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Glucocorticoid pulsatility : implications for brain functioning

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Glucocorticoid pulsatility

Implications for brain functioning

Ratna Angela Sarabdjitsingh

Angela Sarabdjitsingh

Glucocorticoid pulsatility: implications for brain functioning

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Implications for brain functioning

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Ratna Angela Sarabdjitsingh

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List of abbreviations

| | |
|----------|-------------------------------------|
| ABS | automated blood sampling |
| ACTH | adrenocorticotrophic hormone |
| ADX | adrenalectomy |
| ANS | autonomous nervous system |
| AVP | arginine vasopressin |
| ChIP | chromatin immunoprecipitation |
| CNS | central nervous system |
| CORT | corticosterone |
| CRH | corticotrophin releasing hormone |
| Dex | dexamethasone |
| DG | dentate gyrus |
| GH | growth hormone |
| GnRH | gonadotrophin-releasing hormone |
| GR | glucocorticoid receptor |
| GRE | glucocorticoid response element |
| HPA axis | hypothalamic-pituitary-adrenal axis |
| IHC | immunohistochemistry |
| i.p. | intraperitoneal |
| IR | immunoreactivity |
| ISH | in situ hybridisation |
| MR | mineralocorticoid receptor |
| PVN | paraventricular nucleus |
| WO | washout |

Preface

Everything has rhythm, hormones are no exception. Rapid oscillations in steroid levels are a ubiquitous phenomenon in hormonal systems and are not restricted to glucocorticoids. For instance, highly fluctuating levels of gonadotrophin-releasing hormone, growth hormone and insulin have been described previously. Furthermore, frequency encoding via circulating hormones as intracellular signals is a well accepted method of communication within mammalian systems. Accordingly, these ultradian hormone patterns are tightly controlled and are consequently required for appropriate action of receptors and target tissue sensitivity. However, dysregulation of the secretory pattern of single hormones in disease states and subsequently the underlying signalling mechanism, is well defined in most cases.

Pronounced ultradian and circadian rhythms in the hormones of the hypothalamic-pituitary-adrenal (HPA) axis (i.e. glucocorticoids), one of the body's major neuroendocrine axes, were already demonstrated several decades ago. Until now, the clinical relevance of the pulsatile nature of glucocorticoids was poorly understood or sometimes even regarded as not important. Its evolutionary conservation across many species however implies biological significance. Indeed, glucocorticoids have been proven to be crucial for a plethora of bodily functions, for example emotion, cognition and the central mechanism underlying the adaptation to stress. Furthermore, disturbances in the characteristic temporal pattern of glucocorticoid exposure have often been described in stress-related pathology. However, the significance of glucocorticoids secretory patterns for physiology, stress responsiveness and nuclear receptor signalling is still largely unexplored. As such, this thesis will discuss glucocorticoid pulsatile patterns and the implications for HPA axis activity and brain functioning.

