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Article Addendum

Why is intelligence correlated with semen quality?

Biochemical pathways common to sperm and neuron function and their vulnerability to pleiotropic mutations

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Abbreviations: AA, arachidonic acid; AR, acrosomal reaction; DHA, docosahexaenoic acid; GDNF, glial cell line-derived neurotrophic factor; GFRα, GDNF family receptor α; PUFA, polyunsaturated fatty acids; SNAP-25, snaptosome-associated protein of 25 kDa; SNARE, soluble NSF-attachment receptor

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We recently found positive correlations between human general intelligence and three key indices of semen quality, and hypothesized that these correlations arise through a phenotype-wide 'general fitness factor' reflecting overall mutation load. In this addendum we consider some of the biochemical pathways that may act as targets for pleiotropic mutations that disrupt both neuron function and sperm function in parallel. We focus especially on the inter-related roles of polyunsaturated fatty acids, exocytosis and receptor signaling.

In a recent paper we reported a positive association between general intelligence and semen quality in male humans. Specifically, in a sample of 425 Vietnam-era veterans, we found positive correlations between a *g* factor (representing general intelligence, extracted from factor analysis of five well-validated cognitive tests) and three independent measures of semen quality: sperm concentration (r = 0.15, p = 0.002), sperm count (r = 0.19, p = 0.001) and sperm motility (r = 0.14, p = 0.002). None of these correlations were mediated by age, body mass index, combat experience in Vietnam, use of alcohol, tobacco, marijuana or hard drugs or days of sexual abstinence before collection of the semen sample. We argued that although these correlations were small in magnitude, they might be theoretically important for understanding the evolutionary genetics of human phenotypic variation.

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From an adaptationist viewpoint, there is little reason to expect a correlation in functional efficiency between two such disparate traits: intelligence depends mainly on brain function and neural development, whereas semen quality depends mainly on testicular function and spermatogenesis. Nonetheless, we hypothesized that there may be pervasive positive correlations among the functional efficiencies of many organ systems because different organs are influenced by overlapping sets of genes. Since most genes are pleiotropic (affecting several traits in parallel), most mutations are likely to have pleiotropic effects in disrupting several traits in parallel. Potentially, such pleiotropic mutations could produce positive genetic correlations in the functional efficiencies of different organ systems, yielding positive phenotypic correlations in different components of fitness, such as intelligence and fertility.

However, in that paper we did not explore the specific biochemical pathways in brain and semen that might be disrupted conjointly by such pleiotropic mutations. Here we address this gap by reviewing some evolutionarily conserved processes that underlie both neuron function and sperm function, focusing especially on the roles of polyunsaturated fatty acids (PUFAs), exocytosis and receptor signaling. The genetic, biochemical and physiological overlap between brain function and semen function illustrates why pleiotropic mutations may create a general 'fitness factor' across many phenotypic traits—not only in humans, but in all organisms subject to a balance between harmful mutations and purifying selection.

Polyunsaturated Fatty Acids (PUFAs)

Both neurons and sperm have high concentrations of PUFA relative to other body tissues. Specifically, the long chain PUFAs docosahexaenoic acid [22:6(n-3)] (DHA) and arachidonic acid [20:4(n-6)] (AA) are the dominant essential fatty acid components of the brain. They are concentrated at synaptic terminals and play a central role in neurodevelopment function[1] and maintenance. Crawford[2] and Broadhurst[3] described the high degree of

evolutionary conservation of DHA and AA in the brains of land mammals, including humans. While AA is readily available in the land-based food chain, DHA is available largely from the marine food chain, suggesting that hominids probably evolved with access to seafood in addition to hunted land animals.

Regarding semen, a substantial literature describes tight genetic regulation of sperm metabolism of PUFAs during spermatogenesis, with stage-specific differences in lipid metabolism likely driving the morphological and functional changes as the immature germ cells become mature spermatozoa.[4] Moreover, intracellular differentiation in cells such as sperm (which lack the enzymatic machinery to synthesize new membrane proteins) depends upon spatial compartmentalization of membrane microdomains of lipids and proteins (lipid rafts) to coordinate the sequences of signal transduction required for spermatogenesis, maturation, capacitation, acrosomal reaction (AR) and ultimately fertilization. It is likely that DHA metabolism has been conserved over evolutionary time in both sperm and neurons due to its superior efficiency and flexibility in interacting with membrane proteins,[5] providing superior speed and fluidity in coordinated activities such as vesicular traffic of neurotransmitters[6] and signal transduction via lipid raft assembly.[7]

DHA may also contribute π electrons to membranous signal control of potential differences across the lipid bilayer with a quantum precision uniquely afforded by its symmetrical array of alkenyl groups.[2] This mechanism may also function in photo transduction within photoreceptors, where high concentrations of DHA are thought to stabilize photoisomerization of rhodopsin in the plasma membrane.[8]

