Neurobiology of Stress xxx (2017) 1–15

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: http://www.journals.elsevier.com/neurobiology-of-stress/

Circuit and synaptic mechanisms of repeated stress: Perspectives from differing contexts, duration, and development

Kevin G. Bath [a, *], Scott J. Russo [b], Kristen E. Pleil [c], Eric S. Wohleb [d, e], Ronald S. Duman [e], Jason J. Radley [f, **]

[a] Department of Cognitive Linguistic and Psychological Sciences, Brown University, Providence, RI 02912, United States
[b] Fishberg Department of Neuroscience and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, United States
[c] Department of Pharmacology, Weill Cornell Medical College, New York, NY 10065, United States
[d] Department of Psychiatry, University of Cincinnati College of Medicine, Cincinnati, OH 45237, United States
[e] Department of Psychiatry, Yale School of Medicine, New Haven, CT 06508, United States
[f] Department of Psychological and Brain Sciences, University of Iowa, Iowa City, IA 52242, United States

ARTICLE INFO

Article history:
Received 16 December 2016
Received in revised form
3 March 2017
Accepted 4 May 2017
Available online xxx

Keywords:
Early-life stress
Hippocampus
Susceptibility
Resilience
Nucleus accumbens
Bed nuclei of the stria terminalis
Neuropeptide Y
Corticotropin-releasing factor
Prefrtonal cortex
Mammalian target of rapamycin
Major depressive disorder

ABSTRACT

The current review is meant to synthesize research presented as part of a symposium at the 2016 Neurobiology of Stress workshop in Irvine California. The focus of the symposium was “Stress and the Synapse: New Concepts and Methods” and featured the work of several junior investigators. The presentations focused on the impact of various forms of stress (altered maternal care, binge alcohol drinking, chronic social defeat, and chronic unpredictable stress) on synaptic function, neurodevelopment, and behavioral outcomes. One of the goals of the symposium was to highlight the mechanisms accounting for how the nervous system responds to stress and their impact on outcome measures with converging effects on the development of pathological behavior. Dr. Kevin Bath's presentation focused on the impact of disruptions in early maternal care and its impact on the timing of hippocampus maturation in mice, finding that this form of stress drove accelerated synaptic and behavioral maturation, and contributed to the later emergence of risk for cognitive and emotional disturbance. Dr. Scott Russo highlighted the impact of chronic social defeat stress in adolescent mice on the development and plasticity of reward circuitry, with a focus on glutamatergic development in the nucleus accumbens and mesolimbic dopamine system, and the implications of these changes for disruptions in social and hedonic response, key processes disturbed in depressive pathology. Dr. Kristen Pleil described synaptic changes in the bed nuclei of the stria terminalis that underlie the behavioral consequences of allostatic load produced by repeated cycles of alcohol binge drinking and withdrawal. Dr. Eric Wohleb and Dr. Ron Duman provided new data associating decreased mammalian target of rapamycin (mTOR) signaling and neurobiological changes in the synapses in response to chronic unpredictable stress, and highlighted the potential for the novel antidepressant ketamine to rescue synaptic and behavioral effects. In aggregate, these presentations showcased how divergent perspectives provide new insights into the ways in which stress impacts circuit development and function, with implications for understanding emergence of affective pathology.

Contents

1. Introduction 00
2. Impact of early life stress on the timing of neurobehavioral development – Kevin Bath, Brown University 00
   2.1. Stress and the hippocampus 00
   2.2. Stress and development 00
   2.3. Fragmented maternal care as a model of ELS 00

* Corresponding author. Department of CLPS, Brown University, 180 Thayer St., Box 1821, Providence, RI 02912, United States.
** Corresponding author. Department of Psychological and Brain Sciences, E11 Seahorse Hall, University of Iowa, Iowa City, IA 52242, United States.
E-mail addresses: Kevin_Bath@Brown.edu (K.G. Bath), jason-radley@uiowa.edu (J.J. Radley).

