Journal of Chemical Neuroanatomy 54 (2013) 42–49

Contents lists available at ScienceDirect

Journal of Chemical Neuroanatomy

journal homepage: www.elsevier.com/locate/jchemneu

Review

Lifetime achievement from a brain-adrenal perspective: On the CRF–urocortin–glucocorticoid balance

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ARTICLE INFO

Article history:
Received 15 July 2013
Accepted 15 October 2013
Available online 23 October 2013

Keywords:
Depression
Stress
Behavior
Brain
CRF
Urocortins
Glucocorticoids
Mineralocorticoids
Genomics

ABSTRACT

This contribution dedicated to Wylie Vale is focused on the action of the glucocorticoid hormone aimed to counterbalance the stress response orchestrated by the corticotrophin releasing factor (CRF) and urocortin (Ucn) family of peptides. It appears that the release and action of these stress hormones themselves are subjected to intrinsic self-regulatory feedback loops that operate as checks and balances in stress adaptation. One of these feedback loops is operated by the mineralocorticoid (MR) and glucocorticoid receptors (GR) that mediate in complementary fashion the action of endogenous cortisol/corticosterone in brain circuits underlying the onset and termination of the stress response. By affecting appraisal processes MR has an important role in coordinating emotional expression and cognitive flexibility with the onset of the stress response, while GR's role is prominent in the management of behavioral and physiological adaptations during the recovery phase. Genetic variation in interaction with environmental input and experience-related factors can modulate this balance between susceptibility and recovery governed by a balanced MR:GR signaling. Thanks to the Wylie Vale School of scientists a parallel balanced regulation between the CRF/CRF-1 and Ucn/CRF-2 receptor systems is being uncovered, leading inexorably to the question: how do the CRF/Ucn and glucocorticoid systems interact in multiple brain sites to maintain homeostasis and health?

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1. Introduction

The article by Wylie Vale and Norman Fleischer that appeared in the 1968 December issue of Endocrinology (Fleischer and Vale, 1968) spawned my career. The authors reported in this paper that dexamethasone inhibits vasopressin-induced ACTH release *in vitro* from pituitary quarters, while the synthetic glucocorticoid does not suppress the peptide's spontaneous release. That finding was

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0891-0618/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jchemneu.2013.10.003

deemed of importance because my PhD advisor David de Wied, famous for coining the term neuropeptide, had argued also in favor of a pituitary rather than a brain site of action of dexamethasone in the blockade of stress-induced HPA axis activity (de Wied, 1964). It happened that the start of my PhD research, December 1, 1968, did coincide with the appearance of the Fleischer and Vale article; the seminal paper by Bruce McEwen on corticosterone action in brain had been published the day before in Nature's November 30 issue (McEwen et al., 1968).

In this Nature paper Bruce McEwen reported that, if a tracer dose of tritium labeled corticosterone is administered to adrenalectomized rats, the radiolabeled hormone is one hour after injection retained in hippocampal neurons rather than in the hypophysiotropic area of the hypothalamus. By combining in the afternoon of December 1 the messages conveyed by the Fleischer/Vale and McEwen et al. papers, the hypothesis boiled up in The Netherlands that dexamethasone should not only act on the pituitary level, but also in the hippocampus. Because dexamethasone was manifold more potent than corticosterone we expected much higher retention of dexamethasone, and considered our proposal a convenient compromise, and therefore a brilliant plan.

As usual the prediction did not materialize: we found that the tracer dexamethasone was only poorly retained in hippocampus, but very well in pituitary corticotrophs (de Kloet et al., 1974). This finding was in support of Fleischer/Vale & de Wied, but at variance with the McEwen data, even when dexamethasone and corticosterone retention was compared under the very same experimental conditions under the master's eye in Bruce's Rockefeller laboratory (de Kloet et al., 1975). Only thirty years later, in 1998, we discovered why: dexamethasone is a substrate of the multidrug resistance P-glycoprotein (Pgp) in the blood-brain-barrier and therefore poorly penetrates the brain, while the steroid targets preferentially the pituitary corticotrophs (Meijer et al., 1998).

The coincidence of all this breaking news at the dawn of December 1, 1968 teaches in retrospect some lessons. First, it was wise to support the finding of Wylie Vale. Second, it can take 30 years to better understand an initial observation. Third, a timely idea can trigger momentarily a lifetime project. In fact, the actors in this introduction all pursued their very first observations, which incidentally brought them at different years the prestigious Lifetime Achievement Award of the International Society of Psychoneuroendocrinology (ISPNE). To that effect I was in the fortunate position to host Wylie in 2006 at the occasion of the 38th Annual ISPNE Meeting in Leiden (Fig. 1). The awardee was in the spirit to celebrate the occasion and took a whole week off to explore the old city and the university of Leiden, The Netherlands, which was founded in 1574 by Willem van Oranje with the motto *Praesidium Libertatis* (bastion of freedom). I learned Wylie's particular sense of humor. Ever since we received the Vale's annual X-mas card, which felt like being a family member.

