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Studies on the effects of acute and chronic dexamethasone treatment on the expression of both 5-HT_{2A} and glucocorticoid receptor mRNA in rat C6 glioma cells

A. ISLAM, S. L. HANDLEY, K. S. J. THOMPSON* AND S. AKHTAR

*Pharmaceutical Sciences Institute, Aston University, Aston Triangle, Birmingham B4 7ET, and *Knoll Pharmaceuticals, CNS Biology, R3 Pennyfoot Street, Nottingham NG1 1GF*

Corticosteroids secreted by the adrenal cortex readily enter the brain and have a modulatory action upon the expression of 5-HT and other neurotransmitter receptors via specific binding to intracellular receptor proteins, Chaouloff (1995). Adrenal steroids and changes in 5-HT_{2A} receptor expression have been extensively implicated in the pathophysiology of depression and schizophrenia, Hrdina et al (1993). Hence it is important to evaluate fully 5-HT_{2A} receptor expression and function within the CNS. We have been investigating the potential of down-regulating expression of the glucocorticoid receptor (GR) with antisense oligonucleotides in order to abrogate steroidal modulation of the 5-HT_{2A} receptor subtype. In the present study we investigated GR and 5-HT_{2A} receptor mRNA expression in an *in vitro* model comprising rat C6 glioma cells, which are known to express both receptors of interest.

C6 glioma cells were grown to confluency in the presence and absence of 1μM dexamethasone, after both acute (24 hours) and chronic (5 days) treatment. Total RNA samples were then extracted from these cell groups and analysed, by Quantitative Reverse Transcriptase-Polymerase Chain Reaction (QRT-PCR). GR and 5-HT_{2A} receptor mRNA was measured using the expression of a control cell protein (β-actin) for the linearisation and normalisation of the results obtained.

It was seen that acute treatment with dexamethasone resulted in a small but significant 3.7% increase in GR mRNA levels with a consequent significant 9.8% downregulation of 5-HT_{2A} receptor mRNA levels. Conversely, chronic dexamethasone treatment produced a significant 22.2% decrease in GR mRNA levels and a consequent significant 34.3% upregulation of 5-HT_{2A} receptor mRNA levels (table 1).

TABLE 1. Summary of the QRT-PCR results showing the changes in GR and 5-HT_{2A} receptor mRNA expression after acute and chronic 1μM dexamethasone treatment of rat C6 glioma cells compared to untreated cell groups (data from n = 3 ± standard deviation, $p<0.05$ vs control).

Treatment Regimen	% Change in GR mRNA Expression	% Change in 5-HT_{2A} Receptor mRNA Expression
ACUTE (24 hours)	+3.7	-9.8
CHRONIC (5 days)	-22.2	+34.3

In conclusion, the results show that the level of GR mRNA expression in C6 glioma cells is sensitive to the duration of dexamethasone exposure. However, more importantly these results also show that the action of dexamethasone on the GR results in the modulation of 5-HT_{2A} receptor mRNA expression via a possible inhibitory control mechanism through GR and the level of its mRNA expression. Furthermore, the inverse relationship between changes in GR expression and those of the 5-HT_{2A} receptor, are consistent with an inhibitory regulatory mechanism. These data provide a foundation upon which we can test the effects of reducing GR expression with antisense oligonucleotides.

(1). Chaouloff, F. (1995). *Fundam. Clin. Pharmacol.* **9:** 219-233.
(2). Hrdina, P.D. et al, (1993). *Brain Research.* **614:** 37-34.