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Psychophysiological response to social stressors: Relevance of sex and age

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Abstract

Background: Understanding the factors involved in the psychophysiological response of people in acute stressful situations is crucial to the prevention and treatment of stress-related health problems. We aim to integrate the results of studies investigating the role of sex and age in the inter-individual variability in several biomarkers of the stress response **Methods:** We summarize the main findings of our research group and other laboratories regarding sex and age-related differences in the psychophysiological response to psychosocial stress. **Results:** Sex-related differences in the stress response are observed in blood pressure and cortisol, but not in heart rate, heart rate variability, or salivary alpha-amylase. Additionally, age may explain differences in cortisol levels and basal sympathetic nervous system activity. **Conclusions:** The results highlight the importance of taking sex and age into account in order to understand the stress response and its possible negative effects on health.

Keywords: Stress response, cortisol, autonomic nervous system, sex, age.

Resumen

Respuesta psicofisiológica a estresores sociales: relevancia del sexo y la edad. **Antecedentes:** entender los factores involucrados en la respuesta psicofisiológica ante situaciones de estrés agudo es crucial para prevenir y tratar problemas de salud relacionados con el estrés. El objetivo es integrar los resultados de estudios en humanos relacionados con el papel del sexo y la edad en las diferencias individuales en la respuesta de estrés en diferentes biomarcadores. **Metodología:** se integran los principales resultados de nuestro grupo de investigación y de otros laboratorios centrados en las diferencias debidas al sexo y la edad en la respuesta psicofisiológica a situaciones de estrés psicosocial. **Resultados:** se observan diferencias en la respuesta de estrés entre hombres y mujeres en presión sanguínea y en niveles de cortisol, pero no en frecuencia cardíaca, variabilidad de la frecuencia cardíaca y alfa-amilasa. Además, la edad influye en los niveles de cortisol y en la actividad basal del sistema nervioso simpático. **Conclusiones:** los resultados ponen de manifiesto la importancia de tener en cuenta el sexo y la edad de los participantes para poder entender la respuesta de estrés y sus posibles efectos en salud.

Palabras clave: respuesta de estrés, cortisol, sistema nervioso autónomo, sexo, edad.

The physiological response to psychosocial stressors has been related to the onset, maintenance, or exacerbation of numerous and diverse types of dysfunctions that can reduce life expectancy (cardiovascular diseases, cancer, infections, etc.) (Sapolsky, Romero, & Munck, 2001). Considering the relevance of stress in the development of diverse pathologies, it is important to determine the role of different factors that can be involved in the stress response in order to improve the efficacy of prevention and interventions for stress-related disorders and diseases (McEwen, 2015).

Sex and age are considered two important factors in understanding inter-individual differences in the physiological stress response. Within this context, during the past decade, our group has developed a research project focused on investigating the role of sex and age in the relationship between psychosocial stress and cognitive performance in healthy people (i.e., Mneme Project). Here we present a short review focused on findings observed in psychoneuroendocrinological studies that have investigated the response to acute psychosocial stressors. First, we briefly explain the basis of the stress response, and, second, we synthetize the main results obtained in our laboratory on age and sex differences in the stress response in the context of research conducted by other groups; to do so, we reviewed the recent literature published on these two factors in specialized journals. The purpose of this short review is to present the sex- and age-related differences that can be observed in the physiological stress response depending on the biomarkers assessed.

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Stress response

Two body systems are mainly activated in stressful situations. First, the Autonomic Nervous System (ANS) is rapidly triggered, leading to increases in catecholamine levels, blood pressure

(BP), and heart rate (HR), and changes in Heart Rate Variability, among other physiological changes (Allen, Bocek, & Burch, 2011; Chrousos, 2009). Additionally, an increase in salivary alpha-amylase (sAA) levels is observed, with this enzyme being considered a biomarker of the stress-induced response of the sympathetic nervous system (SNS; see Rohleder & Nater, 2009).

