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How lipids may affect risk for suicidal behavior

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A B S T R A C T

Suicide and nonfatal suicidal behaviors are major causes of mortality and morbidity worldwide. Variability in rates of suicide and suicidal behaviors within and between countries has been attributed to population and individual risk factors, including economic status and cultural differences, both of which can have suicide risk effects mediated through a variety of factors, of which perhaps the least understood is the role of diet. We therefore review the scientific literature concerning two major dietary lipid classes, cholesterol and polyunsaturated fatty acids (PUFAs), that have been associated with higher risk of suicide attempts and suicide. We consider potential mechanistic intermediates including serotonin transporters and receptors, toll-like receptors (TLRs), nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), and peroxisome proliferator activated receptors (PPARs). Based on this review, we describe a theoretical model linking cholesterol and PUFA status to suicide risk, taking into account the effects of cholesterol-lowering interventions on PUFA balance, membrane lipid microdomains (rafts) as a nexus of interaction between cholesterol and omega-3 PUFAs, and downstream effects on serotonergic neurotransmission and specific inflammatory pathways.

1. Introduction

1.1. Lipids and suicide

Suicide and suicidal behaviors are among the leading causes of death and injuries worldwide. Approximately 800,000 people die from suicide each year, and suicide is the second leading cause of death in the 15-29 year-old cohort. Ten to twenty times more individuals attempt suicide, indicating that both suicide and non-fatal suicidal behaviors are prevalent and need to be addressed (World Health Organization, 2014).

To understand the causes of suicide, prevalent explanatory models have focused on psychological factors such as feelings of thwarted belongingness, perceived burdensomeness, and hopelessness (Van Orden et al., 2010); neurobiological factors such as genetic risk, serotonergic functioning, and altered stress responses (Mann et al., 1999; Oquendo et al., 2014); and cultural factors (Chu et al., 2018).

Rates of suicide and suicidal behaviors vary geographically, with higher rates of suicide occurring in lower per capita-income regions (World Health Organization, 2017). Some portion of this variability may be attributable to economic and cultural differences that influence nutrition and in this way can impact the diathesis or predisposition to suicide behavior. One nutritional factor proposed to impact suicide and suicidal behavior is dietary lipid intake, presumably through lipid effects on brain. Two major lipid classes have been implicated in suicide risk, cholesterol and polyunsaturated fatty acids (PUFAs). We here review the evidence associating low cholesterol and low n-3 relative to n-6 PUFAs with suicide and suicidal behaviors. Finally, we present a neurobiological model proposing that the actions and interactions of cholesterol and PUFA status may influence suicide risk through effects on decreased serotonergic neurotransmission and/or increased inflammation (see Fig. 1).

1.2. Low cholesterol and suicide risk

Cholesterol and cholesterol metabolites are abundant in the brain. Accounting for 2% of body weight, the brain has 25% of total body cholesterol (Dietschy and Turley, 2001). Cholesterol is essential for cell membrane stability and neurotransmission (Ghaemi et al., 2000). An association between cholesterol and suicide was first reported in a 1990 meta-analysis of primary intervention trials in cardiovascular illness, which found that cholesterol lowering treatments led to an excess in

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; PPARs, peroxisome proliferator-activated receptors; TLR, Toll-like receptor; NF-KB, nuclear factor kappa-light-chain-enhancer of activated B cells; 5-HT, 5-hydroxytryptamine (serotonin); PUFAs, polyunsaturated fatty acids

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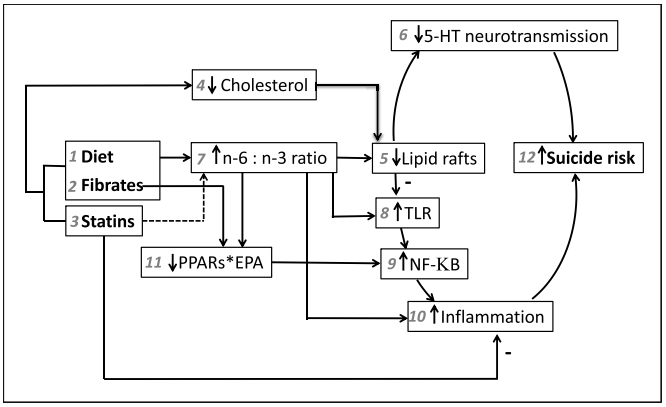

