INTEGRATIVE STUDIES OF THE BODY FLUID HOMEOSTASIS: PHYSIOLOGICAL AND MOLECULAR ASPECTS OF THE NEUROENDOCRINE CONTROL AND CLINICAL AND EXPERIMENTAL EVALUATION

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The hypothalamo-neurohypophysial system plays a fundamental role in the maintenance of body fluid homeostasis by secreting vasopressin and oxytocin in response to osmotic and volume changes of the extracellular volume. ANP (atrial natriuretic peptide) is mostly localized in the heart, but ANP and its receptor are also found in hypothalamic and brainstem areas involved in body fluid volume and blood pressure regulation. Blood volume expansion acts not only directly on the heart, by stretch of atrial myocytes to increase the release of ANP, but also on the brain ANPergic neurons through afferent inputs from baroreceptors. The activation of the neuroendocrine pathways involved in the control of body fluid homeostasis induce: 1) modifications in the water (thirst) and salt intake; 2) alterations of the autonomic nervous system; 3) activation of the rennin-angiotensin-aldosterone system (SRAA); 4) Vasopressin (AVP) and Oxytocin (OT) secretion from neural lobe; 5) and of the atrial natriuretic peptide (ANP) from the heart.

We are interested in the determination of the neuroendocrine pathways, as well as the main phenotypes, the participation of the hypothalamus-hypophyseal-adrenal axis, both in normal conditions and under endotoxic shock, involved in the control of body fluid homeostasis. We will also use an experimental model of diabetes insipidus in rats to evaluate the HPA axis in the absence of magnocellular AVP. Molecular studies and the interaction of ANP and the rennin angiotensin system will be conducted in patients with congenital adrenal hyperplasia under basal conditions and after head down tilting.

This thematic project emphasizes the role played by brain ANP and its interaction with neurohypophyseal hormones in the control of body fluid homeostasis and includes:

- Project 1: The neuroendocrine control of hydroelectrolytic balance
- Project 2: Regulation of Oxytocin (OT), vasopressin (AVP) and prolactin release during the experimental septic shock
- Project 3: Regulation of hypothalamus-hypophyseal-adrenal axis (HHA)
- Project 4: Central diabetes insipidus
- Project 5: Congenital adrenal hyperplasia and the hydroelectrolytic homeostasis.
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- Following isotonic blood volume expansion (EVEC), the expression of FOS protein in oxytocinergic neurons (FOS-OT) indicates their activation, whereas vasopressinergic neurons (Fos-AVP) are inhibited, which correlates with plasma OT and AVP levels. These effects were inhibited by dexamethasone pretreatment.

The FOS expression in different cell populations of the PVN can be differentially regulated by short- and long-term absence of glucocorticoid negative feedback and also by stress-related excitatory and/or inhibitory neural inputs.

Under stress conditions, there is an activation of several systems, including the autonomic, neuroendocrine system (hypothalamic-pituitary-adrenal axis) and cardiovascular system. Nitric oxide has been implicated in the variations of plasma concentrations of several hormones (prolactin, AVP, and OT) in response to stress induced by lipopolysaccharide. The release of AVP induced by endotoxemia involved the production of NO from iNOS that inhibit AVP secretion, and consequently fall of the mean arterial pressure.

High ACTH and corticosterone levels found in rats with pituitary stalk compression under water intake and salt loading conditions suggest an upregulation of the HHA axis, with a preserved adaptive mechanism to chronic stress.

Mineralocorticoid deficiency in 21-OH deficiency is counteracted by a decreased ANP secretion in order to preserve fluid and electrolyte homeostasis.

Mutations in the Hsd3b2 gene induce elevated basal and ACTH-stimulated delta 5-17P levels and delta5-17P/cortisol ratios. Therefore, these data refine the hormonal criteria proposed to predict more accurately 3beta HSD2 deficiency.