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Molecular biology of autism's etiology – An alternative mechanism

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ABSTRACT

Autism is a neuropathologic condition believed to be the consequence of cerebral dysconnectivity. Hypomyelination of axons in brain nerve pathways parallels behavioral abnormalities characteristic of autism. The present discussion will examine the functional association of insulin-like growth factor-1 (IGF1) to neuron myelination, especially in autistic children. These structural defects apparently correlate with a reduced level of circulating IGF. In addition, the potential connection of single nucleotide polymorphism to the etiology of autism is considered. Pharmaceutical and nutritional supplements that may enhance IGF1 to reduce the incidence of autism are proposed.

IGF1 and autism

A study was carried out on sick children visiting a hospital Emergency Room [1]. Those children who were deemed candidates for lumbar puncture for various medical reasons had a portion of the collected spinal fluid tested for IGF as well. In the age range 1–4 years, levels of IGF1 in the CSF of autistic children were found to be consistently lower than that of neurologically normal children. In both groups, the IGF1 levels remained about the same from age 1 year until after 4. Girls characteristically have higher serum IGF1 levels than boys within a given age group, although males overall have autism four times as often as females in the same period [2,3].

Several studies have supported the proposed connection between IGF1 and normal neural function involving the myelination process [2]. In knockout laboratory test animals with reduced IGF1, myelin thickness and impulse velocity are decreased [4]. Biopsies from the brains of autistic humans exhibit thinner myelin layers than non-autistic individuals [5]. Autopsied corpus callosum from autistic patients has revealed changes consistent with immature myelin development [6]. This has also been observed in MRI brain evaluations of the white matter [7].

Translation of IGF1

In humans, insulin-like growth factor-1 (IGF1) biosynthesis is encoded on chromosome #12 bearing six exons [8]. There are at least two promoters regulating this gene transcription. Since IGF1 is not readily transported across the blood-brain barrier, the CNS must largely manifest its own synthetic capability. For example, the Purkinje cell has a high level of IGF1 mRNA until maturation peaks. Also, peripheral brain capillaries in humans have binding sites specific for IGF1 which can accomplish secondary passage of the growth factor.

Insulin-like growth factor-1 is a 70-unit polypeptide chain with three disulfide bonds between residues and a molecular weight of 7649 Daltons [9]. In the blood, 98% is joined to one of seven IGF-binding regulatory proteins ($IGFBP_{1\text{-}7}$) and to acid-labile subunit ALS [10]. At the cellular level, free IGF1 adheres to cell membrane-bound tyrosine kinase surface receptors (IGFR) [11]. Signal transduction is routinely executed by the factors in the transcellular chain [12,13]: IGF1/IGFR/IRS1/PI3K/AKT/mTOR.

The serum level of IGF1 is an indicator of overall availability of this growth factor. In healthy adults, the apparent half-life of serum IGF1 is 10–12 min and that of the carrier protein-bound polypeptide is 20–30 min [14]. The typical total production rate of IGF1 is calculated as 10 mg per day.

The component directly activating oligodendrocyte-based myelinogenesis is myelin regulatory factor (MYRF), supported by IGF1 [15]. IGF2 and insulin can also stimulate this action but to a lesser extent. Before birth, the main locus of IGF1 synthesis is the placenta; postpartum, the primary site is the liver for general distribution, although many other cells in the body can produce it locally as well. Growth hormone (GH) from the pituitary gland is the main postpartum control of IGF production via hepatic stimulation. The level of IGF1 is dependent on dietary intake, pituitary hormone status, age, body mass index, and genetic make-up.

In summary, myelinogenesis is promoted by IGF1. This biochemical messenger directs the differentiation of progenitor cells into oligodendrocytes, ultimately the key producer of myelin [16].

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Biosynthesis of myelin

The axons of many neurons in the central nervous system (CNS) are shielded with myelin [2]. This covering material insulates the neuronal axons, accelerates the passage of nerve impulses from source to objective, and sustains the functional pathways of the neurons. In this manner, dysconnectivity in the brain is minimized [17]. The increased velocity over myelinated axons is due to reduced ion leakage, improved synaptic function, saltatory impulse movement, and decreased cell membrane capacitance [18].

