse compounds have been claimed to be inhibitors of ATP-metabolising ecto-enzymes, but suitable ecto-ATPase inhibitors still appear to be lacking (see Ziganshin *et al.*, 1994a). There is an idea that some subtypes of P_2-purinoceptors and ecto-ATPase possess binding sites for ATP which have similar characteristics; therefore compounds that affect P_2-purinoceptors could also interact with ecto-ATPase (Hoyle *et al.*, 1990).

The aim of the present study was to compare the effects of several α,β-unsaturated sulphones and phosphonium salts on ecto-ATPase activity with their ability to alter purinergic responses in the guinea-pig urinary bladder and vas deferens, tissues that both possess P_{2x}-purinoceptors (see Hoyle, 1992). We tested 9 compounds (B1–B9) with a general structure of



where R_1 and R_2 are organylsulphonyl, phosphono and phosphonium groups (Kataev *et al.*, 1972; Berdnikov *et al.*, 1977, 1979, 1980, 1987). These compounds are distantly related to the previously described antagonist of P_2-purinoceptors, 4,4′-diisothiocyanatostilbene-2,2′-disulphonate (DIDS), in which $R_1 = R_2 = C_6H_3(NCS)SO_3Na$ (Soltoff *et al.*, 1993; Bültmann and Starke, 1994). Furthermore, DIDS has been shown to inhibit plasma

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