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Review

Autism, fever, epigenetics and the locus coeruleus

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ARTICLE INFO

Article history:
Accepted 18 November 2008
Available online 24 November 2008

Keywords:
Gene–environmental interaction
Prenatal stressor
Neuromodulator
Sensorimotor processing
Homeostatic signal
Developmental critical period
Imprinted gene
Pharmacoepigenomic agent

ABSTRACT

Some children with autism spectrum disorders (ASD) exhibit improved behaviors and enhanced communication during febrile episodes. We hypothesize that febrigenesis and the behavioral-state changes associated with fever in autism depend upon selective normalization of key components of a functionally impaired locus coeruleus-noradrenergic (LC-NA) system. We posit that autistic behaviors result from developmental dysregulation of LC-NA system specification and neural network deployment and modulation linked to the core behavioral features of autism. Fever transiently restores the modulatory functions of the LC-NA system and ameliorates autistic behaviors. Fever-induced reversibility of autism suggests preserved functional integrity of widespread neural networks subserving the LC-NA system and specifically the subsystems involved in mediating the cognitive and behavioral repertoires compromised in ASD. Alterations of complex gene–environmental interactions and associated epigenetic mechanisms during seminal developmental critical periods are viewed as instrumental in LC-NA dysregulation as emphasized by the timing and severity of prenatal maternal stressors on autism prevalence. Our hypothesis has implications for a rational approach to further interrogate the interdisciplinary etiology of ASD and for designing novel biological detection systems and therapeutic agents that target the LC-NA system's diverse network of pre- and postsynaptic receptors, intracellular signaling pathways and dynamic epigenetic remodeling processes involved in their regulation and functional plasticity.

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Abbreviations: ASD, autism spectrum disorders; CpG, cytosine dinucleotide; CRH, corticotropin-releasing hormone; LC, locus coeruleus; LC-NA, locus coeruleus-noradrenergic system; LPS, lipopolysaccharide; NA, noradrenaline

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doi:10.1016/j.brainresrev.2008.11.001

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1. Introduction

Autism spectrum disorders (ASD) are heritable developmental disorders characterized by impairments in social interaction, language and communication deficits and repetitive or stereotyped behaviors. Although the genetic contributions to ASD are being intensively explored (Abrahams and Geschwind, 2008; Morrow et al., 2008; Sebat et al., 2007), little is known concerning the relationship of genetic, epigenetic and environmental factors to the core features or neuropathological substrate underlying ASD (Persico and Bourgeron, 2006). We believe the neurobiology of autism may be informed by parent reports, clinical observations and formal studies indicating that autistic behaviors are ameliorated in some children during febrile episodes (Curran et al., 2007). The association of fever and behavioral improvement in ASD provides clues to the pathophysiology of autistic behaviors and to potential therapeutic interventions. Accordingly, we posit that the dramatic fluctuations in behavioral states occurring during febrile episodes suggest the involvement of a pervasive neural system that can effect relatively rapid changes in the functional activity of widespread neural networks involved in the core features of ASD. The locus coeruleus-noradrenergic system (LC-NA) represents such a widespread and versatile neuromodulatory system that we suggest is common to febrigenesis and the modulation of autistic behaviors. We hypothesize that intrinsic and environmental stressors acting upon a substrate of genetic and epigenetic variations during a protracted maturational window of vulnerability developmentally dysregulate the LC-NA system. Febrile episodes ameliorate autistic behaviors by differentially modulating the LC-NA system and transiently restoring the functional integrity of its distributed neural networks primarily involved in mediating social communication, complex motor programs and instrumental behaviors. Several lines of evidence support this hypothesis.

2. The locus coeruleus-noradrenergic system

The locus coeruleus is a small-pigmented nucleus nestled in the rostral dorsolateral pontine tegmentum. The LC in humans consists of approximately 40,000 neurons with the most widespread efferent projections of any neurons in the brain (Foote et al., 1983). All of the noradrenaline (NA) in the cerebral cortex and hippocampus and most of the NA in other parts of the neuraxis including the cerebellum is produced and transported by LC neurons in axons with hundreds of thousands of NA-containing varicosities (Oleskevich et al., 1989). By virtue of their complex but selective patterns of innervation within and across different forebrain structures, LC-NA neurons gain access to a diverse but targeted array of interacting neural networks. For example, there are suggestions that preferential noradrenergic innervation of selective components of the visual system promotes more global visual spatial analysis and elaboration of visuomotor responses as opposed to a greater focus on stimulus feature extraction and pattern analysis, consistent with the visual sensory domains most impaired in autism (Berridge and Waterhouse, 2003). Such networks can be influenced through actions at multiple stages of sensorimotor processing, and by activating distinct intracellular signaling cascades that permit elaboration of a dynamic range of neuronal response properties and rapid reorganization of relevant neural networks for efficient and flexible behavioral adaptations (Berridge and Waterhouse, 2003). The widespread efferent projections of the LC are paralleled by equally diverse afferent projections to LC neuron cell bodies and their dendritic systems (Van Bockstaele et al., 2001). These arise from brainstem catecholamine- and serotonin-containing nuclei that provide homeostatic inputs to modulate LC-NA output properties as well as afferents from the cerebral cortex, amygdala, basal forebrain and hypothalamus that provide integrated feedback modulation based on evolving environmental contingencies. There is also evidence for separate corticotropin-releasing hormone (CRH) inputs to the locus coeruleus that specifically modulate noradrenergic neuronal activation by physiological and environmental stressors (Van Bockstaele et al., 2001).

Earlier views of the preeminent role of the LC-NA system in arousal and attention have been greatly expanded to include involvement of the LC-NA system in virtually all aspects of behavioral adaptations and performance with particular relevance to integrative cognitive domains disproportionately affected in ASD: exploration within a complex and dynamic environment and the acquisition, retention, manipulation and utilization of salient environmental cues (Aston-Jones and Cohen, 2005; Van Bockstaele et al., 2001). A proposal of particular merit analogizes the operation of the LC-NA system in mammals with the neuromodulatory function of neurons that regulate ‘flips’ in complex behavior patterns in invertebrates (Bouret and Sara, 2005). The organizing principle that emerges from recent research is that distributed neural networks, such as those involved in cognitively demanding