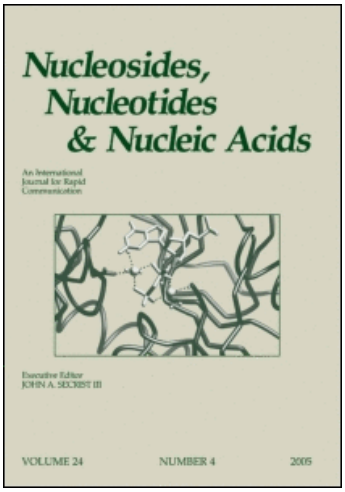

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ADENOSINE RECEPTOR MODULATION OF INOSITOL PHOSPHOLIPID TURNOVER IN THE CENTRAL NERVOUS SYSTEM

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Abstract. Adenosine receptor stimulation results in the selective enhancement or inhibition of histamine H_1 receptor-evoked phosphoinositide turnover in cerebral cortex of guinea pig, mouse and man.

Adenosine does not stimulate phosphoinositide turnover in the CNS. However, it is capable of altering the magnitude of the phosphoinositide response to histamine, both positively and negatively. This modulation is selective, in that adenosine analogues potentiate (guinea pig[1,2]) or inhibit (mouse[3], human[4]) the $InsP_x$ response to histamine (H_1 receptor) without altering the response to carbachol (muscarinic), noradrenaline (α_1-adrenoceptor), or KCl (depolarisation) in cerebral cortical slices.

This action of adenosine is mediated through an extracellular receptor, since a purine nucleoside uptake inhibitor (dipyridamole) increases its' potency, while adenosine deaminase reduces its' action[2,3]. This receptor is a P_1 purinoceptor since theophylline and other methylxanthines are able to antagonise the effects of adenosine analogues[2,3].

Phosphoinositide hydrolysis was assessed in [^{3}H]inositol-prelabelled cerebral cortical slices as previously described[5].

The rank order of agonist potency (i.e. R-PIA > NECA > PAA > S-PIA Table 1) suggests that this receptor is of the A_1 type. However, IC_{50} values for these agonists are in the micromolar range rather than the

TABLE 1: Agonist EC_{50} and antagonist K_i values for the adenosine receptor mediating inhibition of histamine-evoked $InsP_x$ accumulation in mouse cerebral cortical slices

Agonist	EC_{50} (nM)	Antagonist	K_i (nM)
R-PIA	130 ± 38[3]	DPCPX	18 ± 5[5]
NECA	360 ± 35[3]	XAC	62
PAA	425 ± 150	8-*p*SPT	2000
S-PIA	7500 ± 5250	Theophylline	12300 ± 4700[3]

commonly-observed nanomolar range for A_1 receptors. Similarly, antagonist K_i values, although similar in mouse and guinea pig (e.g. DPCPX: mouse 17.6 ± 5.0 nM (n=9); guinea pig 9.0 ± 2.8 nM (n=9)), are also lower than would be expected for a typical A_1 receptor.

In mouse cerebral cortical slices, histamine induces the accumulation of mono-, bis-, tris- and tetrakisphosphates (Table 2). 2-Chloroadenosine, although without direct effect, is able to reduce the histamine-induced accumulations of all of these entities, indicating a general "brake" on the effects of histamine.

Furthermore, although histamine selectively stimulates incorporation of [^{3}H]inositol into phosphatidylinositol 4,5-bisphosphate[6], 2CA is without effect on phosphoinositide labelling.

We have recently been able to exclude cyclic AMP and calcium ions as potential mediators of the modulatory influence of adenosine. These agents have been indicated to be able to modulate phosphoinositide turnover in other systems (cyclic AMP in e.g. platelets[7], trachea[8]; and Ca^{2+} influx[9] in GH3 cells from the anterior pituitary[10]). Although adenosine is able to influence these parameters in preparations of nervous system origin[11-13], the modulatory effects of adenosine receptor stimulation were still apparent under conditions of raised cyclic AMP, and extra- and intracellular Ca^{2+} levels[5,14].

