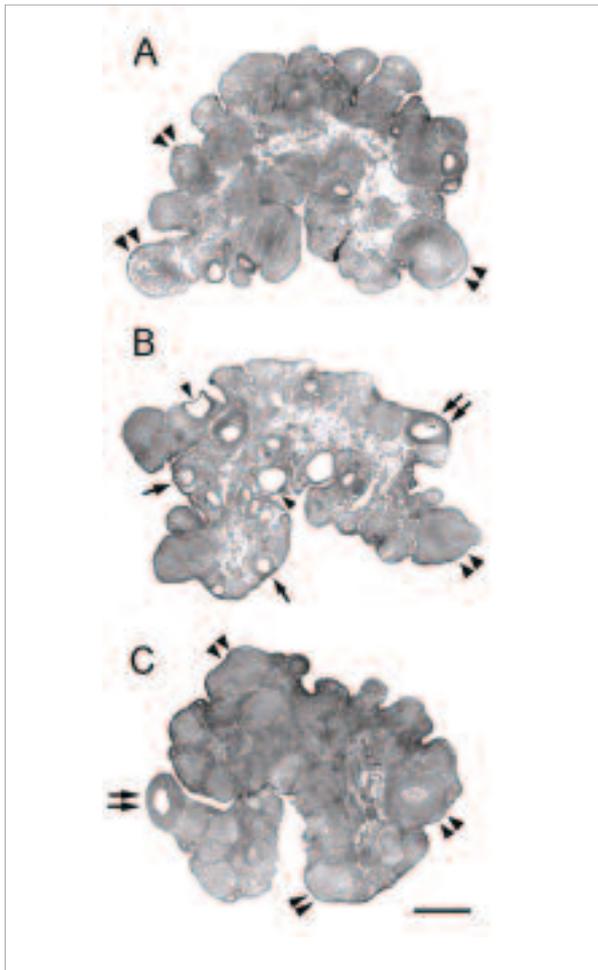


NEUROENDOCRINE REGULATION AND EFFECTS OF STRESS ON THE REPRODUCTIVE FUNCTION OF FEMALE RATS

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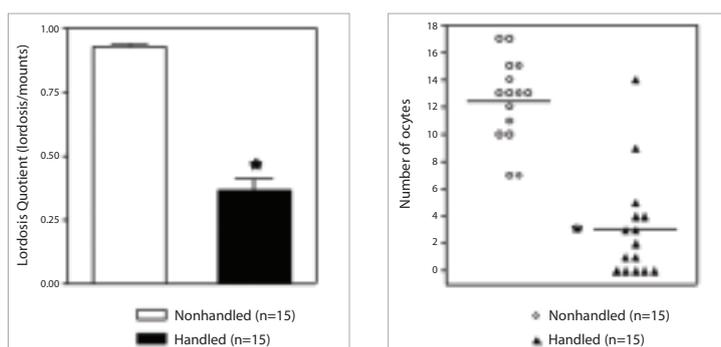


Cold stress effect on ovarian morphology. Ovarian morphology on estrus of rat maintained at ambient temperature (A). Exposed to 8 weeks of cold stress with no surgical treatment (B) or with previous LC lesion (C). Arrow: antral follicle with hyperthecosis. Double arrow: type III follicle. Arrowhead: follicular cyst. Double arrowhead: corpus luteum. Scale bar = 1 mm. Bernuci et al, Endocrinology, in press.

The knowledge of the control mechanisms of fertility has implications in social (e.g., the option of conception or anti-conception in humans, populational control, and therapeutic development), economic (e.g., improvement of the fertility of domestic or captive wild species to provide food and clothing) and environmental (e.g., maintenance or reestablishment of ecosystems equilibrium, environment repopulation) aspects. Natural reproduction depends on complex interactions of hormones produced in the brain, pituitary, gonads and other organs and tissues in order to prepare the gametes and induce sexual behavior to ensure fertilization. It is well known that fertility can be markedly influenced by stress, however the interaction between the hypothalamus-pituitary-gonadal axis (HPG) and stress system (hypothalamus-pituitary-adrenal axis, sympathetic system and neurotransmitters brain systems) remains poorly understood. Gonadotropin-releasing hormone (GnRH) neurones constitute the final output pathway of the neuronal network controlling gonadotropins preovulatory surges and ovulation. This neuronal network depends on direct and indirect actions of several neuromediators whose specific roles are little known, and it is also a pathway through which the stressful stimuli may interfere on gonadotropins release and ovulation. This project investigates: 1) neural circuits and neuromediators (norepinephrine, angiotensin II, neuropeptide Y, nitric oxide, leptin, serotonin, oxytocin) involved in tonic and cyclic control of gonadotropins and prolactin secretion as well as their modulation by ovarian steroids; 2) the neuroendocrine and sympathetic control of ovarian function; and 3) the effects of stressor stimuli in the neonatal period or in adulthood on the control of reproductive functions.

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

We have identified important components of the GnRH neuronal network that regulate gonadotropin release as well as mediate stress effects on reproductive function. It was shown that receptors for neuromediators are expressed in neurons of the GnRH network, and that estradiol and progesterone modulate the ovulation process through their receptors in neurons by producing neurotransmitters such as norepinephrine, serotonin, neuropeptide Y, oxytocin and angiotensin. Noradrenergic neurons of locus coeruleus (LC), classically implicated in the response to stress, are also related to the reproductive function. Thus, the control of both functions by the same neurons provides a link between stress and reproduction. We have found that brief maternal separations during the first 10 postnatal days induce definitive and stable marks in few specific areas of the central nervous system as an important reduction in the number of LC neurons, which, in turn, lead to infertility during their adult life, characterized by a reduction in sexual behavior, in the preovulatory surge of luteinizing hormone (LH), hormone responsible for ovulation, and therefore, a decrease in the ovulation rate. In addition, chronic cold stress induced activation of the LC neurons and a polycystic ovary syndrome (PCOS) condition characterized by the presence of follicular cysts in the ovary, increased estradiol and testosterone plasma levels, irregular estrous cyclicity and reduced ovulation. The involvement of the central norepinephrine in the development of PCOS was proven since rats with LC lesion did not develop PCOS in response to cold stress. These data open a new field to investigate the etiology of the PCOS and suggest that attenuation of the stress effects, such as decrease in the central noradrenergic tonus, could help diminish the symptoms of PCOS and increase fertility in women presenting this syndrome. We also demonstrated that ovarian steroids modulate AT1 receptor expression in the brain which may mediate the deleterious effects of stress.



Neonatal handling decreases sexual behavior and ovulation rate. Lordosis quotient was measured on the evening of proestrus day. The number of oocytes was counted on the estrus day and e symbol represents one animal. * Significantly different from the nonhandled group. Rainecki et al, *Neuroendocrinology* in press

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