Numerous studies employing immediate-early gene expression or functional magnetic resonance imaging have provided evidence of the neural networks which are activated by different stress modalities and which serve to coordinate the different elements of the stress response. For example, as expected from the activation of the hypothalamo-pituitary-adrenal axis, c-fos mRNA or its protein product Fos can be detected in the hypothalamic paraventricular nucleus in response to both psychological (exteroceptive) and physical (introceptive) stress stimuli. However, these two modalities are differentiated by their activation of limbic and brainstem nuclei, notably areas of the amygdala and bed nuclei of the stria terminalis display marked modality-dependent activation. Nevertheless, while different stress modalities may utilize distinct neural pathways which converge on common outputs, each may be generalised to comprise two elements. Firstly, an afferent limb comprising either a cognitive or sensory system that responds to introceptive or exteroceptive stimuli which under certain conditions or above a particular threshold can take on a ‘stressful’ quality. Secondly, an efferent limb comprising a network which distributes this ‘stress signal’ to the various effector systems to generate an appropriate physiological or behavioural response. Diversity of stress responses and integration within this network is proposed to be achieved through a hierarchy of overlapping pathways, with some having the capacity for direct, rapid activation in response to an immediate threat to homeostasis, while higher order pathways provide a distributed signal to several output systems. It serves little purpose to identify the neurochemical phenotype of all the neurones which contribute either to the afferent or efferent limbs of these stress-activated networks. However, certain transmitters have been shown to have a pre-eminent role in regulating stress response, either acting to coordinate activation of diverse elements of the response (notable corticotropin-releasing hormone), or to attenuate activation of the response network and, thereby, have properties of endogenous anti-stress agents (e.g. oxytocin or GABA). It is suggested that the organisation of the response-activating network enables these key transmitters to fulfil important roles in integrating the stress response or in modulating its magnitude. Both classes of transmitter are particularly important as they may play important roles in the aetiology of stress-related disorders and, consequently have become the focus for pharmacological intervention. Furthermore, the involvement of transmitter receptor subtypes opens the possibility for the development of selective ligands for modulating the diverse responses to stress. In this respect an on-going challenge is to translate the knowledge of transmitter involvement into clinically effective therapies.

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of the response to stress and produces lasting effects in preparation of future events. The two complementary modes of operation of cortisol/corticosterone depend on the phase and context of the stress response, the bio-availability of the hormone and the target cell response. The molecular basis of this dual mode of operation of cortisol is formed by two types of receptors - mineralocorticoid (MR) and glucocorticoid (GR) receptors - that bind in vivo cortisol and corticosterone with an order of magnitude difference in affinity. Thus, a concept has evolved in which MR and GR mediate the dual mode of operation of cortisol in limbic brain to coordinate the onset and termination of the physiological and behavioural adaptations to the stress. MR and GR belong to interacting signalling networks that underlie adaptive processes from appraisal of novel situations and prediction of upcoming events to recovery from the challenge and storage of the experience in the memory. Thus questions to be addressed are: which factors determine balanced MR/GR interaction? How is MR/GR imbalance related to a vulnerable phenotype? How does the MR/GR balance contribute to individual differences in vulnerability? Which biomarkers can reveal imbalance in stress system operation related to MR and GR?

Supported by the Royal Netherlands Academy of Arts and Sciences, and the Netherlands Foundation for Scientific Research.

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Symposia 20P

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SA12

Stress, cognitive function and cell adhesion molecules
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Stress is a potent modulator of brain and cognitive function. Depending on the circumstances, stress can either facilitate or impair memory processes. Our research aims to unravel how neurobiological mechanisms related to learning and plasticity are affected by stress conditions leading to opposite effects on memory function (facilitating vs. impairing). By focusing on key plasticity-related proteins, we investigate the mechanisms that translate stress' actions into such diverse cognitive outcomes. Our work has implicated the neural cell adhesion molecules of the immunoglobulin superfamily, NCAM and L1, on the effects of stress on brain and cognitive function (Sandi, 2004; Sandi & Touyarot, 2006). In the hippocampus, memory-facilitating and memory-impairing stress conditions lead to opposite patterns of expression of cell adhesion molecules (Sandi et al. 2005; Venero et al. 2006), which underscore these molecules as potential mediators of the cognitive effects of stress. Although glucocorticoid treatments do not reproduce exactly the changes on plasticity-related proteins induced by stress, available evidence indicates that these steroid hormones play a major role on stress-induced modulation of both cell adhesion molecules, and other plasticity-related proteins. These findings (1) have implications to understand stress-related cognitive disturbances (Cambon et al. 2004).


