Fetal exposure to chemical carcinogens and environmental contaminants

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1 Introduction

In the modern industrialized world, pregnant mothers are inevitably exposed to chemical carcinogens including benzo(a)pyrene (BP). In many cases the exposure is from multiple sources and the exposure levels vary due to lifestyle factors such as diet and smoking. For instance, the most common sources of BP are cigarette smoke, flamed, grilled and smoked food, air pollution, exhausts and occupational exposures (Miller & Ramos, 2001; Dybing et al. 2008).

Currently, there is a growing concern that pollutants, which reach the fetus, may affect their health later in life. This idea, called "fetal origins of diseases", is gaining ground as more studies show how early exposure can alter developmental patterns and lead to diseases, sometimes decades later in life. The thalidomide catastrophe in the 1960´s made it evident that drugs can cross the placenta and may have harmful effects on the fetus. Also environmental contaminants may reach fetus if the mother is exposed.

In mammals placenta separates the maternal and fetal circulations during pregnancy. However, placenta is not merely a passive barrier. In addition to metabolic, endocrine and immunological functions, the placenta transfers oxygen, carbon dioxide, nutrients and waste products between the mother and the fetus. Because passive diffusion alone is not adequate to fulfil e.g. the fetal requirements for nutrients, placenta expresses a large variety of transporter proteins. ABCB1 and ABCG2 are transporter proteins that translocate compounds from placenta back to maternal circulation and thus decrease fetal exposure. Based on human data, both ABCB1 and ABCG2 are significantly expressed in the placenta throughout the pregnancy (for review see Myllynen et al. 2009).

2 Objectives of the research

In this project, we study placental transfer of environmental contaminants. We have also been interested in factors causing person to person variation in placental transfer, especially ABC transporters. Main focus has been on food carcinogens such as heterocyclic amines but for some of these compounds such as benzo(a) pyrene urban air is also considered as an exposure source.

3 Results

We have studied fetal exposure to food carcinogens and environmental contaminants using dual re-circulating human placental perfusion. In the human placental perfusion system the placenta is kept alive after delivery using artificial circulation (see e.g. Myllynen et al. 2008). Donating the placenta for research purposes after delivery does not affect the treatment of mother or newborn in any way because normally human term placentas are disposed after delivery.

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By using human placental perfusion we confirmed that 0.1 μM BP added to the maternal circulation reaches fetal compartment although the transfer rate is slow and the extent of transfer variable (Karttunen et al. 2010 submitted).

We have also recently shown that two food borne chemical carcinogens PhIP (Myllynen et al. 2008) and IQ (Immonen et al. 2010, submitted) cross placenta easily in perfusion. Both of these compounds have been reported to interact with ABCG2 transporter protein in other models. In perfusion of human term placenta, transfer of 14C-PhIP (2 μM) through the placenta resulted in fetal to maternal concentration ratio (FM ratio) of 0.72±0.09 at 6 hours. Interestingly, the specific ABCG2 inhibitor KO143 increased the transfer of 14C-PhIP from maternal to fetal circulation (FM ratio 0.90±0.08 at 6 hours, $p<0.05$) suggesting that ABCG2 restricts placental transfer of PhIP. ABCG2 protein expression in the placentas was inversely correlated with the fetal to maternal concentration ratio of PhIP ($R=-0.81$, $p<0.01$) suggesting that ABCG2 expression may be a source for the interindividual variation in fetal exposure (Myllynen et al. 2008).

In our most recent study, the placental transfer of IQ showed some person to person variation (Immonen et al. 2010, submitted). However, the experiments done using specific transporter inhibitors, as well as the transporter protein expression analyses suggested that ABCG2 does not significantly affect the transplacental transfer of IQ.

4 Relevance of the research

Our results suggest that there is person to person variation in the placental transfer of chemical carcinogens and environmental contaminants. Although most of our studies have been done using compounds to which exposure happens mainly via diet, these findings suggest that when estimating exposure to environmental contaminants, including urban air contamination, factors causing person to person variation should be taken into account. Understanding the toxicokinetic mechanisms and factors causing person to person variation in detail would clearly help in risk assessment processes.

References

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