# DIFFERENCES IN ANTIDEPRESSANT-INDUCED CHANGES IN CYCLIC AMP-DRIVEN GENE TRANSCRIPTION *IN VITRO*.

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Recent findings suggest that antidepressant drugs can cause alterations in transcription and expression of genes related to the cyclic AMP (cAMP) signalling pathway. (Fiore *et al*., 2003). It has been demonstrated, in animal models, that chronic antidepressant treatment results in an increased expression of the transcription factor cAMP response element binding protein (CREB) (Thome *et al*., 2000) although, in recent studies, we showed that some antidepressants reduced cAMP-dependent gene transcription in an *in vitro* cell model Richards *et al*.,2005).

The aim of the present study was to determine the effects of extended concentration ranges of different antidepressants on cAMP-mediated gene transcription in Chinese Hamster Ovary cells expressing the human $\beta_2$ adrenoceptor (CHO$\beta_2$SPAP cells). This was addressed by measuring the product of a secreted placental alkaline phosphatase (SPAP) reporter gene (according to Richards *et al*., 2005) which is under the control of cAMP acting via cAMP response elements in the gene's promoter.

Exposure of the cells to clomipramine, desipramine or norfluoxetine for 18 hours produced biphasic effects on SPAP production (Figure 1). At concentrations less than 2μM they induced significant ($p<0.05$, Student's t-test) increases in SPAP production in response to isoprenaline (1μM) stimulation. None of the antidepressants altered SPAP production in the absence of isoprenaline. However, at concentrations higher than 2μM, they produced concentration-dependent inhibitions of the SPAP production. The response profile of tianeptine (an atypical antidepressant which *enhances* serotonin uptake) was quite different. At sub-micromolar concentrations tianeptine was without effect, but at concentrations of 2 μM and above, SPAP production was increased in the absence or presence of isoprenaline. The stimulatory effect of tianeptine was not inhibited by the $\beta_2$ adrenoceptor antagonist ICI 118551 (1μM).

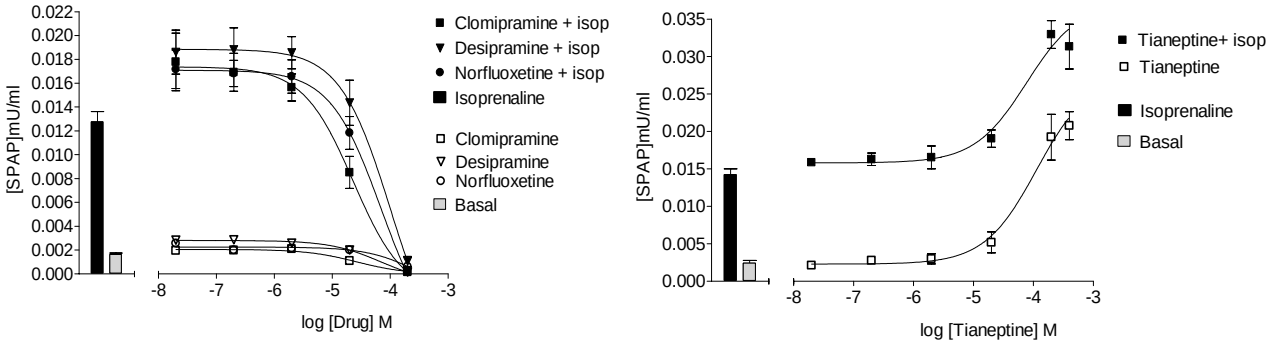


Figure 1 Concentration-response curves of isoprenaline-stimulated and unstimulated SPAP production in CHO$\beta_2$SPAP cells preincubated for 18 hours in presence of clomipramine, desipramine, norfluoxetine and tianeptine. Data points are means ± s.e.m of triplicate (n=3). Curves were constructed using GraphPad Prism software.

Chronic treatment of CHO$\beta_2$SPAP cells with the antidepressants (0.2μM) for periods of up to 3 weeks showed that all, except for tianeptine, slightly reduced maximum isoprenaline-stimulated SPAP production. Clomipramine and desipramine induced significant leftward shifts in the isoprenaline concentration response curve (control $EC_{50}$ = 20.1 ± 1.7nM) after 7 days of treatment ($EC_{50}$ = 4.5 ± 0.3 and 6.7 ± 0.5nM respectively; n=3) and these were maintained for up to 21 days ($EC_{50}$ = 4.2 ± 0.3nM and 6.0 ± 0.8nM respectively; n=3). However, norfluoxetine and tianeptine did not produce significant change in the isoprenaline $EC_{50}$ compared to the control ($EC_{50}$ = 11.7 ±2.5nM and 26.00 ± 4.1nM respectively; n=3).

These observations suggest that the atypical antidepressant tianeptine promotes adaptive responses via a different mechanism than that engaged by the monoamine uptake inhibitors. Whether this is reflected in differences in chronic responses *in vivo* remains to be determined.

Fiore, M. *et al*., (2003) *Current Neuropharmacol.*, **1**, 109-123.
Richards, J.K. *et al.,* (2005) *Biochem.Pharmacol.,* **70**, 762-769.
Thome, J. *et al*., (2000) *J. Neurosci.,* **20**, 4030-4036.