This work was partially supported by grants from the EU VIth Framework Programme (Promemoria), and the Swiss National Science Foundation.

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SA13

Dendritic and synaptic remodelling in mammalian hippocampus following stress
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Chronic restraint stress (CRS), in which rats are held for periods of 6 h/day for up to 21 days, induces raised corticosteroid levels and may result in cognitive impairment. It causes a variety of morphological changes in hippocampal areas, including loss of dendritic arborisation but, at least in area CA3, no signifi-

Figure 1. A 3-dimensional reconstruction from 150 serial ultrathin sections of a 20 µm segment of dendrite from CA3 with thorny excrescences. Note that the thorns show post-synaptic densities (PSD) in red, and there is also a single mushroom spine, with a PSD (scale bar, 3µm).
Glucocorticoids and perinatal programming

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Epidemiological evidence suggests that an adverse fetal environment permanently ‘programmes’ physiology leading to increased risks of cardiovascular, metabolic, neuroendocrine and psychiatric disorders in adulthood. In a variety of animal models, prenatal stress, glucocorticoid exposure or inhibition/knockout of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), the fetoplacental ‘barrier’ to maternal glucocorticoids, reduces birth weight and causes permanent hypertension, hyperglycaemia, increased hypothalamic-pituitary-adrenal (HPA) axis activity and anxiety-related behaviours in the adult offspring. In humans, 11β-HSD2 gene mutations lower birth weight and placental 11β-HSD2 activity correlates directly with birth weight and inversely with infant blood pressure. Low birth weight babies have higher plasma cortisol levels throughout adult life, indicating HPA programming. Maternal glucocorticoid therapy alters programming of GR in different tissues, including hippocampus and the glucocorticoid receptor (GR) itself. Differential programming of specific transcription factors, perhaps key is description-factor binding site-specific, changes in DNA methylation that occur only during specific sensitive periods of development. Curiously, some of these effects appear to be ‘inherited’ transgenerationally, affecting a further generation, itself unexposed to exogenous glucocorticoids at any point in the lifespan. Such effects can follow the male line, indicating epigenetic changes that persist through meiosis, fertilization and embryogenesis. Thus developmental exposure to excess glucocorticoids ‘programmes’ peripheral and CNS functions in adult life that may predispose to pathology and these effects may be transmitted into one or perhaps more subsequent generations.

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SA15

Stress and obesity: the evolutionary roles of glucocorticoids gone awry in our cultures

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Uncontrollable chronic stressors include periods of drought, earthquake, hurricane and famine which demand searching for new territory and the drive and energy to support the search. Glucocorticoids (GC), secreted during stress, appear to adapt the organism perfectly to find a new, more hospitable site to live while maintaining metabolic energy for the search. In the brain, GC act to increase stimulus salience or motivation; the valence of the behaviour emitted depends on the conditions and state of the animal and available outlets. In rats, GC facilitate search and running behaviours, freezing, aggression, anxiety- and fear-like behaviours; they also stimulate ingestion of palatable fat and sugar, but not plain (boring) chow [1-4]. However, GC do stimulate chow intake in diabetic rats in a dose-related fashion, but insulin, acting through the hepatic vagus, stimulates lard ingestion while decreasing chow intake in diabetic rats [5-7]. In the periphery, GC are catabolic and mobilize substrates for hepatic gluconeogenesis, but they also stimulate insulin secretion, which, in turn determines which foods will be eaten. Together these hormones shift caloric stores from the periphery to central fat depots. However, there is a metabolic feedback signal to the hypothalamic-pituitary-adrenal axis as well as the well-known acute GC-mediated feedback at hypothalamus and pituitary. Central fat mass is inversely related to the magnitude of hypothalamic corticotropin-releasing factor expression [4], and voluntary lard ingestion by rats markedly reduces the amplitude of ACTH and corticosterone responses to acute restraint [7], suggesting that stressor-induced eating may serve as self-medication for protection against the central effects of stress. In current civilizations, where perceived stressors abound and palatable foods are readily available with minimum exertion, this evolutionarily brilliant set of actions of stress-induced GC almost certainly contributes to the current epidemic of obesity and the pathophysiological association between abdominal obesity and the metabolic syndrome.


Thanks to collaborators: especially Prof V. Popov, Dr P. Gabbott, and Prof C. Sandi. Supported by BBSRC IABB grant No. BBS/B/15996 and EUFPVI Promemoria Grant contract no 512012.

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