cGMP may be the result of a direct stimulation of the raphe-cerebellar pathway.

The capacity of the 5HT receptor blockers, cyproheptadine and methysergide, to block receptors in the cerebellum has not been investigated, but it has been shown that neither of the drugs are complete blockers of 5HT receptors in the CNS [2, 10]. Such a reduced efficiency may account for the lack of effect of these drugs in terms of blocking 5MeODMT-stimulated increase in cerebellar cGMP.

In conclusion, these data indicate that the concentration of cerebellar cGMP may be controlled by a 5HT mediated pathway which is not blocked by cyproheptadine or methysergide, and which does not appear to require the activation of an intermediate DAergic neurone.

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Stimulation of gluconeogenesis by adenosine in renal cortical tubule fragments from fed rats

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Adenosine has a diverse range of effects upon the physiological and biochemical function of many tissues (see review by Arch and Newsholme [1]). These range from 'hormone-like' effects seen at low concentrations to direct interventions in adenine nucleotide metabolism seen at relatively high concentrations (i.e. approximately 10^{-3}M). In the course of experiments designed to test whether adenosine might alter the response of renal gluconeogenesis to stimulating agents (Ca^{2+}, 3′, 5′ cyclic AMP or α-adrenergic agonists), it was observed that adenosine consistently increased the rate of the process above that seen in the basal state. This effect of adenosine, which was dose-dependent, was surprising and of interest since, by contrast, adenosine causes a considerable decrease in glucose formation from lactate in rat hepatocytes [2].

Chemicals were obtained as described by Macdonald and Saggerson [3]. In addition, adenosine was from Boehringer. Renal cortical tubule fragments were isolated by collagenase treatment of cortex pieces obtained from male Sprague–Dawley rats (160–180g body wt) as described previously [3] using Krebs–Ringer bicarbonate containing 1.27 mM Ca^{2+} as the incubation medium. Finally each preparation of tubules was made up in this medium to give a stock suspension in which the tissue from each original kidney cortex was dispersed in 5 ml. Aliquots (1 ml) of this were then taken for incubation at 37° as described by Macdonald and Saggerson [3] in a final volume of 4 ml with constant shaking under $O_2 + CO_2$ mixture (95.5%).

After incubation glucose was measured enzymically [4] in extracts prepared by deproteinization of incubation flask contents with 0.5 ml of ice-cold 45% (w/v) $HClO_4$. These extracts were neutralized by addition of 1M triethanolamine hydrochloride and concentrated K_2CO_3. In all experiments, the small amount of glucose present initially in non-incubated aliquots of tubules was also determined and subtracted from experimental values. The average basal rate of glucose formation was 2.7 μmole/hr/mg DNA. DNA was measured by the method of Burton [5] in 1.0 ml portions of stock tubule suspensions which generally contained 150–200 μg DNA.

Statistical significance was determined by Student's *t*-test on a paired basis.

Figure 1 shows that adenosine stimulated gluconeogenesis from lactate in a dose-dependent manner. Adenosine (10μm) was sufficient to achieve a significant acceleration of the process and in three out of four experiments 1 μM adenosine was also stimulatory. Larger effects were seen with 0.1 mM and 1 mM, the response with 1 mM being more variable. These observations were surprising in view of the finding of Lund *et al.* [2] that adenosine inhibits gluconeogenesis from lactate in rat hepatocytes. This would appear to suggest a clear and interesting difference between

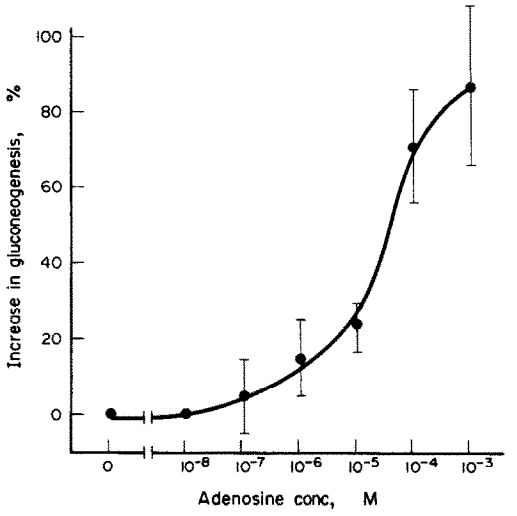

Fig. 1. Effect of adenosine on renal gluconeogenesis. Kidney tubule fragments were incubated for 1 hr in Krebs–Ringer bicarbonate buffer containing 1.27 mM Ca^{2+}, fatty acid-poor albumin (10 mg/ml) and 5 mM sodium L-lactate. The results are means ± S.E.M. of 4–7 independent measurements and are expressed as percentage increases over the values obtained in paired control incubations which contained no adenosine and were performed in all seven experiments. The error bar at 10^{-8}M adenosine lies within the symbol. Significant effects of adenosine were seen at 10 μM (6 measurements, $P < 0.05$), 0.1 mM (5 measurements, $P < 0.01$) and 1 mM (7 measurements, $P < 0.01$).

liver and kidney cortex. It is noteworthy that the maximum inhibitory effects reported by Lund *et al.* [2] also were observed with adenosine in the concentration range 0.1–1 mM. The mechanism(s) by which adenosine affects gluconeogenesis in these tissues is unknown at present. The possibility of the involvement of purinergic receptors [6] should be considered. Unlike the liver, incubation with adenosine does not expand the adenine nucleotide content of renal tubules [2]. It is well documented that adenosine is an effector of adenylate cyclases, being either stimulatory [7–10], inhibitory [11–15] or both [16]. Adenosine has been shown to inhibit adenylate cyclase in liver [11,12,15]. Renal gluconeogenesis can be stimulated by 3′, 5′ cyclic AMP [17], and the proximal tubule, which is the site of gluconeogenesis [18], contains adenylate cyclase activity [19]. However, the possibility that adenosine is stimulating renal gluconeogenesis through activation of adenylate cyclase is not supported by the findings of McKenzie and Bär [12] who showed 55 per cent inhibition of F^--stimulated renal cortex adenylate cyclase by 1 mM adenosine. However, the renal cortex consists of several cell types and at least two adenylate cyclase activities [20].

In conclusion, the stimulatory effect of adenosine on renal gluconeogenesis noted here is directly opposite to the effect of this nucleoside in the liver. The possibility of the involvement of a purinergic receptor and the mechanism of action of adenosine, through adenylate cyclase or through some other process, will be the subject of further study.

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