Synthesis and biological analysis of anti-addiction effect and hepatotoxicity of tow baclofen analogues complexed with β-Cyclodextrin.

ASSIA KENICHE

Abstract: Aim and Objective: The excessive consumption of alcohol and the installation of a dependence is, in most cases, facilitated by favorable psychological factors which trigger and maintain the behavior of consumption. Examples more frequently encountered in individuals having difficulty with alcohol are in particular: one or more anxiety disorders, deficits in the capacities to manage stress and anxiety. The main objective of this work was study in vivo the anti-addiction effect and hepatotoxicity of tow baclofen analogues complexed with β-Cyclodextrin (βCD) on an alcohol-dependent rat model. Materials and Methods:The synthesis of two analogues ABF1 and ABF2 close to baclofen was reported. The structural determination of the two compounds was confirmed by NMR and IR analysis. The complexation of analogues with β-Cyclodextrin (βCD) was performed in water at room temperature (25 °C). The interactions of ABF with β-Cyclodextrin, and the stability constant (Ka) of the inclusion complex formed between them were investigated by using UV-visible spectroscopy. The biological effects of baclofen and the two analogues on alcohol dependence were studied in wistar rats.

The anti-addiction effect of the analogues was tested by measuring the alcohol intake and the variation of the animal behaviour. The toxicity of the compounds was also analysed on liver injury markers. **Results:** The amino-3-phenylbutanoic acid (ABF1) and 3,4,5-trihydroxy-N-(methyl-2-acetate) benzamide (ABF2) were synthesized. The complexation of both analogues of baclofen (BF) with β-cyclodextrin (βCD) (ABF- βCD) was realized and confirmed by the stability constant of the inclusion complex (Ka) and Job's method. The evaluation of anti-addiction activity in vivo showed that ABF1-βCD inhibits the consumption of alcohol at the doses equivalent to those of baclofen. Both baclofen analogues have shown an anxiolytic effect. Regarding the toxicity of the two compounds, our results showed that ABF1-βCD has less toxic effect than baclofen, it reduces the activity of ALT and AST enzymes. Histologically ABF1-βCD has no effect on structure of the liver in addition and has a protective effect against lesions alcohol-induced liver disease. **Conclusion:** Therefore, it can be suggested that ABF1 analogue combined with β-Cyclodextrin can be used as a treatment for alcohol dependence. Further clinical works are needed to confirm its effectiveness.