ANNALS OF GENERAL PSYCHIATRY

MEETING ABSTRACT Open Access

Specific inhibition of adenylyl-cyclase isoform 5 by mood stabilizers may be related to their mechanism of action

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From 1st International Congress on Neurobiology and Clinical Psychopharmacology and European Psychiatric Association Conference on Treatment Guidance
Thessaloniki, Greece. 19-22 November 2009

Lithium, valproate and carbamazepine decrease brain cAMP. Adenylyl-cyclase (AC), which synthesizes cAMP has nine membrane-bound isoforms (AC1-AC9). In this study we used COS7 cells transfected with cDNA of each of the isoforms to study the effect of a therapeutic concentration of each of lithium, carbamazepine and valproate on ACs activity. AC5 was the most inhibitable isoform by lithium and carbamazepine either when stimulated by forskolin or by a D1 agonist. Ten mM Mg2+ reduced lithium-induced AC5 inhibition by 70% and in silico analysis suggested that carbamazepine preferentially affects AC1 and AC5 by interacting with two amino-acids at the catechol-estrogen binding site region. Valproate did not inhibit any AC isoform suggesting it decreases cAMP levels via a different mechanism. AC5 knockout mice behaved in the forced-swim-test similarly to antidepressant- or lithium-treated wildtypes implying that AC5 inhibition may be involved in the antidepressant effect of lithium and carbamazepine. Specific AC5 inhibitors may be mood-stabilizers or antidepressants.

Published: 22 April 2010

doi:10.1186/1744-859X-9-S1-S83
Cite this article as: Mann *et al.*: Specific inhibition of adenylyl-cyclase isoform 5 by mood stabilizers may be related to their mechanism of action. *Annals of General Psychiatry* 2010 **9**(Suppl 1):S83.

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