American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Opinion

Is Cholesterol the Key Factor for Autism?

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To Cite This Article: *Clifford Lingwood, Is Cholesterol the Key Factor for Autism?. 2020 - 7(6). AJBSR.MS.ID.001206.*

DOI: 10.34297/AJBSR.2020.07.001206.

Opinion

It is hard to reconcile the many genetic and environmental risk factors for ASD [1,2] to a single mechanism. However, modulation of transmembrane signaling by cholesterol and/or glycosphingolipids (GSLs), both enriched in lipid rafts, and their interlinked metabolism [3], could provide the basis of such an all-encompassing axis. Membrane cholesterol is important in neuronal development. 25% of the body's cholesterol is in myelin. Most GSLs are also in brain, particularly gangliosides, as the name implies. Surprisingly, the neural distribution of cholesterol (and GSLs) remains poorly defined. Abnormal cholesterol metabolism/transport is associated with many neuropathies [4] -Alzheimer's [5], Parkinson's [6], epilepsy [7] and lysosomal storage diseaneuropathies [8,9]. GSL biosynthesis is central in neuronal development [10], particularly myelination [11], and is also aberrant in neurological disease [9,12-13].

Cholesterol/GSL complex

Membrane cholesterol and GSLs accumulate in lipid rafts, ubiquitous eukaryotic signaling foci, central to many pathways, particularly, in this context, neurotransmitter signaling [14]. Rafts are more ordered than non-raft membranes due to the rigid character of both GSLs and cholesterol. GSLs and cholesterol form a complex (1:3) in which we showed the GSL carbohydrate is reoriented from a membrane perpendicular to parallel format. The steroid OH, key for cholesterol binding, is masked by the membrane parallel GSL carbohydrate 'umbrella' [15,16]. Membrane parallel GSL is far less available for external ligand binding ('trans' recognition)- but may be more prone to lateral ('cis') ligand binding. The membrane complex serves to reduce trans ligand binding to both GSLs and cholesterol. βMethyl cyclodextrin cholesterol extraction remarkably increases tissue and cell GSL 'unmasking' for ligand binding [17]. In cell derived model membranes, cholesterol/GSL masking is also actin dependent [18], suggesting a cytoskeletal role. Cell treatment with a GSL binding ligand e.g. Shigatoxin increased filipin staining of cholesterol, while cell pre-treatment with filipin increased binding of GSL ligands, e.g. Stix, cholera toxin B subunit (binds GM1) [17]. This is a kind of biological 'transistor'.

Common cholesterol ASD pathway?

Many factors impinge cholesterol levels: transcription [19] (SREBP1/2) [20], microRNA [21], transport [22], translation [23], metabolism [24], degradation [25], ERAD [26], and statins[27]. Cholesterol, in GSL-enriched lipid rafts, could link diverse ASD associated genes. Moreover, the synapse Arc protein, a key to long term memory/synaptic plasticity [28], is related to the HIV retrovirus GAG capsid protein, and transports nascent RNA in virus-like exosome particles in, and between, neuronal cells [29]. HIV virus budding is via the cholesterol dependent [30] exosome pathway [31]. Thus, Arc protein intra/inter neurocellular RNA transport will be cholesterol dependent. In turn, exosome formation requires tetraspanin proteins [32], which bind GSLs [33]. Thus, cholesterol and/or GSL dependent defects in this essential RNA transport mechanism, could affect a wide range of neurological gene expression, which, in addition to direct cholesterol/GSL roles indicated below, may impinge ASD.

Brain cholesterol is central to ASD

Several genetic diseases are important in ASD: Smith-Lemli-Opitz Syndrome (SLOS), a cholesterol biosynthesis defect [34], has an 80% ASD incidence [35]. Low serum cholesterol is associated with ASDs [36]. Moreover, increased dietary cholesterol can ameliorate ASD symptoms [37]. Low cholesterol was found in male ASD individuals [38] and a recent retroactive case-controlled study confirmed the overall hypocholesterolemia of ASD individuals [39], speculating this is a basis for treatment. Furthermore, the cholesterol precursor which accumulates in SLOS, is increased in ASD patients in general and proposed as an autism marker [40]. The mouse model of SLOS shows abnormal development of sero-

tonin neurons [41], a feature of ASD [42]. SLOS reduces cholesterol controlled [43] sonic hedgehog signaling *in vitro* [44]. In a significant study [45], the levels of cholesterol in red cells from autistic patients were found consistently lower than normal red cells, and conversely, the level of GM1 GSL, detected using CTB binding, was increased. We contend, based on our GSL masking studies [16] that the lower cholesterol results in decreased masking of GM1 ganglioside in ASD red cells (and all cell types) thereby allowing increased CTB binding. Thus, cholesterol restriction of CTB-GM1 binding is less in these autistic cells. Cerebrospinal fluid GM1[46,47] in autistic children is 'increased' and anti GM1 titre [48] correlates with disease severity. This is consistent with less cholesterol masking of neuronal GM1, and greater membrane fluidity increasing GM1 shedding [49], both promoting GM1 immunogenicity.

In many syndromes in which ASD symptoms are manifest, and animal models of ASD, low cholesterol is a feature [50]. In Sanfilippo Syndrome often misdiagnosed as autism, chondroitin sulfate accumulates [51], including on the cholesterol transporter, apolipoprotein-O [52] to increase regional cholesterol. Fragile X syndrome shows increased ASD incidence [53] and lower cholesterol levels [54,55]. Some studies, however, suggest higher ASD cholesterol [56]. Rett syndrome is associated with high cholesterol and ASD [57]. Other genetic syndromes which show ASD-like symptoms and defects in cholesterol metabolism include Cornelia de Lange syndrome [58], tuberous sclerosis complex [59] and Angelman-like syndrome [60]. The serotonin system is abnormal in ASD [61] and the serotonin1A receptor, a key ASD risk factor [62], has a GSL binding site, binds GM1 ganglioside [63] and binds [64] and is modulated by cholesterol [65]. Nerve growth factor (plays a role in ASD verbal defects [66]) receptor is bound/regulated by gangliosides [67]. ASD mTOR signals are abnormal [68] and cholesterol regulates mTOR signaling [69]. Wnt signaling is also a key feature of neurological development and ASD [70] and is regulated by cholesterol [71]. GABA synapse signaling is affected in ASD [72] and the GABA receptor binds cholesterol [73]. PTEN tumor suppressor is associated with ASD [74]. PTEN phosphoinositide dephosphorylation is regulated by cholesterol [75]. Lower brain cholesterol reduces memory/learning [25]. Lower brain cholesterol is a feature of the valproic acid rat model of ASD [76].

The central role of cholesterol in lipid rafts and the central role played by lipid rafts in neurological transmembrane signaling suggests that membrane hypocholesterolemia typical of ASD, could provide the link between the many identified ASD risk factors. The neurological importance of glycosphingolipids and their modulation by/of cholesterol is likely a component of this neurological enigma.

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