TIME-DEPENDENT AND SEQUENTIAL MODULATION OF SIGNALING CASCADES, CREB ACTIVATION AND BDNF EXPRESSION INDUCED BY ANTIDEPRESSANTS

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Recent studies showed that intracellular pathways modulating gene transcription are involved in depression and antidepressant (AD) action (1). AD effect on cAMP-responsive element binding protein (CREB) and brain-derived neurotrophic factor (BDNF) has been extensively studied. In neurons activity-dependent phosphorylation of CREB is induced by activation of the calcium/calmodulin-dependent kinase (CaMK) and the extracellular regulated kinase (ERK1/2) cascades, pathways involved in both gene expression and AD mechanisms. Conflicting results on the effects of chronic AD on CREB suggest that different effects may depend on drug type, route of administration and different time window of measurement. Here we analyzed the time-course effects of treatment with fluoxetine (FLX) and reboxetine (RBX) on CaMKIV, CaMKII, ERK1/2, CREB activation and BDNF expression in nuclear fraction from hippocampus (HC) and prefrontal/frontal cortex (P/FC) by immunoblotting. Rats were treated with FLX or RBX administered in drinking water according to the following schedule: 1-week treatment, 2-week treatment, 3-week treatment and 3-week treatment + 1-week drug washout. AD did not modify CREB expression. One and two weeks of FLX increased phospho-CREB in HC, while 1-week with RBX induced CREB activation in P/FC. During 3-week treatment and the washout week phospho-CREB returned to basal levels with both drugs. CaMKIV activation followed a temporal profile similar to that of CREB in HC, while in P/FC phosphorylation was sustained up to the washout week. CaMKII activation was downregulated in HC from FLX treated rats. Regarding ERK1/2, 3-week treatment reduced ERK1/2 activation in P/FC, while both drugs persistently activated ERK2 in HC. Finally, BDNF expression showed a profile similar to CREB activation, with an increase of expression at 2 weeks followed by a reduction. Our results show a transient profile of CREB activation by AD, with a peak of phosphorylation in the first weeks and subsequent return to basal levels. This profile is consistent with the activation of CaMKIV in HC and P/FC and ERK2 in P/FC. BDNF expression shows a similar biphasic profile, with an increase following 1-week after the peak of CREB activation. These findings suggest that time-dependent activation of signalling and CREB by AD is a rather early event, followed by sequential activation of the CREB-dependent gene BDNF.

[1] Tardito, D., Perez, J., Tiraboschi, E., Musazzi, L., Racagni, G., Popoli, M., 2006 Pharmacol Rev. 58(1):115-34.