Two-thirds of all the axons in the body are unmyelinated. Such axons have radii of 0.05–0.6 μm and conduction speeds of $1.8\sqrt{a}$, where a is the axonal radius. In contrast, myelinated axons typically have overall radii of 0.5–10 μm and conduction speeds of 12(a + b), where b is the myelin sheath thickness. A typical adult brain has about 100 billion neurons [19].

Myelin sheaths are composed of 80% lipid and 20% protein [20]. The primary protein components are proteolipid protein (PLP), 2′:3′-cyclic nucleotide-3′-phosphodiesterase (CNP), myelin-associated glycoprotein (MAG), and myelin basic protein (MBP). Aggregate cultures from fetal rat brain treated with IGF show marked increases of CNP and oligodendrocytes [21,22]. The emergence of enhanced MBP can also serve as a marker for this transition [23].

Myelination of new neurons in the CNS of the human fetus begins in 24–25 weeks post-conception [24]. The rate peaks at 1-year postpartum and tapers off gradually until about 25–30 years of life. Oligodendrocyte precursor cells (OPCs) arise from pluripotent cells in neurogenesis [25]. OPCs are highly migratory, proliferative, hardy, and vigorously myelogenic. However, if the level of IGF1 is reduced, the differentiation of OPCs to generate functional oligodendrocytes is diminished and rapid death of OPCs ensues [26]. Oligodendrocyte loss results in demyelination [27]. This can lead to impaired neurologic functions such as those changes seen in multiple sclerosis and autism.

In the CNS, functional oligodendrocytes, a type of neuroglia, can each be linked to as many as 50 axons for the purpose of creating and maintaining myelogenesis [16]. In the fetal brain, the first wave of OPC formation occurs in the medial ganglionic eminence; the second wave develops in the medial forebrain; and the third wave, near the time of birth, extends from the dorsal and outer subventricular zones. The dysconnectivity characteristic of autism typically affects the posterior-to-anterior neural pathways, among others, in the brain [17].

Detection of autism potential

As of now, autism is largely an irreversible condition once it is overtly evident through psychological testing. In some cases, autism spectrum disorder (ASD) symptoms may improve to some degree with early psychotherapeutic intervention. The behavior traits characteristic of autism are believed to be the result of brain dysconnectivity developed during the infantile and early childhood years [17,28–33]. ELISA detection of deficient serum IGF1 in umbilical cord blood collected at delivery, for example, may allow early initiation of supplementation to minimize subsequent development of primary symptoms of autism. Antepartum cordocentesis could potentially be employed in highly suspicious cases, especially in gravid women with one or more prior affected offspring.

Multiple SNPs (single nucleotide polymorphisms) have been identified in various conditions. In particular, polymorphic IRS1 (rs1801123) reduces the translation of IGF1 (see pathway above). Allele frequency analysis determined a statistically significant association between this SNP and autism [34]. Deficiency of IGF1 is often associated with enhanced autism potential in young children. This shortage could be alleviated by breast-feeding, vitamin D supplement, or parenteral/oral provision of (Des)IGF or $IGF_{1\text{-}3}$, thereby avoiding this malady at a later age [35–41]. Study of the genotypes and allele distributions of rs878960 polymorphism can distinguish severe from mild/moderate autism groups as well [42].

Thus, the SNP-created reduction in IGF1 expression in the neonate causes inadequate neuronal myelination. As a consequence, altered brain circuitry produces permanent cephalic disarray, resulting in the characteristic behavioral challenges of autism. To varying degrees, the SNPs discussed here reduce, but do not totally eliminate, the influence of IGF1. This is consistent with the broad range and degree of signs/symptoms found commonly within autism spectrum disorder (ASD) cases.

