

New directions in psychoneuroendocrinology: from methods to applications

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The International Society of Psychoneuroendocrinology brings together clinicians and researchers from many different fields, including, but not limited to, neuroscientists, psychiatrists, endocrinologists, immunologists, geneticists and psychologists. The continuous focus of the society is loosely based on stress and endocrine regulation, and its interdisciplinary approach has always been one of its major strengths. Attendees benefit from discussions across a wide range of disciplines. This year's meeting in Berlin, Germany, was under the theme of 'Modern Psychoneuroendocrinology: Circadian Rhythms' and focused on glucocorticoid signaling in the brain, epigenetic mechanisms of stress regulation, the neurobiology of trust and the social brain and personality and pathology. This brief article reviews selected highlights from a total of 18 keynotes, symposia and workshops presented at the conference.

KEYWORDS: α -amylase • ACTH • cortisol • CRF • dexamethasone • hypothalamic–pituitary–adrenal axis • oxytocin • personality • saliva • trust

Glucocorticoid signaling in the brain

The implication for stress-related psychopathology as a consequence of different glucocorticoid signaling in the brain was discussed in this symposium, which was chaired by Ronald De Kloet (Leiden University, The Netherlands).

Numerous studies have shown that the glucocorticoid signaling in the brain might be different in stress-related psychopathology, and the course of the disease, remission and relapse might also be affected by variations in glucocorticoid signaling [1]. However, the exact mechanisms of this effect have so far not been thoroughly investigated.

Elisabeth Binder (Max Planck Institute for Psychiatry, Germany) presented data on the role of FKBP5, a co-chaperone of the heat shock protein 90, which is involved in regulating glucocorticoids [2]. Using different methods including microarray gene expression, and endocrine and epigenetic data, she could show how functional polymorphisms of FKBP5 might affect stress regulation via the hypothalamic–pituitary–adrenal (HPA) axis. Specific alleles

in the *FKBP5* gene might be responsible for an increased induction by glucocorticoids within the ultrashort feedback loop of glucocorticoid receptor (GR) sensitivity in the CNS system. This might dampen the feedback, leading to prolonged or higher glucocorticoid responses after stress. The same portions of the gene might further be associated with depression and post-traumatic stress disorder. Some preliminary data suggest that epigenetic mechanisms might further affect the regulation of this gene. Taken together, the central role of FKBP5 in regulating negative feedback of the HPA axis makes this an important research target to better understand risk and resilience of the individual in developing stress-related disease.

Danielle Champagne (Leiden University) presented data from both rodent and zebrafish models to demonstrate the effects of early life environment on GR expression [3]. In the rodent, the presented data demonstrated how variations in early life maternal care induced by differential amounts of licking and grooming can lead to changes in hippocampal plasticity and emotional learning mediated by GR expression. Extending

from previous studies, she could show how some of these changes might be adaptive, since the stress seems to prime the rodent to learn better under the same conditions present during the critical development periods – that is, low maternal care animals learn better in high-stress conditions as compared with adults, while high maternal care animals learn better in low-stress conditions. Finally, a new model of the effects of variations of sibling quantity in early life social environment on stress regulation in adulthood was presented in zebrafish.

Heather Abercrombie (University of Wisconsin-Madison, WI, USA) was next to present in this symposium, showing human data from a functional MRI (fMRI) study. Depressed subjects and controls received 15 mg hydrocortisone or placebo in a counterbalanced design prior to a memory test. This study tested for the effects of hydrocortisone on brain activation during memory encoding and retrieval of emotional words, comparing depression versus normal controls. After hydrocortisone, brain activation was significantly different only in depressed subjects. Further sex differences were observed in the depressed group, with women showing a different hippocampal response compared with men after hydrocortisone. Also, the effects of hydrocortisone were both related to hippocampal function during memory encoding and recall performance some days later. Of note, only subjects with early-life adversity showed a bias towards negative emotional memory as evidenced by *post hoc* analysis. Taken together, this study demonstrates the possibilities that cortisol administration in combination with memory paradigms in depression and early-life adversity can yield in studies utilizing fMRI.

