# Effects of GHB, NCS- 382 and their combination on the expression of specific genes that affect the catalytic activity of steroid dehydrogenases.


## Abstract

Gamma hydroxybutyric acid (GHB) is a natural neurotransmitter found in the brain in low concentrations. GHB has been used in general anaesthesia and is currently used to treat narcolepsy and alcoholism. The abuse of GHB, especially in date rape sexual assaults, has increased in recent years. GHB has a rapid rate of metabolism causing it to disappear quickly, and criminal cases are often difficult to prosecute. Our previous microarray study aimed at extending the window of detection of GHB beyond 12 hours by measuring the GHBdependent changes in gene expression using blood THP-1 cells revealed that GHB induces changes in expression of specific genes that affect the catalytic activity of steroid dehydrogenases. GHB has been postulated to act as a specific agonist of GHB receptors and as well as a weak GABA (B) receptor agonist. To date, 6, 7, 8, 9-tetrahydro-5-hydroxy-5Hbenzocyclohept- 6-ylideneacetic acid (NCS-382), a compound structurally related to GHB, is the only compound reported to be an antagonist of the GHB receptor. The aim of this study is to determine the effect of NCS-382 alone and in combination with GHB on the relative expression of specific genes encoding steroid dehydrogenases and aldoketo reductases. THP-1 cells were treated with 10μM and 900μM concentrations of GHB, NCS-382 or both and the expression of specific genes was evaluated after 24h exposure to drugs using quantitative real-time PCR analysis. The results show that GHB and NCS-382 induces consistent changes in AKR1C1, AKR1C3, AKR1C4 and DHRS9 gene expression in blood THP-1 cells when they are used alone or in combination. The expression of AKR1C1, AKR1C3, AKR1C4, and DHRS9 mRNA levels were found to be reduced significantly by between 2 and 42 folds ($p<0.01$) in blood THP-1

cells after the treatment with 900μM of either GHB or NCS-382 or their combinations while the expression of HSD11B1 mRNA level was found to be reduced significantly by 2.25 fold ($p<0.05$) in blood THP-1 cells only after the treatment with 900μM GHB but not after treatment with NCS-382 nor their combination. These results indicate that the effect of GHB on the expression of AKR1C1, AKR1C3, AKR1C4, and DHRS9 genes is not mediated through its binding to the GHB receptor, but the effect of GHB on the expression of HSD11B1 may be mediated through its binding to GHB receptor.