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Autism, fever, epigenetics and the locus coeruleus

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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 interrogating 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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Keywords

gene-environmental interactions; prenatal stressors; neuromodulators; sensorimotor processing; homeostatic signals; developmental critical periods; imprinted genes; pharmacoepigenomic agents

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 tasks (Sridharan et al., 2008), are under modulatory control by the LC-NA system and associated homeostatic signals including circadian rhythms to facilitate rapid and widespread neural network remodeling to promote behavioral adaptations to environmental imperatives. It is therefore not surprising that the LC-NA system has been implicated in the etiology of post-traumatic stress disorders, neurodegenerative diseases, schizophrenia, depression and other psychiatric conditions (Aston-Jones and Cohen, 2005; Berridge, 2008; Van Bockstaele et al., 2001). The role of the LC-NA system in autism has escaped attention until now as we seek a parsimonious explanation for the association of febrile episodes and improvement in autistic behaviors.

3. Fever, neural network plasticity and the locus coeruleus system

What is the evidence that febrigenesis involves the LC-NA system? Bacterial lipopolysaccharide (LPS)-induced fever activates preoptic area noradrenergic terminals (Linthorst et al., 1995) and chemical lesions of NA-containing afferents to the paraventricular nucleus inhibit the fever response to interleukin-1 (Ovadia et al., 1989). While it is now well established that preoptic NA mediates LPS-induced fever (Feleder et al., 2007), the NA neurons involved in fever have only recently been elucidated in findings that electrolytic and chemical lesions of LC markedly attenuate LPS-induced fever in laboratory animals (Almeida et al., 2004). Thus LC-NA-hypothalamic pathways activated by febrigenic stimuli alter the excitatory state of LC-NA neurons during fever. Since LC neurons exhibit highly synchronized activity attributable to dendritic electrical interactions, activation of a subpopulation of LC neurons projecting to the hypothalamus could readily spread throughout the nucleus, causing functional remodeling and altered neuronal response properties of differential components of the entire LC-NA system. (Steininger et al., 2001) Altered LC-NA neural network deployment and neuronal activation, we infer, is the restorative event in the transient amelioration of autistic behaviors during fever. This hypothesis is in keeping with studies that have failed to find substantive neuropathological lesions in the cerebral cortex and other brain sites (Amaral et al., 2008), and reports of the paucity of associated anatomical abnormalities in the LC in ASD (Hashemi et al., 2007; Martchek et al., 2006). Early but transient brain overgrowth has been reported in ASD (Courchesne et al., 2007), and this suggests that dynamic developmental dysregulation is occurring through complex gene-environmental interactions (see below). We argue that insofar as ASD is a heterogeneous disorder in which waxing and waning of autistic behaviors occurs during fever and defervescence and also during specific developmental epochs, the neural networks responsible for ASD, particularly in higher functioning patients, should be functionally intact. This has implications for a rational pharmacotherapy of autism that targets the LC-NA system and its diverse pre-and postsynaptic receptors. Although

favorable responses to some alpha-adrenergic agonists have been reported in ASD (Erickson et al., 2007), the diversity of neurochemical, developmental and epigenetic regulatory systems associated with the LC-NA system (see below) suggest that more diverse, selective, versatile and novel therapeutic targets and pharmacoepigenomic agents will soon emerge.

4. Autism-related developmental and epigenetic dysregulation of the locus coeruleus-noradrenergic system

There remains to consider the events and processes that could lead to developmental dysregulation of the LC-NA system and ASD (Cheslack-Postava et al., 2007; Connors et al., 2005). Intricate profiles of developmental cues are elaborated during progressive developmental critical periods to ensure the fidelity of the specification, deployment and refinement of the emerging LC-NA system (Hashemi et al., 2007; Holm et al., 2006). A significant subset of these interacting developmental genes and gene networks has been implicated in ASD (Abrahams and Geschwind, 2008; Morrow et al., 2008; Schanen, 2006). LC-NA developmental genes are under exquisite degrees of epigenetic regulation, suggesting the influence of complex gene-environmental interactions and high degrees of contextual control (Hashemi et al., 2007; Holm et al., 2006; Persico and Bourgeron, 2006; Schanen, 2006). These observations are consistent with emerging observations suggesting the dysregulation of multiple epigenetic regulatory processes in ASD (Persico and Bourgeron, 2006; Schanen, 2006). These include multiple imprinted loci implicated in ASD and encompassing complex genomic regulatory regions under the control of multiple diverse epigenetic processes and involved in orchestrating numerous seminal brain maturational and plasticity processes that are selectively dysregulated in ASD (Badcock and Crespi, 2006; Mehler and Mattick, 2007; Schanen, 2006). Interestingly, there are specific imprinted genes involved in LC-NA deployment and in mediating behavioral responses to novel environmental conditions (Plagge et al., 2005). ASD-associated epigenetic alterations in the fidelity of regional patterning, specification and progressive maturation of the LC-NA system would result in a complex amalgam of core behavioral deficits and a spectrum of clinical severity depending on the profile of maturational deficits associated with epigenetic dysregulation of specific developmental critical periods (Aston-Jones and Cohen, 2005; Berridge and Waterhouse, 2003; Bouret and Sara, 2005; Hashemi et al., 2007; Holm et al., 2006; Persico and Bourgeron, 2006; Schanen, 2006).

