Institutionen för Fysiologi och Farmakologi

CYP2C19 AND BRAIN DEVELOPMENT: IMPLICATIONS FOR SUSCEPTIBILITY TO ANXIETY IN A TRANSGENIC MOUSE MODEL

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ABSTRACT

The cytochrome P450-2C19 enzyme is involved in the metabolism of about 10 % of all drugs used today and displays high genetic polymorphism, causing absent, decreased or elevated enzyme activity that divides the population into different metabolic phenotypes. CYP2C19 enzymatic activity is also highly influenced by different substances including drugs and *in vivo* studies have shown that estradiol and 17α-ethinylestradiol, commonly used in hormone replacement therapy and oral contraceptives, decreased CYP2C19 mediated metabolism *in vivo* in humans. We investigated by which mechanisms this inhibition is mediated and found that the estrogens at rather high concentrations competitively inhibit CYP2C19 activity, but more importantly, at low clinically relevant concentrations caused a decreased gene transcription through a novel estrogen responsive element half-site in the *CYP2C19* promoter region. Such estrogen CYP2C19 interactions are important to consider during drug development.

Recently is was described by our laboratory that subjects lacking functional CYP2C19 enzyme had lower depressive symptoms based on analyses of a large twin cohort. To investigate CYP2C19's potential effect on behavior and brain function a transgenic mouse model expressing the human *CYP2C19* gene was characterized. We found that CYP2C19 is expressed in the developing fetal but not in adult brain. Newborn pups homozygous for the *CYP2C19* gene insert display high neonatal lethality and severe brain malformations with complete commissural agenesis and a severely reduced hippocampus. Hemizygous mice (CYP2C19Tg-Hem) showed less extensive phenotypes, thus survived and were characterized at 7 (adolescent) and 15 weeks (young adult) of age. CYP2C19Tg-Hem mice display increased stress sensitivity and anxiety-like behavior, which was more pronounced in young adult mice. Furthermore, a smaller hippocampal formation was seen at both ages as measured by manual outlining of brain sections and confirmed in adult mice by magnetic resonance imaging. The CYP2C19Tg-Hem mice hippocampal formation furthermore displayed an increased neuronal activation, or *c-fos* expression, after acute stress. This might be explained by the drastic reduction of immature neurons and the reduced number of GABAergic interneurons observed in the dentate gyrus of the hippocampus in the *CYP2C19* transgenic mice.

The results indicate that CYP2C19 expression during brain development increases the susceptibility to develop anxiety-related disorders later in life. This is interesting since, as mentioned above, absence of CYP2C19 enzyme is protective against depressive symptoms in humans, a phenotype displaying high comorbidity with anxiety disorders. Since the pathophysiology behind major depressive disorder and anxiety disorders is still mostly unknown, the model presented could be used for the investigation of factors important in the pathogenesis of these disorders and might also be used in the development of novel anxiolytic drugs.