The second system involved in stressful situations is the hypothalamus-pituitary-adrenal axis (HPA-axis). When the HPA-axis is activated, glucocorticoids are released into the bloodstream (Jacobson, 2005), and cortisol is the most important glucocorticoid in humans. This increase in glucocorticoids peaks approximately 20 to 40 minutes after the onset of the stressor, and the return to basal levels occurs after approximately one hour (Ulrich-Lai & Herman, 2009). Importantly, the activity of the HPA-axis and the secretion of glucocorticoids are steadily regulated by a negative feedback system that maintains glucocorticoids within tolerable levels (Sapolsky et al., 2001). Two types of receptors, the mineralcorticoid receptors (MRs) and glucocorticoid receptors (GRs), are involved in this negative feedback, which is mainly performed by the frontal cortex, amygdala, and hippocampus. These structures have a large number of MR and GR. When high levels of glucocorticoids are received, they send inhibitory inputs to the paraventricular nucleus through an indirect pathway that blocks the synthesis and secretion of corticotropin-releasing hormone and arginine vasopresine, which, in the long run, reduces the secretion of glucocorticoids (Sapolsky et al., 2001).

Sex-related differences in the stress response

Earlier studies reported that a larger BP response to acute stress is observed in young men than in young women, whereas the opposite results are found for HR (Kajantie & Phillips, 2006), suggesting that men are vascular reactors, whereas women are cardiac reactors (Allen, Stoney, Owens, & Matthews, 1993). However, these results have not been consistently observed (e.g., Kelly, Tyrka, Anderson, Price, & Carpenter, 2008), and more recent research has shown a different pattern of findings. Using the Trier Social Stress Test (TSST), a laboratory-based psychosocial stress task (Kirschbaum, Pirke, & Hellhammer, 1993), we observed a similar HR response in men and women in five different studies that included healthy young (age range: 18–35) and older (age range: 54-78) participants, (Almela et al., 2011; Almela, 2014; García-Rubio, Espin, Hidalgo, Salvador, & Gómez-Amor, 2017; Puig-Pérez et al., 2015; Zandara et al., 2016). As in the case of HR, we did not observe significant differences in HRV between men and women in a recent study with healthy young adults and adults with generalized social phobia symptoms, with HRV measured as the Low-frequency/High-frequency balance (a marker of sympathetic/parasympathetic balance) and measured as the root mean square of R-R intervals (a marker of parasympathetic activation) (García-Rubio et al., 2017; results observed with healthy participants only). Together, our results for HR, and HRV coincide with a recent meta-analysis that explored 186 studies and concluded that no differences between men and women in HR and HRV are observed, but that men show higher BP responses to stress than women (Brindle, Ginty, Phillips, & Carroll, 2014). Thus, recent research supports the idea that sex differences would be observed in BP, but not in HR or HRV.

In addition to HR, sex does not moderate the stress-induced sAA response. In fact, we failed to find sex-related differences in stress-induced sAA (Almela et al., 2011; García-Rubio et al., 2017; Hidalgo et al., 2012; Pulopulos et al., 2013), and these results are consistent with previous findings from other research groups (for a review, see Rohleder & Nater, 2009).

Together, these results indicate that sex plays an important role in the BP response to stress, but not in other ANS activity indicators such as HR, HRV, or sAA. These differences may have important implications, given that sex-related differences in the BP response to stress may contribute, at least in part, to the fact that a higher prevalence of coronary heart disease is observed in men than in women (Mozaffarian et al., 2015). However, it is important to investigate whether different types of stressors (social vs physical) might modulate these sex differences.