Carmine Pariante (King's College London, UK) finished the symposium by presenting data on the involvement of glucocorticoids in neurogenesis in humans [4]. In his studies, Pariante uses hippocampal fetal progenitor cells treated with antidepressants to show an increase of neuronal differentiation. When adding the GR antagonist RU486, this effect is abolished. On the other hand, using the GR agonist dexamethasone in combination with the antidepressant increases progenitor cell proliferation, which is also abolished when using the GR antagonist. Taken together, the data were interpreted as showing that the neurogenesis effects of antidepressants in the hippocampus are dependent on GR-dependent mechanisms, including protein kinase A signaling, GR phosphorylation and specific gene activation. At the end of this talk, a critical discussion ensued, alerting the audience to the fact that only a few studies currently exist on the topic, and further research is needed.

New methods & approaches in psychoneuroendocrinology

The direct or mediating impact of specific phenotype variables on the regulation of different hormonal systems was discussed in this symposium, which was chaired by Markus Quirin (University of Osnabrueck, Germany) and Jens Pruessner (McGill University, QC, Canada).

While many studies have reported some associations between phenotype variables and endocrine regulation in the past, these investigations were often limited by the fact that they

concentrated on one component of one hormonal system. Although it is well known that significant inter-relationships between different systems exist, limitations in methodologies and resources have, in the past, often led to single-hormone or single-system approaches [5]. The present symposium thus showed some new approaches to considering multiple systems when studying hormone–phenotype relationships.

The first study, presented by Rainer Düsing (University of Osnabrueck, Germany), combined oxytocin with HPA axis regulation and investigated how high or low emotional regulation (ERA) abilities are associated with the effects of oxytocin on HPA stress regulation. Using a double-blind placebo-controlled design, 36 male students with either high or low ERA were randomly receiving either 24 IU of oxytocin or placebo. They were then exposed to a public speaking stressor, and cortisol was repeatedly measured.

Subjects with impaired ERA showed a reduced cortisol response to stress after oxytocin, and an increased cortisol response after placebo. The results suggest that subjects with low ERA benefit from oxytocin, while this hormone has no effect on stress regulation if ERA is high. These findings were discussed against the current background of oxytocin literature showing differential effects of oxytocin administration on trust and attachment [6,7]. Further studies should take into account phenotype characteristics such as ERA when studying oxytocin.

The next presentation by Daina Crafa (University of Osnabrueck) on the relationship between the cortisol awakening response (CAR) and the menstrual cycle phase took into account experienced self-determination. In 33 young women not using any contraceptives, first individual differences in self-determined control were assessed using standard questionnaires, as well as measures of the CAR and subjective stress both during the luteal and follicular phases of menstruation. The results showed a significant effect of cycle phase on the relationship between CAR and self-determination: while there was no relationship between these two variables during the follicular phase, during the luteal phase the CAR of women with low self-determination was significantly different from those with high self-determination. Furthermore, only during the luteal phase did high CAR levels predict an increase of experienced stress in individuals with low self-determination.

The findings were discussed as highlighting the importance of considering other hormonal systems – including, but not restricted to, the hypothalamic–pituitary–gonadal axis as demonstrated here – when studying the relationship between HPA axis regulation and personality variables [8,9].

In the third presentation, Julie Andrews from the Douglas Mental Health University Institute (Montreal, QC, Canada) presented a new investigation method – the combined dexamethasone/Trier Social Stress Test (TSST) paradigm. The rationale for this new method is the idea that to better understand the interaction between different stress systems, one approach could be to control for the activity of one system while studying the other. Along this line of thought, this study aimed to develop a new stress paradigm that keeps HPA axis activity constant while exposing subjects to psychosocial stress.