5. Developmental stress, epigenetic modulation and potentially reversible locus coeruleus-noradrenergic system dysregulation in ASD

Prenatal stressors, appropriately timed and sufficiently intense, could also be important in dysregulating the LC-NA system. In view of the metabolic load LC neurons bear in supporting vast axonal networks with millions of NA laden vesicles, we suspect that they might be selectively vulnerable to stress-induced functional dysregulation. Prenatal stressful events are reported more frequently in mothers of autistic children than mothers of control children (Beversdorf et al., 2005). Natural disasters are compelling in this respect. These have revealed a significant increase in autism prevalence following maternal exposure to hurricanes and tropical storms over a 15-year period in Louisiana (Kinney et al., 2008). A dose-response effect was related to the severity of storm exposure. Interestingly, maternal exposure to severe storms at mid-gestation resulted in the highest prevalence of autism in affected cohorts.

To the extent that high levels of maternal stress-induced cortisol might affect fetal LC-NA regulation, it is of interest that at mid-gestation the catalytic enzyme that inactivates cortisol, 11 β-hydroxysteroid dehydrogenase-2, is downregulated in the placenta, thereby enhancing transplacental transport of the stress hormone into the fetal brain (Holmes et al., 2006). In

addition, during this critical period for progressive phases of locus coeruleus development, 11 β-hydroxysteroid dehydrogenase-2 is under dynamic and potentially dysregulated epigenetic modulation through the actions of differential promoter cytosine dinucleotide (CpG) island methylation, methyl CpG-binding proteins and specific transcriptional regulators associated with ASD (Abrahams and Geschwind, 2008; Alikhani-Koopaei et al., 2004). These intrauterine perturbations can significantly alter the normal neuronal and regional noradrenergic receptor subunit complement, electrotonic coupling and associated early attachment learning and environmental discrimination (Moriceau and Sullivan, 2005). Interestingly, *Crh* gene expression is elevated in a Rett syndrome (MeCP2 mutant) mouse model and is associated with abnormal stress responses (McGill et al., 2006). MeCP2 is known to bind the *Crh* promoter that is normally enriched in methylated CpG dinucleotides, and exogenous NA administration ameliorates the abnormal neural response networks observed in MeCP2 mutant mice (McGill et al., 2006; Viemari et al., 2005). These observations suggest that in addition to intrinsic epigenetically mediated ASD developmental abnormalities occurring during progressive stages of locus coeruleus development, there are concurrent and continuing epigenetically dependent environmental stressors that have the potential to further compromise the functional integrity of LC-NA neural networks.

6. Conclusions

The importance of our hypothesis, apart from its ability to explain widely divergent and complex features of ASD, including the ‘fever effect’, lies in its promise for the development of innovative diagnostic and therapeutic approaches to autism. We anticipate that the design of advanced molecular genetic platforms and functional neuroimaging paradigms for pre-clinical disease detection and the identification of early biomarkers will permit the analysis of disease progression and responses to pharmacologic and behavioral interventions. Additionally, generation of more relevant and robust animal models of autism will help to elucidate novel classes of therapeutic agents that target the evolving LC-NA system and its mature and widely distributed but selective neural networks, signaling pathways and epigenetic modifiers of network plasticity and connectivity. Recent studies emphasize the potential power of evolving molecular genetic as well as newer pharmacoepigenomic therapies to promote “recovery” of seemingly irrevocably lost long-term memories and higher-order cognitive and behavioral functions and even “rejuvenation” of dying neurons in advanced cases of neurodegenerative diseases (Chan et al., 2007; Fischer et al., 2007). Thus complementary therapeutic approaches organized within the context of translational research initiatives in developmental neuroscience, epigenomic medicine, systems biology and maternal and environmental health will allow for permanent reversal of the higher-order cognitive and behavioral deficits observed in ASD and perhaps in other pervasive and presently intractable neuropsychiatric disorders.

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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