Autism biomarkers

To date, no major genetic mutation has been identified in the preponderance of studied classical autism cases. This would preclude such conditions as Rett Syndrome and Fragile X which resemble autism in only some physiological and psychosocial characteristics, and occur much less frequently. Whereas individuals with Rett Syndrome are characterized by microcephaly, frontal cortex pathology, occurrence almost exclusively in females, and cholinergic neuron dysfunction, classical autism is contrariwise in these features [43]. Furthermore, in Rett Syndrome cases, a specific mutation (MECP2) is typically present, whereas this genetic anomaly is found in only about 1% of autism occurrences [44].

The present report has enumerated biochemical features of true autistic cases which distinguish them from less common disorders bearing some, but not all, analogous characteristics. One or more early-warning biomarkers detected at birth (or earlier) could be anticipatory for the later appearance of authentic autistic disease [41,45]:

1) Deficient serum IGF1
2) Anti-myelin basic protein
3) Elevated serotonin
4) Single nucleotide polymorphism rs1801123; or
5) Single nucleotide polymorphism rs878960.

Such timely detection could conceivably allow prompt correction of the biochemical fault(s) before permanent neuro-psychological abnormalities appear.

Reduction of autism potential

Using this information, it may be possible to reduce or eliminate the appearance of autism in babies. Plausible preventive treatments include:

1) Human breast milk contains a high level of IGF1. Children breast-fed exclusively for the first several months of life present a significantly lower incidence of autism than those fed bovine milk or formula [35,36].
2) Oral supplementation of vitamin D increases the circulating level of IGF1 significantly [37–39]. Gravid women who were deficient in vitamin D at mid-gestation were twice as likely to deliver children who eventually developed autism than those who were normal in this nutrient. The recurrence rate of producing autistic children in mothers who already have affected offspring is 20%. In a successive pregnancy, where the mother was given vitamin D supplement during the gestation and the neonate was fed the same vitamin postpartum, only 5% of the new babies were autistic.

Conclusions

Since the initial psychological report by Leo Kanner in 1943 [46], relatively little formal biochemical/neurological research on the cause of autism had been carried out until the end of the 20th century. As a result of studies of autism in twin sets, numerous investigations have addressed possible genetic abnormalities, in particular [47]. However,

researches into cases of classical autism accompanied by major genomic mutations can deduce a plausible etiology in only a small percentage of instances.

Key bio-molecular characteristics of this neurologic syndrome have since been uncovered. Findings related to biochemical deficiencies appearing early in the newborn, such as depressed IGF1 in neurogenesis, are becoming emphasized. Progress leading to timely diagnosis and subsequent prevention of CNS dysconnectivity seems plausible. The tendency for an infant to develop autism may now be determinable and preventable before irreversible psychosocial disturbances become established.

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Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.109272.