Our recent studies have investigated the potential mediatory role of protein kinase C (PKC) in receptor cross-talk. Phosphoinositide turnover not only gives rise to inositol phosphates but also produces diacylglycerol, which is able to activate PKC. A potential feedback

TABLE 2: Histamine (HA, 1 mM) and histamine plus 2-chloroadenosine (HA+2CA, 30 µM) effects on [^{3}H]inositol phosphate fractions from mouse cerebral cortical slices

Agonist	HA	HA + 2CA
	dpm	dpm
[^{3}H]InsP$_1$	98356 ± 11635	39067 ± 5384 (40 %)
[^{3}H]InsP$_2$	20749 ± 2289	5215 ± 994 (25 %)
[^{3}H]InsP$_3$	8596 ± 934	1053 ± 142 (12 %)
[^{3}H]InsP$_4$	685 ± 78	76 ± 50 (11 %)

role of this enzyme has been suggested[15], based on the inhibitory effects of phorbol esters (chronic activators of PKC) on receptor-induced InsP$_x$ accumulation. Interestingly, there also appears to be a receptor-induced inhibition of this enzyme, mediated via sphingolipid turnover[19]. Thus, it is conceivable that both inhibitory and augmentory influences on phosphoinositide turnover exist, mediated through alteration of PKC activity. 4-ß-Phorbol 12,13-dibutyrate (PDBu) and 12-*O*-tetradecanoyl 4-ß-phorbol 13-acetate were found to inhibit the histamine H$_1$ response (e.g. in the mouse, with IC_{50} values of 265 nM and 1.9 µM). In contrast, 4-α-phorbol, a poor activator of PKC, was inactive. Staurosporin, a PKC inhibitor, dose-dependently inhibited the effect of PDBu, and, also directly increased the histamine response (by 120 % at 3 µM) without altering basal [^{3}H]InsP$_x$ levels. However, in both the mouse and guinea pig, 2-chloroadenosine was still able to modulate the histamine response in the presence of PDBu or staurosporin. This indicates that PKC is not involved in the adenosine receptor modulation of histamine-induced phosphoinositide turnover.

Conclusions. Adenosine receptor modulation of CNS histamine-evoked phosphoinositide turnover is apparent in mouse, guinea pig, and human cerebral cortical slices. This modulation is seemingly not mediated through polyamines, protein synthesis, eicosanoids[2,3], cyclic AMP[5], calcium ion fluxes[14], changes in phosphoinositide labelling or protein kinase C.

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REFERENCES

1. Hollingsworth, E.B.; de la Cruz, A.; Daly, J.W. *Eur J Pharmacol* **1986** *122*, 45.
2. Hill, S.J.; Kendall, D.A. *Br. J. Pharmacol.* **1987** *91*, 661.
3. Kendall, D.A.; Hill, S.J. *J. Neurochem.* **1988** *50*, 497.
4. Kendall, D.A.; Firth, J.L. *Br. J. Pharmacol.* **1990** *100*, 37.
5. Alexander S.P.; Kendall, D.A.; Hill, S.J. *Br J Pharmacol* **1989** *98*, 1241.
6. Alexander S.P.; Kendall, D.A.; Hill, S.J. *Biochem. Pharmacol.* **1990** in press.
7. Kaibuchi, K.; Takai, Y.; Ogawa, Y.; Kimura, S.; Nishizuka, Y.; Nakamura, T.; Tomomura, A.; Ichihara, A. *Biochem. Biophys. Res. Commun.* **1982** *104*, 105.
8. Hall, I.P.; Donaldson, J.; Hill, S.J. *Br. J. Pharmacol.* **1989** *97*, 603
9. Eberhard, D.A.; Holz, R.W. *TiNS* **1988** *11*, 517.
10. Vallar, L.; Vicentini, L.M.; Meldolesi, J. *J. Biol. Chem.* **1988** *263*, 10127.
11. Sattin, A.; Rall, T.W.; *Mol. Pharmacol.* **1970** *6*, 13.
12. Dolphin, A.C.; Forda, S.R.; Scott, R.C. *J. Physiol.* **1986** *373*, 47.
13. Schubert, P.; Heinemann, U.; Kolb, R. *Brain Res.* **1986** *376*, 382.
14. Alexander, S.P.H.; Hill, S.J.; Kendall, D.A. *J Neurochem* **1990** *55*, in press
15. Labarca, R.; Janowsky, A.; Patel, J.; Paul, S.M. *Biochem. Biophys. Res. Commun.* **1984** *123*, 703.
16. Hannun, Y.A.; Bell, R.M. *Science* **1989** *243*, 500.