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NEUROEPIGENETICS OF STRESS

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Abstract—Stress, a common if unpredictable life event, can have pronounced effects on physiology and behavior. Individuals show wide variation in stress susceptibility and resilience, which are only partially explained by variations in coding genes. Developmental programing of the hypothalamic–pituitary–adrenal stress axis provides part of the explanation for this variance. Epigenetic approaches have successfully helped fill the explanatory gaps between the influences of gene and environment on stress responsiveness, and differences in the sequelae of stress across individuals and generations. Stress and the stress axis interacts bi-directionally with epigenetic marks within the brain. It is now clear that exposure to stress, particularly in early life, has both acute and lasting effects on these marks. They in turn influence cognitive function and behavior, as well as the risk for suicide and psychiatric disorders across the lifespan and, in some cases, unto future generations.

Key words: histone modifications, DNA methylation, HPA axis, corticosteroids, non-coding RNA, developmental programing.

Contents

INTRODUCTION

Stress is a common, if unpredictable, life event, and can have both adaptive and maladaptive consequences for an organism. In the natural environment, many stressors can have profoundly negative, even lethal, consequences and for this reason organisms require the capacity to rapidly and effectively adapt to stressful circumstances. They also need to keep account of lessons learned with regard to stress in terms of memories as well as behavioral and physiologic adaptations. This requirement for rapid, yet persistent, change is a challenge both to the largely fixed genome and to a brain primarily comprised of terminally differentiated neurons. Mammalian brains meet this challenge in a variety of interrelated ways, from structural and functional plasticity to epigenetic reprograming of neural genomes.

Epigenetics is most broadly defined as transmission of information above the level of DNA sequence. The term ‘epigenetic’ has evolved substantially since its coinage decades ago and it now encompasses a range of effects from behavioral or even cultural transmission of information across and within generations down to the molecular modifications of nucleic acids and their

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Abbreviations: 5-HT, Serotonin; ACTH, adrenocorticotropic hormone; AVP, arginine-vasopressin; BDNF, brain-derived neurotrophic factor; BLA, basolateral amygdala; COMT, catechol-O-methyltransferase; CpG, cytosine-guanine dinucleotides; CRH, corticotropin-releasing hormone; CSD, chronic social defeat; DCS, D-cycloserine; ERK1/2, extracellular signal-regulated protein kinases 1 and 2; GC, glucocorticoid; GR, glucocorticoid receptor; H3K4, H3 lysine 4; H3K9, H3 lysine 9; HATs, histone acetyltransferases; HDACs, histone deacetylases; HDMs, histone demethylases; HMTs, histone methyltransferases; HPA, hypothalamic–pituitary–adrenal (HPA); HT, hypertonic saline solution; lncRNA, long non-coding RNA; LTM, long-term memory; Met, methionine; miRNAs, microRNAs; MR, mineralocorticoid receptor; MS, maternal separation; NaBu, sodium butyrate; NMDAR, N-methyl-D-aspartate receptor; OXTR, oxytocin receptor; piRNA, piwi-interacting RNA; POMC, proopiomelanocortin; PTSD, post-traumatic stress disorder; PVN, paraventricular nucleus; SC, skin conductance; snoRNA, small nucleolar RNA; SNP, single nucleotide polymorphism; TEs, transposable elements; Val, valine; VPA, valproic acid.

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packaging proteins. While one might defend making a hard distinction for molecular epigenetics for the latter set of phenomena, it is not clear where the line between the molecular and what it is tempting to call behavioral epigenetics, properly lies. This is clear even in what is perhaps the most famous case of epigenetic effects in the nervous system, maternal transmission of stress responsiveness described by Meaney and collaborators (see below) where maternal behavior and molecular mechanisms are both demonstrably involved. A more useful distinction might be between the acute changes in epigenetic marks, which contribute to short-term defense of homeostasis and longer term responses to environmental change that might be regarded as allostatic, to borrow a term from the stress literature (McEwen and Wingfield, 2010). Allostasis, is defined in contrast to homeostasis as ''maintaining stability through change'' (McEwen and Wingfield, 2003). Homeostatic epigenetic alterations would return to a baseline level over a fairly brief period of time (say hours to days), while allostatic changes might persist through the lifespan and into future generations in the absence of a countermanding perturbation. It suffices to say that this isnot a definitive distinction, but it is clear the field is presently large enough that some more precise terminology is wanting.

