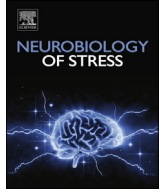




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## Circuit and synaptic mechanisms of repeated stress: Perspectives from differing contexts, duration, and development

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## 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.

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### List of abbreviations

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

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