Glucocorticoid pulsatility : implications for brain functioning

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voordat je het kunt zijn

Loesje

Table of contents

List of abbreviations

ABS	automated blood sampling
ACTH	adrenocorticotropic 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.