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Age, sex, and hormonal status can be additional variables in prenatal dexamethasone exposure

Libor Velíšek, MD, PhD

Saul R. Korey Department of Neurology, Dominick P. Purpura Department of Neuroscience, Albert Einstein College of Medicine, 1300 Morris Park Ave, K 314, Bronx, NY 10461, USA

Abstract

This Letter to Editors refers to “Prenatal dexamethasone exposure affects anxiety-like behaviour and neuroendocrine systems in an age dependent manner” by M. Nagano et al. (60)364-371, 2008. The letter points to unexpected decrease of glucocorticoid receptors, which is rather consistent with anxiolytic effects and suggests that age, sex, and hormonal status of subjects may represent additional confounding variables.

Keywords

corticotropin-releasing factor; glucocorticoid receptors; anxiety; postnatal development; sex; ovarian cycle

Sirs,

I have read with great interest the paper of M. Nagano et al. titled “Prenatal dexamethasone exposure affects anxiety-like behaviour and neuroendocrine systems in an age dependent manner”. In this article the authors show that prenatal exposure to 50 µg/kg of dexamethasone daily between gestational day 16-21 has age-specific effects on postnatal behaviors and expression of molecules associated with HPA axis function. Specifically, rats at postnatal week (PW) 10 (adults), but not at PW4 (prepubertal) and PW7 (barely postpubertal), exhibit signs of increased anxiety behaviors. CRF in the hypothalamus is decreased in PW4 and PW10 rats and glucocorticoid receptor expression is attenuated in central and medial nuclei of amygdala at PW7 and PW10.

The anxiety results in the adulthood correlate well with the data of Wellberg et al. (Wellberg et al., 2001). Experiments performed in my laboratory expand these findings and indicate that in very young rats (PW2) the effects of prenatal exposure to a synthetic steroid are different. After exposure to two injections of 400 µg/kg of betamethasone on gestational day 15, we found a decrease in anxiety determined by an elevated plus maze paradigm and in the open field. As these tests for anxiety involve rather (ventral) hippocampus than amygdala, which is associated with more prominent fear (Treit et al., 1993; Bannerman et al., 2004), we further substantiated these results by demonstrating an increase in hippocampal expression of NPY (Velíšek, 2006), a powerful anxiolytic molecule (Heilig, 2004). While the data on the

Corresponding Author: Dr. Libor Velisek, MD, PhD, Corresponding Author's Institution: Albert Einstein College of Medicine.

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expression of CRF and glucocorticoid receptors shown in the paper are compelling, the discussion (or lack of thereof) on their link to anxiety behaviors is puzzling: CRF is a strong anxiogenic substance and its increase in relevant structures as indicated above could account for increases in anxiety (Stenzel-Poore et al., 1994). However, the authors investigated only mRNA, not looking at the actual product, which in fact may be differentially regulated by posttranscriptional effects of corticosteroids (Muller et al., 2002). On the other hand, decrease in glucocorticoid receptors provides fewer targets for glucocorticoids, which are also anxiogenic molecules: Thus, the net effect of glucocorticoid receptor decrease is anxiolytic (Tronche et al., 1999). The unexpected finding of the present study warrants further discussion. Finally, interpretation of rearing behavior for anxiety is very difficult and some authors associate increased anxiety with increased rearing rate instead of decreased (McGregor et al., 2004).

Some differences from other studies can be indeed explained by different experimental protocols (stress versus injection; single versus repeated exposure; dose; etc.) and substances used (dexamethasone vs. betamethasone vs. natural corticosteroids). However, important additional variables appear to be the **age**, **sex**, and probably also **status of gonadal hormones** in experimental subjects. As proposed by Bruce McEwen (McEwen, 2007), the effects of steroid hormones frequently follow an inverted U-shape curve and this observation may also apply to the additional variables listed above. The results of the study warrant further research in the field because many women receive synthetic corticosteroids (betamethasone and dexamethasone) during the second half of pregnancy and it appears that with repeated exposures some behavioral problems may develop in children (French et al., 2004).

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