Here, 30 healthy male participants were tested, either after a dose of placebo, or dexamethasone the night before being exposed to the TSST. As expected, saliva cortisol levels were at the lower detection limit after dexamethasone, and showed a normal robust increase in the placebo group. Interestingly, there were no effects of suppressing HPA axis activity on salivary α -amylase, systolic or diastolic blood pressure. However, there was a marginal higher subjective stress response during the TSST in the dexamethasone group and, most pronounced, a 10 base point increase in the experimental group after suppressing HPA axis activity.

The results were discussed as demonstrating a significant interaction between the two stress systems, albeit not entirely in the expected direction [10]. The main effect seemed to be on the baseline heart rate, which warrants further investigation but could be an interesting point of study for research into the long-term effects of stress.

The final presentation of the symposium was given by Nida Ali, also from the Douglas Mental Health University Institute, on the effects of early-life adversity on the relationship between the sympathetic nervous system and the HPA axis. Previous research has

repeatedly shown strong effects of early life adversity on the regulation of each system, but few studies have looked at these systems together. In the current study, the two systems were compared by computing a dynamic ratio of amylase over cortisol and cortisol over amylase, respectively, and investigating the association with early life adversity and current levels of chronic stress. In 37 healthy subjects with either high or low early life adversity, a systematically higher positive relationship with measures of chronic stress and depression was found as compared with salivary α -amylase or cortisol alone.

These findings were discussed as demonstrating the importance of looking into several systems together, rather than concentrating on stress associations of either system alone [11].

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References

- Chrousos GP, Kino T. Glucocorticoid signaling in the cell. Expanding clinical implications to complex human behavioral and somatic disorders. *Ann. NY Acad. Sci.* 1179, 153–166 (2009).
- Binder EB. The role of FKBP5, a co-chaperone of the glucocorticoid receptor in the pathogenesis and therapy of affective and anxiety disorders. *Psychoneuroendocrinology* 34(Suppl. 1), S186–S195 (2009).
- Claessens SE, Daskalakis NP, van der Veen R, Oitzl MS, de Kloet ER, Champagne DL. Development of individual differences in stress responsiveness: an overview of factors mediating the outcome of early life experiences. *Psychopharmacology (Berl.)* 214(1), 141–154 (2011).
- Anacker C, Zunszain PA, Cattaneo A *et al.* Antidepressants increase human hippocampal neurogenesis by activating the glucocorticoid receptor. *Mol. Psychiatry* 16(7), 738–750 (2011).
- Cicchetti D, Rogosch FA. Personality, adrenal steroid hormones, and resilience in maltreated children: a multilevel perspective. *Dev. Psychopathol.* 19(3), 787–809 (2007).
- Bartz J, Simeon D, Hamilton H *et al.* Oxytocin can hinder trust and cooperation in borderline personality disorder. *Soc. Cogn. Affect. Neurosci.* DOI: 10.1093/scan/nsq085 (2010) (Epub ahead of print).
- Kosfeld M, Heinrichs M, Zak PJ, Fischbacher U, Fehr E. Oxytocin increases trust in humans. *Nature* 435(7042), 673–676 (2005).
- Nepomnaschy PA, Altman RM, Watterson R, Co C, McConnell DS, England BG. Is cortisol excretion independent of menstrual cycle day? A longitudinal evaluation of first morning urinary specimens. *PLoS One* 6(3), e18242 (2011).
- Wolfram M, Bellingrath S, Kudielka BM. The cortisol awakening response (CAR) across the female menstrual cycle. *Psychoneuroendocrinology* 36(6), 905–912 (2011).
- Lee RM, Borkowski KR, Leenen FH, Tsoporis J, Coughlin M. Interaction between sympathetic nervous system and adrenal medulla in the control of cardiovascular changes in hypertension. *J. Cardiovasc. Pharmacol.* 17(Suppl. 2) S114–S116 (1991).
- Gordis EB, Granger DA, Susman EJ, Trickett PK. Salivary α -amylase-cortisol asymmetry in maltreated youth. *Horm. Behav.* 53(1), 96–103 (2008).