References

[1] Riikonen R. Cerebrospinal fluid insulin-like growth factors IGF-1 and IGF-2 in infantile autism. Devel Med Child Neuro 2006;48(9):751–5.
[2] Steinman G, Mankuta D. Insulin-like growth factor and the etiology of autism. Med Hypoth 2013;80:475–80.
[3] Yuksel B, Ozbek MN, Mungan NO, et al. Serum IGF-1 and IGFBP-3 levels in healthy children between 0 and 6 years of age. J Clin Res Ped Endo 2011;3(2):84–8.
[4] Beck KD, Powserll-Braxton L, Widmer HR, et al. IGF-1 gene disruption results in reduced size, CNS hypomyelination, and loss of hippocampal granule & striatal parvalbumin-containing neuron. Neuron 1995;14:717–30.
[5] Zikopoulos B, Barbas H. Changes in prefrontal axons may disrupt the network in autism. J Neurosci 2010;30(44):14595–608.
[6] Koul O. Myelin and autism. In: Bauman ML, Kember TL, editors. The neurobiology of autism. 2nd ed.Johns Hopkins University Press; 2005 chapter 11.
[7] Deoni SCL, Murcure E, Blasi M, et al. Mapping infant brain myelination with magnetic resonance imaging. J Neuro Sci 2011;31(2):784–91.
[8] Hoppner JW, de Pagter-Holthuizen P, VanKessel AH. The human gene encoding insulin-like growth factor I is located on chromosome 12. Hum Genet 1985;69(2):157–60.
[9] Rindelknecht E, Humbel RE. The amino acid sequence of human insulin-like growth factor 1 and its structural homology with proinsulin. J Biol Chem 1978;253(8):2769–76.
[10] Boisclair YR, Rhoads RD, Ueki I, et al. The acid-labile subunit (ALS) of the 150 kDa IGF-binding protein complex: an important but forgotten component of the circulating IGF system. J Endocrin 2001;170:63–70.
[11] Chen J, Alberts I, Li X. Dysregulation of the IGF-I/PI3K/AKT/mTOR signaling pathway in autism spectrum disorders. Int J Devl Neurosci 2014;35:35–41.
[12] Manning BD, Cantley LC. AKT/PKB signaling: navigating downstream. doi: 10.1016/J.Cell.2007.06.009.
[13] Bibollet-Bahena O, Almazan G. IGF-1-stimulated protein synthesis in oligodendrocyte progenitors requires PI3K/mTOR/AKT and MEK/ERK pathways. J Neurochem 2009;109(5):1–8.
[14] Guler HP, Azpf J, Schmid C, et al. Insulin-like growth factors I & II in healthy man. Estimations of half-lives and production rates. Acta Endrocrinol (Copenh) 1989;121(6):753–8.
[15] Emery B, Agalliu D, Cahoy JD, et al. Myelin gene regulatory factor is a critical transcriptional regulator required for CNS myelination. Cell 2009;138:172–85.
[16] Kessaris N, Forgarty M, Iannarzelli P, et al. Competing waves of oligodendrocytes in the forebrain and postnatal elimination of an embryonic lineage. Nat Neurosci 2006;9:173–9.
[17] Steinman G. Plausible etiology of brain dysconnectivity in autism. Med Hypoth 2015;85:405–7.
[18] Purves D, Augustine GJ, Fitzpatrick E, editors. Neuroscience. fifth ed.Sunderland, Mass.: Sinauer Associates; 2012. p. 25–40.
[19] Herman P. Physics of the human body, Nerve conduction, Springer-Verlag, Heidelberg, 2007, p. 721.
[20] Baumann N, Pham-Dinh D. Biology of oligodendrocytes of the mammalian central nervous system. Phys Rev 2001;81(2):871–927.
[21] Gravel M, Peterson J, Yong VW, et al. Overexpression of 2',3' cyclic nucleotide-3'-phosphodiesterase in transgenic mice alters oligodendrocyte development and produces aberrant myelination. Mol Cell Neurosci 1996;7:453–66.
[22] Fox IJ, Daley GQ, Goldman SA, et al. Use of differentiated pluripotent stem cells in replacement therapy for treating disease. Science 2014;345(6199). https://doi.org/10.1126/Science.1247391.
[23] Mozell RL, McMorris FA. Insulin-like growth factor I stimulates oligodendrocyte development and myelination in rat brain aggregate cultures. J Neurosci Res 1991;30(2):382–90.
[24] Bradl B. Oligodendrocytes: biology and pathology. Acta Neuropathol 2010;119:37–53.
[25] Cameron-Curry P, LeDouarin NM. Oligodendrocyte precursors originate from both the dorsal and ventral parts of the spinal cord. Neuron 1995;15(6):1299–310.