The study of neuroepigenetics in general and the neuroepigenetics of stress has undergone substantial growth over the last decade (Hunter et al., 2013; Sweatt, 2013; Reul, 2014). This is due to both the adoption of novel technical approaches such as next generation sequencing, and to the clear need to explain persistent, environmentally sensitive behavioral variations that were not due simply to genetic polymorphisms (e.g. the ''Missing Heredity'' problem in psychiatric genetics (Crow, 2011; Danchin et al., 2011)). Stress has long been known to play a role in brain plasticity (Hunter et al., 2013; Hunter and McEwen, 2013). As stress is one of stronger environmental influences on human and animal behavior, it is a logical means to examine genome-environment interactions with an epigenetic lens (with the caveat that the distinction between environmental, genomic and other stochastic factors is, if anything, less clear in the present age than previously).

STRESS AND THE HYPOTHALAMIC–PITUITARY–ADRENAL AXIS

Stress can be conceived of as any threat to bodily homeostasis—real or imagined—that urges the organism to act in defense of that homeostasis. These actions often require behavioral or physiologic changes on the part of the organism and are therefore referred to as allostatic (McEwen and Wingfield, 2003), while the stressor itself represents an allostatic load. Stressors are defined both by their duration as well as by the capacity of the organism to respond to them. Controllable stresses, such as voluntary exercise, can be both physically and psychologically beneficial (Adlard and Cotman, 2004; Aschbacher et al., 2013). Opinion varies on whether such events are properly called 'stress', though they do actuate many of the same physiologic

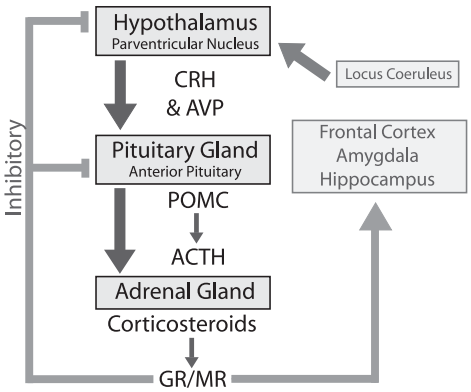

Fig. 1. The HPA axis. Stress triggers a cascade of signaling in the hypothalamic–pituitary–adrenal (HPA) axis. The hypothalamus releases corticotropin-releasing hormone (CRH) and arginine-vasopressin (AVP) into the pituitary portal. The pituitary converts proopiomelanocortin (POMC) to adrenocorticotropic hormone (ACTH) and releases it into the bloodstream, where it binds to the adrenal gland. Corticosteroids released by the adrenal gland bind to glucocorticoid (GR) and mineralocorticoid (MR) receptors. These receptors inhibit the HPA axis influencing other brain regions and serotonin receptors (5-HTR).

mechanisms. In contrast, in situations where the organism does not have meaningful control of the outcome of the stressor, the effects can be negative (Maier and Watkins, 2010). This is true of both severe acute traumas, which can induce Post-Traumatic Stress Disorder (PTSD), and of more chronically aversive situations such as social subordination or chronic unpredictable stress, which can contribute to depressive behavior. In a successful stress response, once the individual has escaped the situation, the body will return to a pre-stress state. In these instances, stress is a positive response that keeps the individual alive and well, and can even increase resilience to future stressors. Both negative and positive stress adaptations cause the nervous system to undergo epigenetic changes that influence its future responses.

The mammalian stress response is orchestrated, in part, by the activity of the hypothalamic–pituitary–adrenal (HPA) axis (Fig. 1). Perturbation of glucocorticoid (GC) feedback in the HPA axis is one of the best-established biomarkers for a number of complex diseases, including depression and PTSD. The hypothalamus is the first structure in this common pathway. Activation of the parvocellular neurons of the paraventricular nucleus (PVN) of the hypothalamus induces three distinct responses. Activation of the pathway begins with the release of corticotropin-releasing hormone (CRH) and arginine-vasopressin (AVP) into the pituitary portal. This triggers the next step in the HPA cascade. CRH and AVP release into the pituitary portal increases the production of proopiomelanocortin (POMC) in the anterior pituitary. POMC is converted to adrenocorticotropic hormone (ACTH), which is then released into general circulation in the blood (Aguilera, 2012).

The adrenal gland produces corticosteroids (predominantly cortisol in humans, corticosterone in rodents) in the presence of ACTH. Corticosteroids bind to mineralocorticoid (MR) and glucocorticoid (GR)