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Macrocephaly and the control of brain growth in autistic disorders

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Abstract

Autism is a childhood-onset neuropsychiatric disorder characterized by marked impairments in social interactions and communication, with restricted stereotypic and repetitive patterns of behavior, interests, and activities. Genetic epidemiology studies indicate that a strong genetic component exists to this disease, but these same studies also implicate significant environmental influence. The disorder also displays symptomatologic heterogeneity, with broad individual differences and severity on a graded continuum. In the search for phenotypes to resolve heterogeneity and better grasp autism's underlying biology, investigators have noted a statistical overrepresentation of macrocephaly, an indicator of enlarged brain volume. This feature is one of the most widely replicated biological findings in autism. What then does brain enlargement signify? One hypothesis invoked for the origin of macrocephaly is a reduction in neuronal pruning and consolidation of synapses during development resulting in an overabundance of neurites. An increase in generation of cells is an additional mechanism for macrocephaly, though it is less frequently discussed in the literature. Here, we review neurodevelopmental mechanisms regulating brain growth and highlight one under-considered potential causal mechanism for autism and macrocephaly—an increase in neurogenesis and/or gliogenesis. We review factors known to control these processes with an emphasis on nuclear receptor activation as one signaling control that may be abnormal and contribute to increased brain volume in autistic disorders.

Keywords: Autism; Macrocephaly; Genetic syndromes; Brain size; Nuclear receptor; Valproate; Retinoic acid

Contents

Abbreviations: ACTH, adrenocorticotropin hormone; DNA, deoxyribonucleic acid; EGF, epidermal growth factor; ES, embryonic stem cells; FGF2, fibroblast growth factor 2; FMR-1, fragile X mental retardation 1; FMRP, fragile X mental retardation protein; FoxP2, forkhead box P2; HAT, histone acetyltransferase; HDAC, histone deacetylase; HPA, hypothalamus-pituitary-adrenal gland axis; IGF1, insulin-like growth factor 1; MECP2, methyl CpG binding protein 2; NCoR, nuclear receptor corepressor; NMDA, N-methyl-D-aspartate; NSD1, nuclear receptor binding SET domain protein 1; PACAP, pituitary adenylate cyclase-activating polypeptide; PTEN, phosphatase and tensin homolog; RAR, retinoic acid receptor; SMRT, silencing mediator of RAR and thyroid hormone receptor; SO, superior olive; T3, 3,5,3′-triiodothyronine; T4, thyroxine

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1. Introduction

1.1. Symptomatologic heterogeneity in autism

The autism spectrum of diseases is broadly characterized as disorders of impaired social interaction and communication combined with features such as repetitive behaviors and restricted interests. The highly variable intensity and mix of each of these features is why autism is tagged as a spectrum. Adding further to the complexity of the phenotype is the fact that symptomatology is on a graded continuum. Though the majority of cases suffer from mental retardation, some individuals with less severe forms of the disorder (e.g. Asperger syndrome) are somewhat intellectually spared (Volkmar et al., 1998). Attempts to subcategorize the disease have been based on the levels of social interaction, development or cognition, yet it is clear that its highly variable symptomatology frustrates subgrouping (Beglinger and Smith, 2001; Shao et al., 2003; Tager-Flusberg and Joseph, 2003).

1.2. Etiologic heterogeneity of autistic symptomatology: genetic syndromes and pathogens

A second form of heterogeneity is etiologic. A number of specific medical conditions are associated with one or more features of autistic symptomatology (Deutsch, 1998, 2005; Geerts et al., 2003; Gilberg and Coleman, 1992). This is not to say that all of these diseases are necessarily equivalent to autism but these syndromes may share disruption in one or more genes or molecular pathways. These disorders include: Cornelia de Lange syndrome (Berney et al., 1999) [Gene map locus 3q26.3]; fragile-X (FMR-1) syndrome (Blomquist et al., 1985; de Vries et al., 1995) [Gene map locus Xq27.3]; Joubert syndrome (Ozonoff et al., 1999) [Gene map locus 9q34.3]; Moebius syndrome (Gillberg and Steffenburg, 1989) [Gene map locus, Type 1: 13q12.2-q13, Type 2: 3q21-q22]; Neurofibromatosis (Mbarek et al., 1999) [Gene map locus Type 1: 17q11.2]; Rett syndrome (Samaco et al., 2004) [Gene map locus Xq28]; and Tuberous sclerosis (Smalley, 1998) [Gene map locus Type 1: 16p13.3, 12q14, 9q34; Type 2: 16p13.3]. There is also a report of autism in Hypermelanosis of Ito, thought to be a marker of chromosomal mosaicism (Pascual-Castroviejo et al., 1988). The association between these identifiable conditions and autistic symptomatology may provide important insights into the underlying biology of autism, even among those individuals whose etiology is currently unknown.

Autistic symptoms are also sometimes seen among patients prenatally exposed to infectious disease. These include herpes encephalitis, cytomegalovirus, and rubella (reviewed by Lipkin and Hornig, 2003). Recently, mutations in the *Aristaless*-related homeobox gene ARX have been found to be associated with autistic symptomatology, as well as a host of other phenotypes, including myoclonic epilepsy and brain malformations (agenesis of the corpus callosum, midbrain dysmorphology, lissencephaly, reviewed by Sherr, 2003). However, the majority of autistic cases currently have no identifiable etiology (Deutsch, 2005; Moldin, 2003). It is remarkable that this assortment of conditions, with varying etiologies and symptoms, can share aspects of the autistic phenotype (Deutsch, 1998).

1.3. Macrocephaly as an endophenotype in autism

How might one obtain more homogeneous groups for the study of etiology and development in autism? One strategy is to utilize an endophenotype that is biologically related to the more complex behavioral phenotype, but which provides a simpler dependent measure (Gottesman and Gould, 2003). This endophenotype may also find application in subgrouping the heterogeneous disorder.

Typically in the choice of an endophenotype a balance is struck between the theoretical value of a measure and the practicality of its assessment on substantial samples of probands and/or relatives. Histopathologic findings are impractical, for obvious reasons, and there is also the problem of the miscellany of such findings in autism. These include anomalies of the cerebral cortex, the brainstem, the limbic system and the cerebellum, with significant heterogeneity (reviewed by Bauman and Kemper, 2003), although Bauman and Kemper's classic studies have shown some pattern of consistency across cases in the feature of reduced numbers of Purkinje cells in the cerebellum, and small tightly packed