http://dx.doi.org/10.1016/j.ynstr.2017.05.001
2352-2895/

2.4. ELS and measures of neural maturation 00
2.5. ELS and cognitive and affective outcomes 00
2.6. Conclusions and new research directions 00
3. Plasticity of reward circuitry and stress disorders – Scott Russo, Icahn School of Medicine at Mount Sinai 00
3.1. Glutamatergic stress circuits in the NAc 00
3.2. Stress-induced plasticity is cell and spine-type specific in NAc 00
3.3. Sex differences in synaptic plasticity 00
3.4. Conclusions and new research directions 00
4. Stressing thalamo-limbic circuits with repeated drinking – Kristen Pleil, Weill Cornell Medical College 00
4.1. Mouse models of binge alcohol drinking 00
4.2. The roles of extrahypothalamic corticotropin-releasing factor (CRF) and neuropeptide Y (NPY) in binge drinking 00
4.3. The bed nuclei of the stria terminalis (BNST) as a site for peptide-peptide interactions 00
4.4. Thalamo-limbic drive of binge drinking behavior 00
4.5. Conclusions and new research directions 00
5. Disruption of mTORC1 signaling contributes to synaptic deficits caused by chronic stress: reversal by rapid-acting antidepressants - Eric Wohleb and Ronald Duman, Yale University 00
5.1. Stress-induced up-regulation of REDD1 drives synaptic deficits and depressive-like behaviors via decreased mTORC1-p70S6K signaling 00
5.2. GABA interneurons in the prefrontal cortex are critical mediators of rapid-acting antidepressants 00
5.3. Potential sex differences in stress-induced neuronal atrophy in the medial prefrontal cortex and responses to rapid-acting antidepressants 00
5.4. Conclusions and future research directions 00
6. General summary 00
Acknowledgements 00
References 00

List of abbreviations

AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BEC	blood alcohol content
BNST	bed nuclei of the stria terminalis
CRF	corticotropin-releasing factor
CSDS	chronic social defeat stress
CUS	chronic unpredictable stress
D1	dopamine receptor type 1
D2	dopamine receptor type 2
DID	Drinking in the Dark model of binge drinking
ELS	early-life stress
GABA	gamma-aminobutyric acid
$GABA_A$	gamma-aminobutyric acid type A receptor
GPCR	G-protein coupled receptor
ILT	intralaminar thalamus
mAChR	muscarinic acetylcholine receptor
MBP	myelin basic protein
MDD	major depressive disorder
MSN	medium spiny neuron
mTOR	mammalian target of rapamycin
mTORC1	mammalian target of rapamycin complex 1
NAc	nucleus accumbens
NMDA	*N*-methyl-D-asparate
NPY	neuropeptide Y
P70S6K	p70 ribosomal protein S6-kinase
PFC	prefrontal cortex
PV	parvalbumin
PVT	paraventricular nucleus of the thalamus
REDD1	regulated in development and DNA damage responses 1
RT-qPCR	real-time quantitative polymerase chain reaction
SCVS	subchronic variable stress
uEPSC	unitary excitatory postsynaptic current
VGLUT	vesicular glutamate transporter
Y1R	neuropeptide Y type 1 receptor

1. Introduction

Stress profoundly alters neural and behavioral development, drives changes in physiology and behavior, and contributes to increased morbidity and earlier mortality across nearly all species studied. A stressor may be any stimulus that disrupts, or is perceived to disrupt, selective homeostatic responses within the individual. Stressful stimuli can range from an attack by a predator or rival, diminished maternal care, an immune challenge, to a lack of available energy to run cellular processes (e.g. hunger) (Karatsoreos and McEwen, 2011; McEwen and McEwen, 2016), and organisms have a highly evolved set of responses to adapt to this wide range of challenges. The biological responses in stress adaptation involve the reallocation of metabolic resources until homeostasis can be restored, thereby enhancing the probability of survival and promoting reproductive success, the ultimate selection process driving evolutionary change.

On the one hand, moderate levels of stress exposure may well serve as catalysts for experience-dependent structural and functional changes associated with memory consolidation, behavioral regulation, and developmental processes (Hostinar and Gunnar, 2013; Karatsoreos and McEwen, 2011; Lupien et al., 2009; McEwen, 2004). However, chronic or excessively high levels of stress has been shown to have deleterious effects, impacting neural structure and functional plasticity of the brain and contributing to a variety of negative health outcomes (Bath et al., 2016; Chattarji et al., 2015; Liston et al., 2006; McEwen et al., 1992; Popoli et al., 2012; Radley et al., 2008; Vyas et al., 2006). Moreover, significant

Please cite this article in press as: Bath, K.G., et al., Circuit and synaptic mechanisms of repeated stress: Perspectives from differing contexts, duration, and development, Neurobiology of Stress (2017), http://dx.doi.org/10.1016/j.ynstr.2017.05.001