Several studies have shown that sex moderates the cortisol response to stress. Increases in cortisol levels during laboratory-based psychosocial stress tasks are up to twice as high in men as in women (Kudielka, Hellhammer, & Wust, 2009) when cortisol levels are measured with saliva samples and the menstrual cycle phase is not considered. It has been proposed that this sex-related difference might be explained by the circulating levels of corticosteroid binding globulin protein (CBG) (Kudielka & Kirschbaum, 2005). As the cortisol concentrations measured in saliva reflect only the cortisol not bound to CBG (approximately 5-10% of the total cortisol secreted), these sex differences could be explained by higher concentrations of CBG in women than in men (Kajantie & Phillips, 2006). Moreover, when the menstrual cycle is considered, differences between women can also be observed. In a study where we strictly controlled the menstrual cycle by measuring basal body temperature, we observed that women in the luteal phase showed a higher cortisol response than women in the follicular phase or those taking oral contraceptives (Espin et al., 2013). In another study, we confirmed a blunted cortisol response to stress in these two latter groups compared to men (Hidalgo et al., 2012). However, when we analyzed the area under the curve with respect to the increase (AUCi) in the two groups of women, comparing the stress and control situations, only women

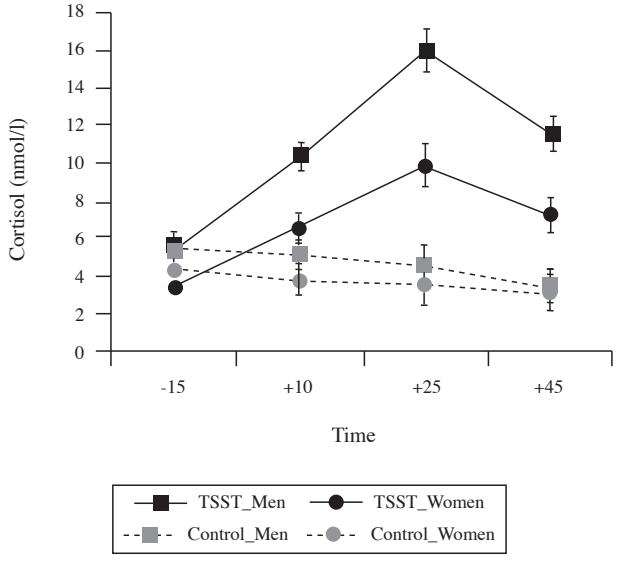

Figure 1. Cortisol response to stress. Means (±SEM) of salivary cortisol concentrations in the TSST and control conditions for men (N = 51) and women (N = 48). Adapted from Hidalgo et al. (2015)

in the follicular phase responded significantly to the stressor (unpublished data). Finally, regarding postmenopausal women, older men tend to show a higher cortisol response to stress than older women (Almela et al., 2011; Pulopulos et al., 2013). Figure 1 shows the differences in the cortisol response to stress in young and older men and women.

Our results are consistent with previous research showing that the cortisol response of women in the luteal phase is similar to the one observed in men and higher than the one observed in women in their follicular phase or when taking oral contraceptives (Kajantie & Phillips, 2006; Kudielka & Kirschbaum, 2005). It has been proposed that these differences are due to differences in estrogen levels because this hormone increases CBG concentrations (Kudielka & Kirschbaum, 2005). Together, these results highlight the importance of considering sex and hormonal status, including menstrual cycle differences, when studying the stress response and its effects.

Age-related differences in the stress response

Following initial research, Seals and Dinenno (2004) suggested that the primary effect of aging on the human ANS is an elevation of the tonic sympathetic activity. However, the specific change in the ANS response to stress observed in older people is controversial. Studies investigating age-related differences in the response to stress in terms of HR or plasma catecholamines have reported no changes (Almela et al., 2011; Esler et al., 1995; Wood, Maraj, Lee, & Reyes, 2002), a decreased response (Kudielka et al., 2004; Strahler et al., 2010), or even an enhanced response to stress in older people compared to young adults (Pascualy et al., 1999; Uchino, Uno, Holt-Lunstad, & Flinders, 1999). Brindle et al. (2014), in their meta-analysis, found an association between aging and a decrease in sympathetic activation under stress, especially in the HR response, as older people tend to show a lower HR response to stress. In contrast, no age differences in HRV (as a measure of the vagal tone) were observed (Brindle et al., 2014). Regarding age differences in the sAA response, and coinciding with Seals and Dinenno (2004), we observed that older people have an elevation in tonic sympathetic activity. However, we did not find differences in the sAA response to stress between young and older people (Almela et al., 2011). In contrast to our results, an attenuated response was observed in older adults in Strahler et al. (2010). Importantly, to induce the stress response, both studies used the same stress task (i.e., TSST). However, in our study we used a longer preparation phase (anticipatory stress), which could have made the stress task more stressful, triggering a higher stress response in our participants (González-Bono et al., 2002). Considering these results, it is possible that age differences in the sAA response would be observed in mild, but not more intense, stressful conditions. However, more research is clearly needed to understand the age differences in the sAA response to stress.

