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Immunohistochemical Investigation of Heat Shock Proteins in Mice Teratomata after *in vivo* Administration of Sodium Valproate

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INTRODUCTION

The purpose of this study was the investigation of the mechanisms of valproic acid teratogenicity. It aims to identify and to enlighten the over-expression of the heat shock protein (HSP) by immuno-histochemical labelling, using the monoclonal antibody of heat shock protein 70 (Neomarkers, HSP70 Ab-2, Clone W27). The HSP is initiated and produced to serve a protective role against the cytotoxic and teratogenic drug administration. We focus mainly on the aetiology of the mechanisms involved in embryonic development, resulting in the production of malformed and diffused embryological tissues, the so-called teratomata. These are the defective and sub-developed embryonic masses, which were described morphologically by SEM and TEM, in our previous studies. The teratomata were counted and collected during an extended experimental study, applied on experimental animals, concerning valproic acid teratogenicity in embryonic and maternal organs.

Valproic acid (2-n-propylpentanoic acid) is a drug proved useful for the treatment of seizures, and is one of the major antiepileptic drugs in clinical use. Valproic acid is not recommended for women of child bearing age, as it has been shown to be teratogenic in humans, producing mainly multiple malformations on the neural tube, and secondary diverse types of malformations elsewhere. However, sometimes the administration of this drug is mandatory in women suffering from very persisting seizures, because seizures themselves can be harmful for the embryo and foetus, since they can provoke an oxidative stress, leading to massive cell apoptosis and teratogenicity.

METHODS

The sodium valproate, which we used, was obtained from Sanofi Winthrop Industry, France. Pregnant mice, treated with the drug were sacrificed with a lethal dose of CO_2, on the early morning of gestation day 18. The uteri were removed and the implantation sites were recorded and counted.

RESULTS AND CONCLUSIONS

We localized immuno-histochemically the heat shock proteins, on parts of embryonic tissues, where this protein is over expressed, due to a defend mechanism against the stressogenic agent that was administered, that is the valproic acid. Heat shock proteins are considered proteins, which are mostly over expressed in the cellular cytoplasm, as a signal protection of the cell against stressogenic actions, as apoptosis, due to teratogenic factors.

The results of our study show that there is a development of an oxidative stress, when valproic acid is administered in pregnant mice. This important finding may be used to enlighten the mechanisms of the teratogenic impact of the drug administration. Further studies, focused to explain the cell-to-cell interactions, are scheduled to be further applied in our experimental protocol.