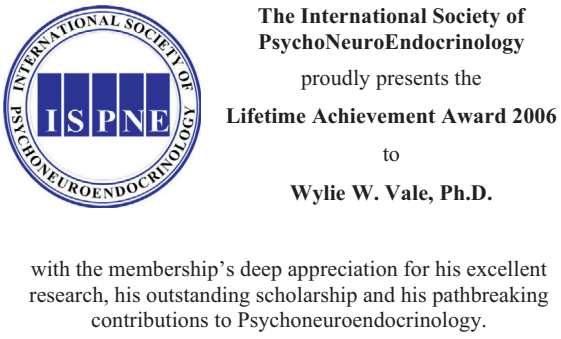

Fig. 1. Award presented at the 37th Annual ISPNE Conference in Leiden, The Netherlands, August 23, 2006.

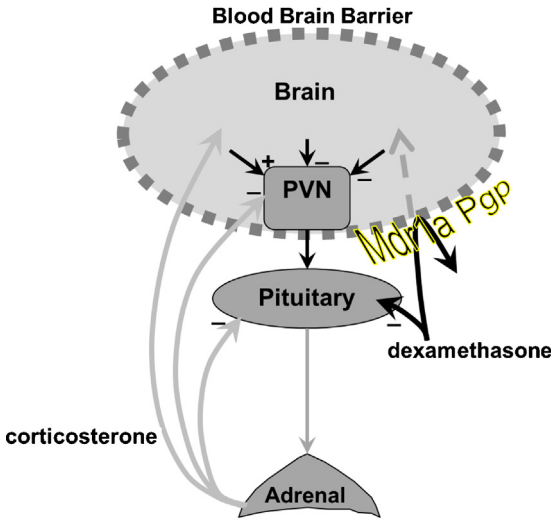

Fig. 2. Dexamethasone action in the HPA axis. Note that dexamethasone targets the pituitary in the suppression of stress-induced HPA axis activity and poorly penetrates the brain. As a consequence the brain is depleted of endogenous glucocorticoid hormone, while GR activation is partly restored by exogenous dexamethasone. Accordingly, this has profound consequences for brain corticosteroid receptor occupancy and function, particularly for the MR. See Karssen et al. (2005).

Wylie has founded a School of eminent researchers in the science of stress neuroendocrinology highlighting corticotropin-releasing factor (CRF) and its CRF type 1 receptor as the driver, the initiator, the organizer, the *on-button* of the stress response. In line with this, a productive binational Israelian-American collaboration using a triple urocortin (Ucn) knockout mouse model generated convincing arguments for Ucn/CRF type 2 receptors as the *off-button* (Neufeld-Cohen et al., 2010). In this contribution dedicated to Wylie Vale, it is my intention to further elaborate on the peculiar phenomenon that not only the CRF/urocortin (Ucn)-family of peptides themselves, but also the glucocorticoid feedback system has intrinsic checks and balances that are crucial for homeostasis and health (Fig. 2).

2. Neuroendocrinology of stress

The Greek philosophers knew it: to maintain balance in life, every force triggers a counterforce. More recently in the mid 19th century Claude Bernard advocated that this equilibrium critically depends on the stability of the *milieu intérieure*. Cannon in the early 20th century called this balanced stability 'homeostasis', a state that is characterized by a set-point determining among others the precise pH, O_2/CO_2 and electrolyte concentration. Hans Selye launched the 'stress' concept, where a stressor is defined as any stimulus that disturbs homeostasis (Selye, 1936).

Today the stress response is considered to be the spectrum of physiological reactions to a stimulus or stressor aimed to promote behavioral adaptation and to restore homeostasis. Accordingly, Selye's physiological stress concept has grown toward a psychological construct of subjective experience and handling of a stressor in which social context and a sense of safety are important variables. Most stressful is an aversive threatening situation where lack of information and inability to predict renders the individual with uncertainty and poor control over upcoming events.

An individual, indeed, usually spends more time to *anticipate* such a serious stressor – either real or imagined – than actually suffering from it. In fact, in anticipation of a stressful event, changes in structure and function of the brain already may occur and this process of maintaining equilibrium by change is called *allostasis* (McEwen and Wingfield, 2010). The maintenance of this