Regarding cortisol levels, evidence suggests that young and older people would also show a different HPA axis response to stress (for a review see, Kudielka et al., 2009). Supporting this idea, a higher cortisol response to stress has been observed in healthy older people compared to young people (e.g., Almela et al., 2011; Kudielka et al., 2004; Strahler et al., 2010; Traustadóttir, Bosch, & Matt, 2005). However, these results have not always been found (Kudielka et al., 2000; Rohleder et al., 2002). In this regard, in a recent study we observed a higher cortisol response in young adults than in older people (Hidalgo et al., 2015). When we compared the protocol of this study to our previous experiment using the same stress task (i.e., TSST) (Almela et al., 2011), the most important difference was found in the age of the panel. In Almela et al. (2011), the age of the panel was similar to the age of the older group, whereas in Hidalgo et al. (2015) the age of the panel was similar to that of the young group. Thus, it is possible that older people show a greater cortisol response when they are evaluated by their peers than by younger people.

As an explanation for the higher cortisol response observed in older people, several authors have suggested that this age-related change might be due to a reduction in the density of the cortisol receptors (MR and GR) in the aging brain, which would cause worse regulation of cortisol levels in older individuals (Buechel et al., 2014; Mizoguchi et al., 2009; Nichols, Zieba, & Bye, 2001). Supporting the hypothesis of a loss of HPA-axis negative feedback with aging, studies using pharmacological stimulation of the HPA-axis have consistently observed an elevated HPA-axis response in older people compared to young adults (e.g., Born, Ditschuneit, Schreiber, Dodt, & Fehm, 1995; Luisi et al., 1998). These results suggest that older people may be less sensitive to changes in cortisol levels, decreasing the effectiveness of the negative feedback system in reducing the secretion of cortisol by the HPA-axis.

It is important to note that personality dimensions may play a key role in ANS and HPA-axis functioning in basal and stress conditions. Thus, they should be taken into account when investigating age-related differences because they could also contribute to inter-individual differences in the biological stress systems (Carver & Connor-Smith, 2010). In line with studies carried out in the last decade to analyze the associations between negative psychological factors and pathogenesis, as well as positive attitudes toward health (Chida & Hamer, 2008; Steptoe, Dockray, & Wardle, 2009), our group investigated the role of some traits and state psychological factors in the stress response in older people. Regarding negative psychological factors, several studies showed that trait neuroticism and depressive symptomatology could be related to a disrupted physiological stress response in young people (Lahey, 2009), but few studies have investigated this relationship in older people. In our study, we observed that people with higher depressive symptomatology showed higher cortisol release, but decreased cardiovascular response, whereas trait neuroticism was not relevant to the psychophysiological stress response in healthy older people (Puig-Pérez, Villada, Pulopulos, Hidalgo, & Salvador, 2016). On the other hand, we observed that trait optimism, a protective factor, contributed to a better psychophysiological response, facilitating a less exacerbated cardiovascular and endocrine response to stress in healthy older people (Puig-Pérez et al., 2015) and an increase in the similarity of the stress response of older people with type 2 diabetes to the response of their healthy older counterparts (Puig-Pérez, Hackett, Salvador, & Steptoe, 2017). Moreover, other dimensions and state variables should be taken into account, such as appraisal, self-efficacy, or coping style, in addition to the behavior shown in the response to stress. For instance, we found that in post-menopausal women, behaviors that reflect active coping strategies (i.e. affiliative behaviors) were related to better autonomic regulation, whereas in premenopausal women, cortisol increases and recovery seemed to be modulated by passive and reactive behaviors (i.e. Submission and Assertion) (Villada et al., 2017). Together, these

results highlight the importance of considering trait and state psychological factors when investigating age-related differences in the stress response.

