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SUSCEPTIBILITY OF THE VASCULARIZATION IN THE PARAVENTRICULAR NUCLEUS OF THE HYPOTHALAMUS TO ALTERED GABA RECEPTOR SIGNALING, ENDOGENOUS SEX HORMONES, AND PRENATAL STRESS

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The paraventricular nucleus (PVN) of the hypothalamus plays important roles in regulating sympathetic vasomotor tone, food intake, stress responses and cardiovascular function (1). The PVN also contains a denser matrix of blood vessels than the surrounding brain regions that develops postnatally in rats (2) and mice (3). A series of studies are being conducted to determine factors that are important for the development of this unique vascularization. Antisera directed against platelet endothelial cell adhesion molecule, which is present on endothelial cells that line blood vessels, were used to visualize large and small diameter blood vessels by immunohistochemistry. $GABA_B$ receptors play a role in PVN development during fetal life (4) and mice lacking the R1 subunit of the $GABA_B$ receptor were examined to see if this influence extends to the postnatal vascularization. Vascular branching was taken as an index of vascularization in a region of interest inside the PVN. Results showed $GABA_B$ receptor knockout mice had a significant decrease in vascular branching than wild type control mice on postnatal days 19 and 20 (5). There was a trend for females to have more branch points than males in $GABA_B$R1 subunit knockout and control, indicating that sex hormones may also play a role during development. Since endothelial cells contain estrogen receptor β (ERβ), this suggests the potential for circulating sex hormones to alter the density in vascularization in the PVN. To test this hypothesis, steroidogenic factor 1 knockout (SF-1 KO) mice are being used. SF-1 is a key regulator of gonadal and adrenal development (6). SF-1 KO mice are born without gonads and adrenal glands and are not exposed to endogenous gonadal sex steroid hormones. Therefore, it is hypothesized that male SF-1 KO mice will have more branch points compared to wild type. In addition, the synthetic glucocorticoid dexamethasone has been shown to increase the number of endothelial cells in vitro (7), which suggests the potential to increase angiogenesis in vivo. Dexamethasone is administered prenatally for proper lung development in humans, but the extent this plays on the developing vascularization in brain is unknown. To being to test this role in a preliminary experiment, dexamethasone was injected into pregnant heterozygous SF-1 KO mice from embryonic days 11 to 17. Results will determine if excess levels of glucocorticoid stimulation, alone or in combination with the lack of endogenous sex steroids during postnatal development, will alter the vascularization in the PVN. Changes in vascular branching may alter the ability of the PVN to properly receive signals and respond appropriately.

References

1. Swanson LW, Sawchenko PE. Hypothalamic integration rganization of the paraventricular and supraoptic nuclei. Annu Rev Neurcosci 1983; 6: 269–324.

2. Menendez A, Alvarez-Uria M. The development of vascularization in the postnatal rat paraventricular nucleus: a morphometric analysis. J Hirnforsch 1987; 28(3): 325–9.

3. Schow MJ, Knoll JG, Frahm KA, Zhang Q, Tobet SA. Abstracts of the 40th Annual Meeting of the Society for Neuroscience. San Diego, 2010.

4. McClellan KM, Stratton MS, Tobet SA. Roles for gamma-aminobutyric acid in the development of the paraventricular nucleus of the hypothalamus. J Comp Neurol 2010; 518(14): 2710–28.

5. Frahm KA, Schow MJ, Tobet SA. Abstracts of the 40th Annual Meeting of the Society for Neuroscience. San Diego, 2010.

6. Luo X, Ikeda Y, Parker KL. A cell-specific nuclear receptor is essential for adrenal and gonadal development and sexual differentiation. Cell 1994; 77(4): 481–90.

7. Maca RD, Fry GL, Hoak JC. The effects of glucocorticoids on cultured human endothelial cells. Br J Haematol 1978; 38(4): 501–9.