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The interplay of sex and gender on the reactivity of the endocrine stress axis in humans

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In response to psychological and physiological stressors, metabolic systems of the human body change their activation to increase energy availability, and allow the organism to cope with the real or perceived increase in demand. An inappropriate stress response, perhaps caused by a dysregulation of the metabolic stress response systems, is believed to be associated with an increased risk for development of (psycho) pathology.The observation that men and women differ in their stress responsivity is important in this context, as men and women also systematically differ in their risk for developing disease. Women are more likely to suffer from autoimmune disorders, anxiety disorders, dementia, to name just a few. Investigating the reasons for the stress responsivity differences between men and women has thus been an important area of research for several decades, and we are now at a point where we better understand some of the underlying mechanisms. There are both biological and cultural effects at play that contribute to establishing these reactivity differences between men and women, with recent findings providing limited support for the idea that cultural effects might have the greater impact. The current selective review summarizes some of the key findings from the last 25 years to provide an overview of this interesting topic.

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"Every cell is sexed, every organism is gendered"

Motto of the Institute of Gender and Health of the Canadian Institutes of Health Research (CIHR)

Introduction

There is no question that men differ from women during their reproductive years in their stress reactivity. Stress reactivity is measured in different ways, including subjective perception of stress, autonomic nervous system markers like heart rate, galvanic skin response, or blood pressure, and endocrine stress markers like the human stress hormone cortisol. Especially the endocrine system has been under intense investigation, as a dysregulation of the hormonal system in charge of secreting cortisol, the hypothalamic-pituitary adrenal (HPA) axis, is considered a significant risk factor for various forms of psychopathology, including depression, anxiety disorders, burnout, and psychosis [1]. Interestingly, women are more likely to be affected by these disorders than men, in a ratio that varies from 2:1 to 4:1, depending on the specific disorder in question [2•].

However, the direction of these stress reactivity differences is actually inconsistent between studies, with women sometimes showing a stronger, and sometimes a weaker response, when compared to men. What factors are contributing to these differences, and the direction of these differences, has been under intense investigation for almost three decades, and has identified methodological aspects (the type of stressor used), biological (the interaction of the endocrine stress response system with other endocrine systems), and cultural (the beliefs and values that are different between men and women). In the following, these factors will briefly be reviewed, with specific examples illustrating their effects.

Of stressors, hormones and culture

One of the best known stress tests in the laboratory, the Trier Social Stress Test (TSST), consists of 5 min public speaking and 5 min mental arithmetic in front of an audience, with the audience typically consisting of at least two people of mixed gender. In addition, the performance is video-taped, and audio-recorded. The typical scenario is that of a mock-job interview, where the subject is asked to deliver a five minute speech to justify why he or she is the best candidate for a hypothetical job. In contrast to a real interview, there is no interaction with, or feedback from, the audience — they keep a neutral facial expression throughout, and if the subject pauses in his or her presentation, they remain silent for up to 20 s before asking the subject to continue to talk as long as there is still time.

After the five minute speech, the subject is asked to solve an arithmetic task — something like counting down from

3867 in steps of 17, with the instruction to start over when making a mistake. This laboratory test is effective in 70 to 100% of participants, with increases in the sympathetic nervous system (heart rate, blood pressure) and endocrine stress axis (ACTH, cortisol) that for cortisol range between 50 and 100% over baseline [3].

Early on, it was observed that men showed higher cortisol reactivity than women [4•,5•], and the question arose where these differences were coming from. Subsequent research investigated mainly two hypotheses: One, that the differences had to do with biological differences between men and women, that is, they were a function of sex. Two, that the differences had to do with sociocultural differences between men and women, that is, they were a function of gender. For both hypotheses, supporting results could be found.

Looking into sex differences, researchers soon identified the interplay of the endocrine stress axis with another endocrine system, the hypothalamic-pituitary-gonadal (HPG) axis, as a possible mechanism with which differences could be explained. The HPG axis in women during their reproductive years predominantly stimulates production of estrogens from the gonads. Estrogens, in return, are associated with two- to three fold higher numbers of cortisol binding globulin (CBG), which — as the name suggests — bind cortisol [6]. As cortisol bound to CBG can't bind to receptors, or cross the blood-brain barrier, this in effect reduces the availability of active cortisol in the system. This further explains the difference in cortisol concentration in saliva versus plasma, as only the free fraction is transferred into saliva. This is the case for both men and women as up to 95% of cortisol is bound at all times — however, in women the larger numbers of CBG might imbalance the distribution further. It is as if the women have a blunted, or temporarily impaired, stress response system, when estrogens and thus CBG levels are high.

As estrogen production and availability itself varies over the course of the menstrual cycle, soon the question emerged whether free cortisol availability would then be systematically linked to the different stages of the menstrual cycle in women. During the follicular phase, which is the first to follow the menses, the follicles in the ovaries (the female gonads) begin to grow and start to produce estrogens. Thus, during the follicular phase, which roughly lasts the first half of the menstrual cycle, estrogen levels are very low in the beginning but then continue to rise more and more until just before ovulation, they reach their highest levels. After ovulation, they remain high for a short period but if no pregnancy occurs, they drop continuously over the second half of the menstrual cycle until they are at their lowest point at the time of the menses. This picture is changed completely when women during their reproductive years are taking estrogen-containing oral contraceptives; here, estrogen levels are continuously high (even higher than during the follicular phase) during much of the menstrual cycle with the exception of the last seven days of the cycle.

Given the various levels of estrogens in these different scenarios, Kirschbaum *et al.* [5•,7] investigated this systematically and observed that the greater the level of estrogens in circulation, the smaller was the observed endocrine response to the standardized TSST. This was quite convincing as the level of free cortisol followed a dose response of the (assumed) amounts of circulating estrogens: oral contraceptive users showed the smallest response, followed by follicular phase women, luteal phase women, and men [5•].

Progesterone, which is particularly high around ovulation and during the first half of the luteal phase, has also been shown to have dampening effects on cortisol reactivity when pharmacologically administered [8], but effects on cortisol reactivity during the menstrual cycle phase appear to be less consistent, perhaps because progesterone is also produced from the adrenals in response to stress [9].

As a side note, postmenopausal women and women who are pregnant show a very different HPG activity — in menopausal women not undergoing hormonal treatment therapy, estrogens and progesterone production has come to an almost complete halt and thus no effects on HPA axis activity are observed [10]. In contrast, pregnant women especially during the third trimester show a significantly increased activity of both the HPA and the HPG axis, having to do with fetus development, thus preventing investigations of HPG / HPA axis interaction [11].

In addition to biological factors, almost from the beginning, there was also evidence that gender and socialization played a role in the stress response — here, studies that manipulated the effects of the perception of the situation contributed to this. Again it was Kirschbaum *et al.* [12•] who provided the pioneering work in this area by showing that if men received social support when being exposed to psychosocial stress, their HPA axis response to the TSST was reduced as a function of the closeness to the individual providing social support. In comparing three groups (no support, stranger support, and partner support), they could show that while the stranger support diminished the cortisol response somewhat, the partner support showed the strongest decline in cortisol response when compared to the control group with no support. However, the opposite could be shown when women were stressed — here, women in the no support group showed smaller responses than the men, but these responses actually increased when they were supported by a stranger, and were strongest when their own partner