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Differential mRNA expression of neuroproliferative/neuroplastic transcription factors induced by venlafaxine and RS67333 assessed in organotypic hippocampal slice cultures

VI Vargas[1,2], B Martínez-Villayandre[1,2], A Pazos[1,2], EM Valdizán[1,2]. *[1]Universidad de Cantabria, Departamento de Fisiología y Farmacología 39011, Spain, [2]IBBTEC- CIBERSAM, Universidad de Cantabria-CSIC-SODERCAN;Instituto de Salud Carlos III, Spain*

Depressive disorders are currently treated with drugs that mainly act by increasing brain monoamine levels. These drugs usually exhibit a delayed onset to achieve a full antidepressant action (2–4 weeks). It has been suggested that RS67333, a 5-HT4 receptor partial agonist, induces both, antidepressant-like responses and neuroplasticity-associated changes with a short onset of action (3-7 days). This opens a new strategy for developing faster-acting antidepressant drugs, though their mechanism of action has not been fully elucidated. Recent data suggest the involvement of neuroproliferative/neuroplastic signalling pathways in the mechanisms of the antidepressant action.

The objective of the present study was to analyze, by real time PCR, the time course of expression of plasticity-related genes induced by both RS67333 and venlafaxine (a serotonin norepinephrine reuptake inhibitor) in organotypic hippocampal slice cultures obtained from P7 Sprague Dawley male rats (Stoppini L, Buchs P.A, Muller D. Journal of Neuroscience Methods, 37: 173-182,1991).

In each experiment, slices from 4 animals were pooled and used to evaluate the effect of each drug (each analysis was run 3 times). The slices were exposed to 1 uM of either RS67333 or venlafaxine dissolved in culture medium for 1, 3 or 7 days. We tested mRNA levels of Wnt/β-catenin pathway related genes: β-catenin gene (Ctnnb1), Axin1, Axin2, Myc, as well as Wnt/β-catenin-nonrelated genes: Notch1 and Ccnd1. Relative expression levels were expressed as fold of change using the 2-ΔΔCt method with GAPDH as internal reference.

RS67333 up-regulated Ccnd1 (9.22±0.46; 27.58±0.92; 3.74±0.77; $p<0.05$ respectively for 1, 3 and 7 days) and Notch1 (11.50±0.65; 48.41±0.98; 14.19±0.71; $p< 0.05$ respectively for 1, 3 and 7 days), but not the Wnt/β-catenin related genes Ctnnb1, Axin, or Myc. Moreover, venlafaxine up-regulated Wnt/β-catenin genes such as: Ctnnb1 (3.80±0.16; 13.16±0.50; 4.92±0.41;$p< 0.01$ respectively for 1, 3 and 7 days), Axin1 (4.50±0.13;$p< 0.01$ at 1 day); Axin2 (5.06±0.36;$p< 0.001$ after 3 days), Myc (4.96±0.44; 1.20±0.43;$p< 0.01$, after 3 and 7 days), but not Ccnd1 and Notch1 genes expression. One way analysis of variance (ANOVA) showed a significant treatment effect between venlafaxine and RS67333 for Ctnnb1 ($F: 15.,02$ and $F:47.72$; $p<0.001$ respectively at 3 and 7 days), Axin1 ($F: 14.34$; $p<0.05$, and $F: 12.09$; $p<0.01$ respectively at 1 and 7 days), Axin2 ($F: 20.75$; $p<0.01$ and $F: 34.50$, $p<0.001$ respectively at 1 and 3 days), Myc ($F: 24.48$; $p<0.01$ and $F: 66.75$; $p<0.001$ respectively at 1 and 3 days), Notch1 ($F: 290.40$; $F: 1373.60$ and $F: 235.53$, $p<0.001$respectively at 1, 3 and 7 days) and Ccnd1 ($F: 171.98$ and $F: 28.59$; $p<0.001$ respectively at 3 and 7 days).

Our results show a differential gene expression profile of venlafaxine and RS67333 upon neuroplastic/neuroproliferative pathways: venlafaxine increases mRNA expression of the Wnt pathway genes whereas RS67333 increases expression of Ccnd1 and Notch1 genes. This drug-dependent regulation of neuroplasticity may account for the different onset of the antidepressant like-action of venlafaxine and RS67333.

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