095P ADENOSINE A_{2A} RECEPTOR STIMULATION CAUSES VASODILATATION IN HUMAN ISOLATED MIDDLE MENINGEAL ARTERIES.

J.A. Root, R.A. Borman & K.L. Clark, Pharmagene Laboratories Ltd, 2 Orchard Road, Royston, Herts., UK. SG8 5HD

There is significant interest in the therapeutic application of adenosine A_{2A} receptor agonists, however, headache is a potential side effect which warrants consideration. It has previously been reported that adenosine A_{2A} receptors are responsible for the vasodilatation of human middle cerebral arteries induced by the non-selective adenosine agonist 5'-(N-ethylcarboxamido)-adenosine (NECA) (Root *et al*., 2004). Here we report an extension of these studies to the human meningeal artery, dilatation of which is proposed to contribute to the pain of certain types of headache (Cumberbatch *et al*., 1999).

Human middle meningeal arteries were obtained from 3 donors (2 female, 1 male, aged between 61 and 90) at *post mortem* (PM) with the informed consent of next of kin, and with the approval of local ethics committees. Tissues were placed in PBS at 4°C, and transported overnight for use the following day, the mean (± s.e.m.) PM delay was 6.3 ± 0.4 hours. Rings of middle meningeal artery were mounted under isometric conditions and an initial tension of 5mN, in 10ml tissue baths containing gassed (95% O_2/5% CO_2) Krebs solution with indomethacin (3μM) at 37°C. The integrity of the endothelium in each case was not established. After 60 minutes equilibration, a cumulative concentration-effect curve to phenylephrine was constructed. After washing, the selective adenosine A_{2A} antagonist ZM241385 (Ongini *et al*., 1999), or vehicle (DMSO), was added at 100nM or equivalent and left in contact with the tissues for 30 minutes. Vessels were constricted with an approximate EC_{50-70} concentration of phenylephrine (1 – 10 μM) and responses allowed to plateau, after which the selective adenosine A_{2A} agonist 2-*p*-(2-carboxyethylphenethylamino-5'-ethylcarboxamido-adenosine), (CGS21680, 1nM – 100μM) was added by cumulative application. After addition of the final concentration of CGS21680, prostacyclin (1μM) was administered to induce a standard relaxation. The Gaddum Schild equation ($\log_{10}$ (concentration ratio – 1) = – ($\log_{10}$ [antagonist])) was used to estimate pA_2 values from these single concentrations.

Cumulative administration of CGS21680 to pre-constricted arteries in the absence of antagonist resulted in a concentration-dependent vasodilatation (pEC_{50} of 6.8 ± 0.4, n=3). The adenosine A_{2A} antagonist ZM241385 produced a significant rightward shift of the concentration-effect curve to CGS21680 (pEC_{50} of 4.6 ± 0.6, pA_2 of 9.2 ± 0.03). The estimated pA_2 value for ZM241385 compares well with its published affinity (pK_i=9.1) for human recombinant adenosine A_{2A} receptors (Ongini *et al.,* 1999).

In conclusion, adenosine A_{2A} receptors are present in human middle meningeal arteries and when stimulated cause vasodilatation.

Cumberbatch, M.J. *et al*., (1999). *Br. J. Pharmacol.,* 126,1478-86
Ongini, E., *et al.* (1999). *Naunyn-Schmiedeberg's Archives of Pharmacology*, 359, 7-10.
Root, J.A., *et al.* (2004). *Br. J. Pharmacol., In press.*