Similarly, sperm and retinal photoreceptor cells, in addition to olfactory sensory neurons, seem to share functional similarities in employing cyclic nucleotide-gated ion channels in response to chemotactic, photonic and odorant signals, respectively.[9] Many of these channels in sperm are T-type voltage-gated Ca^{2+} ion channels involved in AR regulation,[10,11] while other odorant gene family receptors that are sperm-specific appear to directly regulate sperm motility and chemotaxis by downstream activation of $Ca_V3.2$ ($\alpha 1_H$) Ca^{2+} ion channels.[12,13] The *CACNA1H* gene encodes this ion channel, which is heavily expressed in the neocortex as well, and various mutations have been implicated in case studies of childhood absence seizures[14] and idiopathic generalized epilepsy.[15]

Exocytosis and Receptor Signaling

In addition to odorant receptors, mammalian sperm are known to express many other "neuronal" and classical neurotransmitter receptors implicated in essential roles of sperm function,[16] particularly exocytosis. While the adaptive functions of sperm and neurons are ostensibly different, exocytosis is central to their individual abilities to perform these functions, and striking parallels in exocytosis function have been described. Neurons use exocytosis for neurite outgrowth and to release neurotransmitters from synaptic vesicles, while sperm use exocytosis to perform the acrosomal reaction (AR), in which the plasma membrane of the sperm fuses with the egg's plasma membrane to facilitate fertilization.[17] The acrosome is thus a modified secretory vesicle,[18] containing enzymes and other fertilization factors, and seems analogous to the neurotransmitter vesicles that fuse with the plasma membrane of the neuron to release its contents into the synaptic cleft. Biochemically, conception is a sort of synaptic communication between gametes—or synaptic communication is the way neurons impregnate each other with information.

To perform this exocytosis, sperm and neurons both use an intricate system of plasma membrane proteins consisting of syntaxin [a SNARE (soluble NSF-attachment receptor) protein], SNAP-25 (synaptosome-associated protein of 25 kDa), and synaptobrevin, among others.[19] PUFAs directly modulate this system by increasing the physiological efficacy of lipid rafts aggregating these proteins, as well as undergoing intracellular phospholipase action (due to their favorable dissociation mechanics) to produce arachidonic acid, a soluble PUFA not requiring a protein chaperone.[20] AA in turn activates the membranous protein complex to initiate membrane fusion in exocytosis.[21]

Another physiological example that nicely highlights the relationship of "neural" factors, PUFAs and ion channel signaling in sperm concerns glial cell line-derived neurotrophic factor (GDNF), a factor originally described for its integral role in maintenance of midbrain dopaminergic neuron[22] as well as motor neuron populations[23] of the brain. In an elegant study, Meng et al.[24] demonstrated that GDNF, also known to play a key role in genital morphogenesis, tightly regulates the rate of self-renewal and differentiation of spermatogenic stem cells in the seminiferous tubule via the paracrine secretions of adjacent Sertoli cells. In animal models with GDNF haploinsufficieny, spermatogenic stem cells are depleted and there is an increase in differentiated spermatogonia, until the stem cells are depleted and the seminiferous tubules are occupied by Sertoli cells only. This would reduce semen quality over the long term. Conversely, when GDNF levels are too high, the spermatogenic stem cells selectively self-renew and there is a paucity of differentiated cells. Interestingly, GDNF has been the subject of intense medical research due to its demonstrated neuroprotective and neurorestorative properties in the dopaminergic neurons of animal models simulating the pathobiology of Parkinson's disease.[25]

Notably, GDNF exerts its intracellular effects through a complex pathway that involves initial binding to and dimerization of specific GDNF family receptor α (GFRα) proteins. The dimerized GFRα structure then recruits and dimerizes two molecules of Ret protein that undergo transphosphorylation, activating downstream signaling involving the MAP kinase, phosphoinositide 3-kinase (PI3K), and phospholipase Cγ (PLC-γ) pathways, among others.[26] Phospholipase C cleaves membranous phospholipids to release soluble inositol 1,4,5-triphosphate (IP3), which is the primary mechanism for non-voltage gated receptor-activated Ca^{2+} signaling. The recruitment and dimerization of plasma membrane proteins, the activity of intracellular phospholipase activity, and the utilization of Ca^{2+} channel signaling are all thus contingently mediated by the underlying quality of PUFAs.

Conclusion

The inter-related biochemistry of PUFAs, exocytosis and receptor signaling, all show commonalities across sperm and neurons. The many genes and genetic regulatory systems that

influence this common biochemistry may provide common targets that could be disrupted by pleiotropic mutations, which would disrupt both sperm function and brain function in parallel. Such effects could partially explain the modest correlation between semen quality and intelligence. These examples of overlapping sperm and neuron biochemistry do not constitute our hypothesized mechanism for fully explaining the observed semen-intelligence correlation. Rather, they are intended only to illustrate the types of genetic and biochemical pathways that make pleiotropic mutations a plausible mechanism for explaining diverse positive correlations in functional efficiency across apparently unrelated organ systems. Evolution tends to conserve basic cellular biochemistry across different organs, tissues and cell types, so it should not be surprising that the mutations tend to create correlated disruptions in functional efficiency across different physical and psychological adaptations. These correlated disruptions must give rise to positive correlations in measures of adaptive function across different organic systems, even those at opposite ends of the spinal cord, and opposite extremes of consciousness.

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