# EFFECT OF THE $Na^+$ IONOPHORE MONENSIN ON BASAL AND NORADRENALINE-STIMULATED GLUCONEOGENESIS IN RAT RENAL TUBULE FRAGMENTS

José A. S. VEIGA+, Carol A. CARPENTER and E. David SAGGERSON*
*Department of Biochemistry, University College London, Gower Street, London WC1E 6BT, England*

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## 1. Introduction

Gluconeogenesis in rat renal cortex is stimulated by catecholamines through an α-type of adrenoceptor [1,2] which shows characteristics of the $\alpha_1$-subtype [3]. It was shown in [4] that the $Na^+/K^+$-ATPase inhibitor ouabain or removal of extracellular $K^+$ abolished α-adrenergic stimulation of this process. The mechanism underlying these effects was not established, but it was suggested that the α-adrenergic effect was dependent either upon maintainence of normal cellular levels of $K^+$ and/or $Na^+$ or upon normal movements of one or both of these ions (possibly in association with $Ca^{2+}$). An increase in intracellular $[Na^+]$ is to be expected in the presence of ouabain. The same should be found with the $Na^+$ ionophore monensin [5]. Accordingly, we have tested the effect of this compound upon basal and agonist-stimulated gluconeogenesis.

## 2. Materials and methods

These were as in [4]. In addition, monensin was a gift from Dr E. J. Harris (Biophysics Department, UCL).

## 3. Results and discussion

Hughes et al. [6] have investigated the effect of monensin upon hepatocyte intracellular sodium $[Na^+]$ and upon phosphorylase activation. We are unaware of any study of the effect of this compound on gluconeogenesis. Fig.1 shows that renal gluconeogenesis from lactate was profoundly inhibited by monensin. Inhibition of 50% of the process was observed with 0.5 μg ionophore/ml (0.75 μM). It is assumed that gluconeogenesis (an ATP-requiring process) is decreased as a consequence of increased energy utilization to pump $Na^+$ out of the monensin-treated cell. In support of this, monensin (1 μg/ml) inhibited gluconeogenesis from lactate by 60% whereas with 5 mM fructose, the conversion of which to glucose requires less ATP, only 24% inhibition was observed (3 expt). It is noteworthy that in the perfused kidney of the prednisolone-treated rat, $Na^+$ transport and gluconeo-

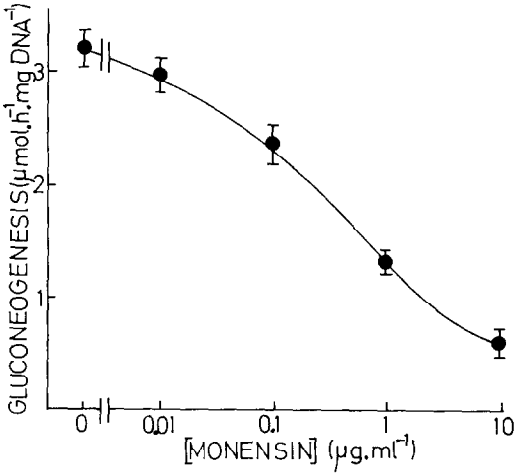


Fig.1. Effect of monensin on basal gluconeogenesis. Tubule fragments from fed rats were incubated with 5 mM lactate for 60 min with the indicated concentrations of monensin. The values are means ± SEM of 7 expt. The mean tubule DNA/ml flask contents was 56 ± 3 μg.

* To whom correspondence should be addressed

+ Present address: Instituto de Biologia Médica and Agricola, Campus de Botucatu, Universidade Estadual Paulista, CEP 18.610 Botucatu, Brazil

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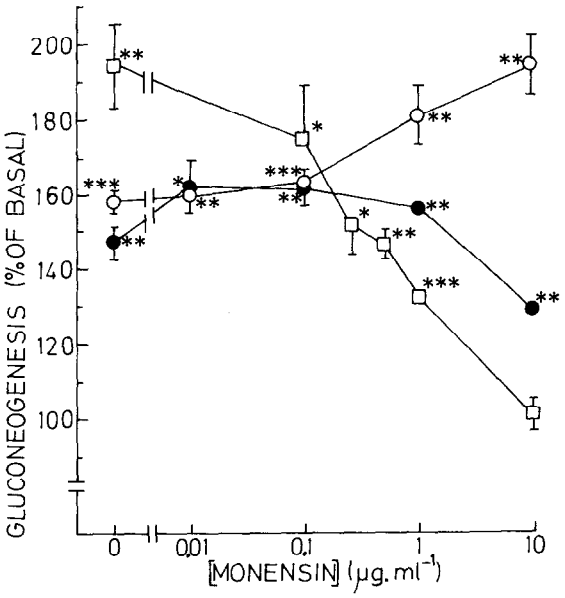


Fig.2. Effect of noradrenaline, oxymetazoline and 3′:5′-cyclic AMP on gluconeogenesis in the presence of monensin. Tubule fragments from fed rats were incubated with 5 mM lactate for 60 min. The bars indicate SEM. Where these are not shown they lie within the symbol: (○) with noradrenaline (1 μM), 4 expt; (●) with oxymetazoline (0.1 μM), 3 expt; (□) with 3′:5′-cyclic AMP (0.1 mM), 4 expt; *, **, *** indicate $p < 0.02$, 0.01 and 0.001, respectively, for effects of the agonists.

genesis appear to be competing energy-dependent processes [7,8].

Besides decreasing basal gluconeogenesis (fig.1), monensin also decreased the rate of the process in the presence of noradrenaline, oxymetazoline or 3′:5′-cyclic AMP. However, stimulation by these agents was still observed in the presence of monensin (fig.2). Surprisingly, the percentage stimulation of gluconeogenesis with noradrenaline was actually increased by monensin. This may be contrasted with the effect of ouabain which completely blocks stimulation of tubule gluconeogenesis by noradrenaline [4]. The synthetic α-agonist oxymetazoline differed from noradrenaline in that high concentration of monensin reduced its percentage effect. Although classified as an α-agonist, the actions of oxymetazoline in this system differ somewhat from those of noradrenaline [2,4,9]. 3′:5′-Cyclic AMP-stimulated gluconeogenesis was appreciably more sensitive to inhibition by monensin with 10 μg ionophore/ml abolishing the stimulatory effect of the cyclic nucleotide. The reason for this is unclear.

We conclude that blockade of the noradrenaline stimulation of gluconeogenesis by ouabain [4] is unlikely to be due simply to elevation of intracellular [$Na^+$]. There still remains the possibility that interaction of ouabain with the $Na^+/K^+$-ATPase interferes with the function of the α-adrenoceptor and its role in the generation of putative second messengers. Alternatively, a hitherto unknown action of ouabain has to be invoked.

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