Project: Cognitive Adverse Effects of In Utero Exposure to Medications: Role for Impaired Delivery of Thyroid Hormones into the Fetal Brain (293800 Fetal Thyroxine)

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Final report

The focus of the project has been shifted to investigating the effects of antiepileptic drugs (AEDs) on placental transporters, including those of thyroid hormones, folate and medications.

AEDs are among the most common teratogens prescribed to women of childbearing age. In particular, in utero exposure to valproic acid (VPA) has consistently been associated with worse pregnancy outcomes than exposure to other AEDs, in terms of structural malformations, poorer cognitive function of the offspring, and increased risk for childhood autism. Yet, it is recognized that situations exist in which VPA prescription to pregnant women is appropriate. Thus, it is important to better understand the molecular mechanisms of AED teratogenicity in order to minimize it.

Over the past few years we identified the placenta as a target of AED effects and a potential mediator of their teratogenicity. We demonstrated that several AEDs, mostly VPA, affect the expression of transporters for folates, thyroid hormones and xenobiotics in a human placental cell line (Figure 1).

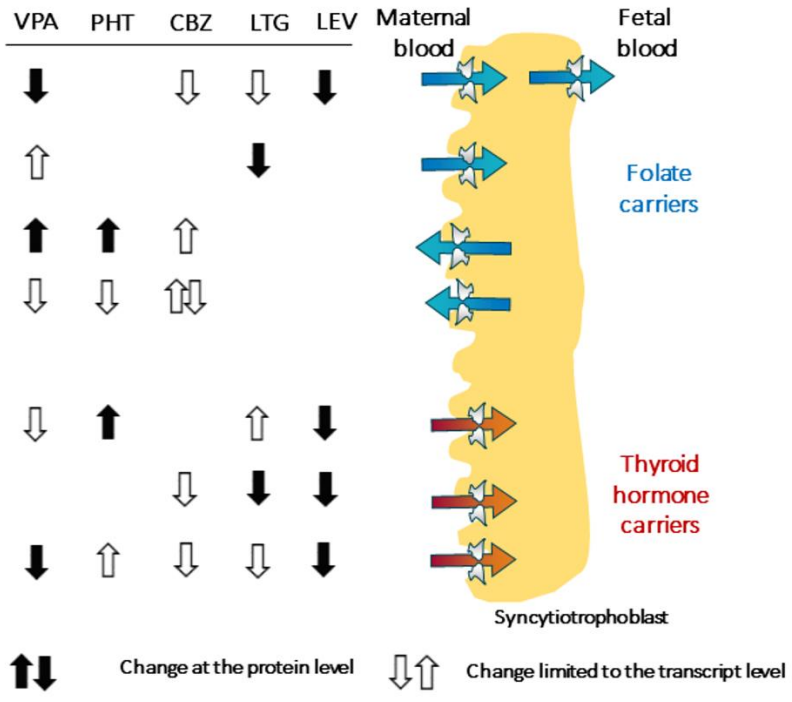

Figure 1. An overview of AED-induced alterations in BeWo cell carrier expression. Arrows demonstrate statistically significant changes in carrier protein or transcript levels with

regard to control, untreated cells. From: Rubinchik-Stern et al., Epilepsia. 2015;56:1023-32.

In parallel to the in vitro studies, we developed a near infrared imaging methodology, with indocyanine green (ICG) as a marker of placental barrier function. ICG is the only US Food and Drug Administration-approved near infrared (NIR) fluorophore and is being used in pregnant women with minimal transplacental transfer. Changes in fetal concentrations of this probe can indicate altered placental diffusion or transport. Using this method, we demonstrated that drugs that interact with transporters at the placenta and other body tissues can alter fetal exposure to ICG and potentially other compounds as well (Figure 2).

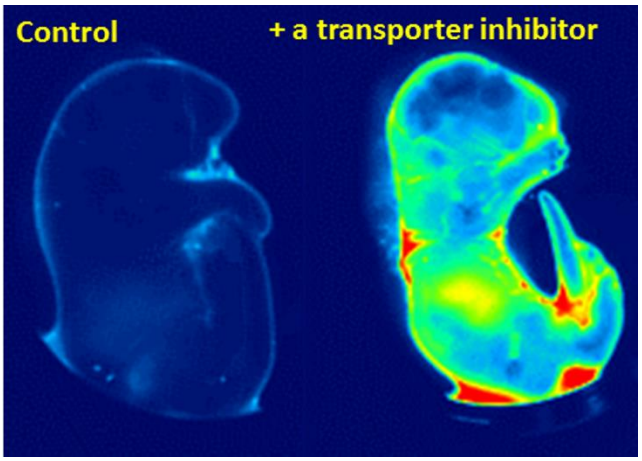

Figure 2. Near infrared fluorescence images of mice fetuses whose mothers were treated with ICG in the absence and the presence of rifampin. From: Bishara, Meir, et al., Mol Pharm. 2015;12:3351-7.

Our follow-up study evaluated the effect of valproic acid on the mouse placenta in terms of both transporter expression and probe distribution into the fetus. VPA treatment was associated with a 40% increase in ICG's accumulation in maternal liver in mid-pregnancy and a decrease by one fifth in late-pregnancy. Ex vivo, VPA treatment led to a 20% increase in fetal ICG emission in mid-pregnancy. In mid-pregnancy, the placental expression of several transporters for thyroid hormones and folic acid were lower in VPA-treated mice.

The observed changes in placental transporter expression and function support further research into the potential role of the placenta in the adverse pregnancy outcomes of VPA and other AEDs. We further demonstrated that near infrared imaging provides a non-invasive, non-radioactive tool for future studies on the effects of epilepsy and AED on tissue transport functions.