

# matters arising

## Possible mechanism for biological action of lithium

FRAUSTO DA SILVA and Williams<sup>1</sup> have presented a theoretical chemical rationale for the postulate that lithium may have its pharmacological action by competition with magnesium<sup>2-4</sup>. But though they have dealt in detail with the role of ATP as a "masking" agent they have not considered the direct binding of lithium to the nucleotide.

Since lithium might interfere in the many biological processes which are magnesium dependent<sup>5</sup> and since changes do occur in the tissue distribution of magnesium following lithium<sup>6</sup> my colleagues and I investigated five magnesium-dependent enzymes and found that three were inhibited by lithium<sup>7</sup>. These enzymes seemed to be "Mg-ADP dependent".

We determined, by gel filtration on Sephadex G-10, the association constants of lithium and magnesium with either ADP or ATP both independently ( $K_i$ ) and also in a solution containing both metals<sup>8</sup>. The constants determined in the (Li·Mg) solution were calculated *a*, assuming that the nucleotide complexed Li and Mg independently ( $K_{ii}$ ) and *b*, assuming that the metals competed for sites ( $K_{iii}$ ). All experiments were carried

**Table 1** Association constants (log  $K_{ass}$ ) for complexes of Mg and Li with ADP + ATP in conditions described in the text<sup>8</sup>

		ADP	ATP
K(i)	Mg	3.02 (a)	3.97
	Li	2.48 (b)	2.71
K(ii)	Mg	3.12 (c)	4.00
	Li	3.00 (d)	2.79
K(iii)	Mg	3.22 (e)	4.05
	Li	3.14 (f)	3.07

By *t* tests the following pairs are significantly different at  $P < 0.001$ : (a) against (e), (b) against (d), (b) against (f).

out at pH 7.4 in 0.108 mol l<sup>-1</sup> triethanolamine hydrochloride buffer. The results are shown in Table 1.

Our values for  $K_{ass}$  differ from those of Frausto da Silva and Williams but agree with other reports<sup>9,10</sup>. But they are effectively "conditional constants" with respect to the nucleotide buffer-metals system at pH 7.4. We have concluded that there is preliminary evidence for a ternary complex of the Li-Mg-ADP type<sup>8</sup> though this awaits confirmation by physical methods.

In relation to magnesium, ADP has a rather higher affinity for lithium than

ATP and if the lithium complex were a poor substrate this might have implications in the kinetics of ATPases during lithium therapy. In any case the increased binding of lithium induced by the presence of magnesium must indicate configurational or other changes which might affect the kinetics of any ADP requiring enzyme.

Our findings with biologically occurring nucleotides therefore suggest that the sequestering agent (ATP) may also be affected by lithium due to effects on the ATP-ADP equilibria. We might expect two loci of lithium action in nucleotide dependent enzymes; ( $O^-$ , N,  $O^-$ ,  $O^-$ ) coordinating sites on the protein and the nucleotide itself.

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<sup>1</sup> Frausto da Silva, J. J. R., and Williams, R. J. P., *Nature*, **263**, 237-239 (1976).

<sup>2</sup> Birch, N. J., *Br. J. Psychiat.*, **116**, 461 (1970).

<sup>3</sup> Birch, N. J., *Biol. Psychiat.*, **7**, 269-273 (1973).

<sup>4</sup> Williams, R. J. P., in *Lithium, its Role in Psychiatric Research and Treatment* (edit. by Gershon, S., and Shopsin, B.), 15-13 (Plenum, New York, 1973).

<sup>5</sup> Birch, N. J., *Lancet*, **ii**, 965-966 (1974).

<sup>6</sup> Birch, N. J., and Jenner, F. A., *Br. J. Pharmacol.*, **47**, 586-594 (1973).

<sup>7</sup> Birch, N. J., Huilin, R. P., Inie, R. A., and Leaf, F. C., *Br. J. Pharmacol.*, **52**, 139P (1974).

<sup>8</sup> Birch, N. J., and Goulding, I., *Analyt. Biochem.*, **66**, 293-297 (1975).

<sup>9</sup> Khan, M. M. T., and Martell, A. E., *J. phys. Chem.*, **66**, 10-15 (1962).

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WILLIAMS AND FRAUSTO DA SILVA REPLY—We accept the points made by Birch. The major point of our paper was to show how lithium could act on vesicles which contained transmitters even in situations where magnesium ions might be thought to be protective against any lithium effect.

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## Uniqueness of plasminogen activators

THE report of Åstedt and Holmberg<sup>1</sup> relating their demonstration of the immunological identity between human urokinase and plasminogen activator from human ovarian carcinoma includes a quotation from the summary of one of our papers on plasminogen activators from transformed cells<sup>2</sup>. Because of the interest in the role of plasminogen activators in tumorigene-

sis, we feel that it is important that there is no misinterpretation of our statement: "Neoplastic cells, whether transformed by oncogenic viruses or chemical agents, release a fibrinolytic factor not released by normal cells". In the text of our article, this sentence is qualified to indicate that by 'normal cells', we mean the parental primary cultures from which the transformants were derived. Our purpose in characterising the plasminogen activator from a transformed line was to determine whether or not it differed from the plasminogen activators known to be produced by normal mammalian tissues. We have, in fact, published data which demonstrate that the plasminogen activator which we purified from SV40 transformed hamster cells is immunologically identical to that produced by normal hamster lung cells and that it differs from the plasminogen activator(s) produced by hamster kidney cells<sup>3</sup>.

Although there is no doubt that there is a tantalising correlation between plasminogen activator production by cells *in vitro* and their ability to cause tumours in immune-competent hosts<sup>4,5</sup> or in nude mice<sup>6</sup>, we feel that it is worth stressing once again that not all cultured cells which produce plasminogen activator are tumorigenic, nor do all cells capable of forming tumours in immune-competent hosts produce plasminogen activators *in vitro* (for example, Friend erythroleukaemia cells). In addition, as is confirmed by the work of Åstedt and Holmberg, the plasminogen activators produced by tumour tissues are not 'tumour-specific' proteins but probably reflect the expression of genetic information in 'inappropriate' cells.

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<sup>1</sup> Åstedt, B., and Holmberg, L., *Nature*, **261**, 595-597 (1976).

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