[26] Hseih J, Aimone JB, Kaspar BK, et al. IGF-1 instructs multipotent adult neural progenitor cells to become oligodendrocytes. J Cell Biol 2004;164(1):111–22.
[27] Goldman SA, Kuypers NJ. How to make an oligodendrocyte. Development 2015;142:3983–95.
[28] Kana RK, Libero LE, Moore MS. Disrupted cortical connectivity as an explanatory model for autism spectrum disorders. Phys Life Rev 2011;8:410–37.
[29] Mohammad-Rezazadeh I, Frohlich J, Loo SK, et al. Brain connectivity in autism spectrum disorder. Curr Opin Neurol 2016;29(2):137–47.
[30] Belmonte MK, Allen G, Beckel-Mitchener A, et al. Autism and abnormal development of brain connectivity. J Neurosci 2004;24(42):9228–31.
[31] Woodward ND, Giraldo-Chica M, Rogers B, et al. Thalamocortical dysconnectivity in autism spectrum disorder: an analysis of the autism brain imaging data exchange. Biol Phys Cogn Neurosci Neuroim 2017;2(1):76–84.
[32] Pereira AM, Campos BM, Coan AC, et al. Differences in cortical structure and functional MRI connectivity in high functioning autism. doi: 10.3389/ fneur.2018.00539.
[33] King JB, Prigge BD, King CK, et al. Evaluation of differences in temporal synchrony between brain regions in individuals with autism and typical development. JAMA Network Open 2018;1(7):1–14.
[34] Park HJ, Kim SK, Kang WS, et al. Association of IRS1 gene polymorphism and autism spectrum disorder: a pilot case-control study in Korean Males. Int J Mol Sci 2016;17:1227–36.
[35] Steinman G, Mankuta D. Breastfeeding as a possible deterrent to autism a clinical perspective. Med Hypoth 2013;81:999–1001.
[36] Tseng PT, Chen YW, Stubbs B. Maternal breastfeeding and autism spectrum disorder in children: a systematic review and meta-analysis. Nutr Neurosci 2017;18:1–9.
[37] Ameri P, Giusti A, Boschetti M, et al. Vitamin D increases circulatory IGF1 in adults: potential implication for the treatment of GH deficiency. Eur J of Endocrin 2013;169:767–72.
[38] Vinkhuyzen AAE, Eyles DW, Burne THJ, et al. Gestational vitamin D deficiency and autism spectrum disorder. BJPsych Open 2017;3:85–90.
[39] Stubbs G, Henley K, Green J. Autism: will vitamin D supplementation during pregnancy and early childhood reduce the recurrence rate of autism in newborn siblings? Med Hypoth 2016;88:74–8.
[40] Steinman G, Mankuta D. Gene polymorphism in the genesis of autism. BAOJ Neurol 2018;4(2):58–60.
[41] Steinman G. IGF autism prevention/amelioration. Med Hypoth 2019;122:45–7.
[42] Jiao Y, Chen R, Ke X, et al. Single nucleotide polymorphisms predict symptom severity of autism spectrum disorder. J Autism Dev Disord 2012;42(6):971–83.
[43] Riikonen R. Neurobiological regulators of brain growth in autism. In: Zimmerman AW, editor. Autism current theories and evidence. Totowa, NJ: Humana Press; 2008. p. 239.
[44] Nagarajan RP, Hogard AR, Gwye Y, et al. Reduced MeCP2 expression is frequent in autism frontal cortex and correlates with aberrant MECP2 promoter methylation. Epigenetics 2006;1(4):e1–11.
[45] Steinman G, Mankuta D. Umbilical cord biomarkers in autism determination. Biomark Med 2014;8(3):317–9.
[46] Kanner L. Autistic disturbances of affective contact. Nerv Child 1943;2:217–50.
[47] Bespalova IN, Reichert J, Buxbaum JD. Candidate susceptibility genes for autism. In: Bauman ML, Kember TL, editors. The neurobiology of autism. 2nd ed.Johns Hopkins University Press; 2005 chapter 16.

Glossary

AKT: protein kinase B
ALS: acid-labile subunit
ASD: autism spectrum disorder
CNS: central nervous system
CSF: cerebrospinal fluid
IGF1: insulin-like growth factor-1
IGF2: insulin-like growth factor-2
IGFR: IGF receptor
IRS1: insulin receptor substance-1
mTOR: mammalian target of rapamycin
OPC: oligodendrocyte precursor cell
PI3K: phosphoinositide-3-kinase
RNA: ribonucleic acid
SNP: single nucleotide polymorphism