Conclusions

In this review, we have presented results and findings of several studies carried out in our laboratory and others that have investigated the role of sex and age in the physiological response to acute psychosocial stress.

We found that sex and age affect the stress biomarkers studied differently. Thus, sex-related differences can be observed in the cortisol and BP response to stress, but not in HR, HRV and sAA responses (e.g., Almela, 2014; García-Rubio et al., 2017; Puig-Pérez et al., 2015; Zandara et al., 2016). Young and older men show higher cortisol responses to stress than women (e.g., Hidalgo et al., 2012; Pulopulos et al., 2013), although this difference is not observed when men are compared to women in the luteal phase of the menstrual cycle (Espin et al., 2013). In addition, age-related differences are found only in the cortisol response to stress, with older people showing higher cortisol increases than young people (Almela et al., 2011). However, it is important to note that older people may show lower cortisol response when they are evaluated by young people (Hidalgo et al., 2012). Additionally, a heightened sympathetic tone is observed in older people (Almela et al., 2011). Therefore, a general conclusion is that sex and age factors modulate the HPA-axis response to stress, with men (and especially older men) showing a larger cortisol response. Moreover, a heightened SNS activity is observed in older people, and men show a higher stress-induced BP increase than women. However, no sex or age-related differences are observed in the SNS response to stress when sAA and HR are used as biomarkers. Taking these results into account, we consider that it is crucial to include a similar number of participants of both sexes when investigating the stress response because the results can vary considerably depending on the composition of the sample. Additionally, the hormonal status and menstrual cycle and the age of the participants should always be controlled because they can affect the cortisol response to stress and the sympathetic tone.

Some questions and issues remain unanswered. One important question is at what age the differences in the stress response can be observed. The response to this question would offer critical information about when people may be more prone to developing stress-related diseases common in older people (e.g., cardiovascular diseases). Moreover, it is necessary to address the modulating role of psychological factors in the stress response and, consequently, the effect of stress on cognitive processes (Puig-Pérez et al., 2015; Puig-Pérez et al., 2016; Pulopulos et al., 2015). It is important to investigate whether these factors play a different role in the stress response depending on the sex and age of the participants.

It should be noted that there are a number of confounding factors that may also contribute to the differences described in this short review. Apart from the effect of age, it is also possible that other factors such as previous and current health problems (e.g., Hypertension, type 2 diabetes) and medication use can affect the circadian rhythm of cortisol (e.g., Pulopulos, Hidalgo, Puig-Pérez, & Salvador, 2016; Puig-Pérez et al., 2016; Strahler et al., in press) and the physiological response to stress (Puig-Pérez et al., 2016; Strahler et al., in press). Moreover, although all the studies included in this review used the TSST or similar stress tasks (speech delivery, arithmetic task, or a combination of these two along with cognitive tasks) as methods to induce the stress response, variations in the stress tasks protocols, such as the length of the habituation phase, the sex of the panel and/or their attitude toward the participant may affect the cortisol response (Goodman et al., 2017). It is possible that such variations, or others not investigated in Goodman et al. (2017), also affect other biomarkers' response to stress. Further studies are needed to systematically investigate which changes in the stress task protocol can affect the sex- and age-related differences in the physiological response to stress.

In conclusion, sex and age modulate the HPA-axis response to stress, with men showing a larger cortisol response. Moreover, a heightened SNS activity is observed in older people, and men show a higher stress-induced BP increase than women. However, no sex or age-related differences are observed in the ANS response to stress when sAA, HR, and HRV are used as biomarkers. This review highlights the relevance of taking sex and age into account in understanding the stress response.

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