Fig. 1. Treatment with (*1*) diet, (*2*) fibrates and (*3*) statins that lower (*4*) cholesterol can cause (*5*) disruption of lipid rafts with functional consequences, due to lipid raft regulation of serotonin transporters and receptors, resulting in (*6*) decreased serotonergic neurotransmission, which has been shown to increase (*12*) suicide risk. (*1*) Diets replacing saturated fats with polyunsaturated oils high in n-6 PUFAs and (*2*) fibrates also can cause an increase in (*7*) the ratio of n-6 to n-3 PUFAs. This is, effectively, a lowering of n-3 that also is expected to contribute to (*5*) destabilization of lipid rafts, although directional effects of PUFAs on lipid rafts are complex and incompletely understood. More clearly, a higher n-6 to n-3 PUFA ratio directly promotes (*10*) inflammation, which is associated with (*12*) suicide risk. Also, lower n-3 PUFAs can indirectly result in increased inflammation by lowering DHA-mediated inhibition of (*8*) TLR dimerization and activation, resulting in downstream increased activation of (*9*) NF-KB, a (*10*) pro-inflammatory molecule. Either (*1*) decreased n-3 intake or (*2*) fibrate competition with EPA can reduce EPA binding to PPARs. Since (*11*) the EPA*PPARs complex acts as a brake on (*9*) NF-KB, interference with the EPA*PPARs complex via both mechanisms also contributes to activation (disinhibition) of (*9*) NF-KB. Counter to these pro-inflammatory forces, (*5*) decreased lipid raft functioning could decrease (*8*) TLR recruitment into lipid rafts and activation; and (*3*) statins may have lesser effects on (*7*) the n-6 to n-3 ratio and they also exert pleiotropic (*10*) anti-inflammatory effects that may mitigate (*12*) suicide risk. See text for all references substantiating these relationships.

non-illness mortality, mostly suicide and injury (Muldoon et al., 1990). A second meta-analysis was carried out by the same group 11 years later, after hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, or statins, became the most commonly used cholesterol-lowering drug class. The authors concluded that overall, cholesterol-lowering treatments were not related to non-illness mortality, and that statins showed a tendency to reduce non-illness mortality (Muldoon et al., 2001). Non-statin treatments, however, including diet, did exhibit a trend ($p = 0.06$) toward increased mortality from suicide, accidents and trauma (Muldoon et al., 2001).

In parallel, observational studies of cholesterol status in psychiatric populations have been summarized recently in a meta-analysis of 65 epidemiological studies, involving 510,392 participants, studying associations between serum lipid levels and 'suicidality' (Wu et al., 2016). Included were studies that assessed total serum cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and/or triacylglycerols (TAG). The outcome measure of 'suicidality' was defined as including suicidal ideation, suicide attempt, having threatened suicide, or death by suicide. The main results were that TC and LDL-C levels were lower in suicidal patients than in non-suicidal patients and healthy controls; HDL-C levels were lower in suicidal patients than in healthy controls; and TG levels were lower in suicidal than in non-suicidal patients. When all three groups were pooled, lower serum TC was associated with higher risk of suicidality, suicide attempts, and suicide.

1.3. Low dietary intake of polyunsaturated fatty acids and suicide risk

Another lipid class implicated in suicide risk is polyunsaturated fatty acids (PUFAs), and it has been suggested that PUFA status may be an important factor in cholesterol associations with suicide risk (Hibbeln and Salem, 1996), as has also has been postulated for cardiovascular risk (de Lorgeril et al., 2005). Comprised of long carbon chains with two or more double bonds and categorized as n-3 or n-6 based on the number of carbon atoms from the terminal methyl (omega) end to the first double bond of the carbon chain, PUFAs are found in every cell of the human body and present in multiple lipid classes: esterified to triacylglycerol, cholesterol (as cholesteryl esters) and phospholipids, as well as existing as non-esterified ('free') fatty acids (reviewed in (Jump, 2002)). Both n-3 and n-6 PUFAs are defined as essential because humans and most other mammals cannot synthesize these compounds *de novo* (Spector, 1999), although ingested shorter-chain fatty acids, alpha linolenic acid (ALA, 18:3n-3) and linoleic acid (LA, 18:2n-6) can be converted to long-chain PUFAs in the liver through a series of elongation and desaturation reactions. In the modern diet, whereas n-6 PUFAs are abundant in many plant-based oils and in meat from animals fed corn-based diets, the major source of n-3 PUFAs is seafood (Meyer et al., 2003; Simopoulos, 2011).

Several studies have linked PUFAs with suicide risk. A case-control study of emergency room patients showed that red blood cell levels of eicosapentaenoic acid (EPA, 20:5n-3) were lower in suicide attempters in comparison with controls (Huan et al., 2004). In a pilot study, low docosahexaenoic acid (DHA, 22:6n-3) percentages of total phospholipid fatty acids and elevated n-6 to n-3 ratios predicted suicidal behavior in patients with major depression (Sublette et al., 2006). Finally, a large ($n = 1600$) retrospective case-control study of active duty US military personnel determined that low n-3 PUFA levels were associated with increased risk of suicide compared with other causes of death (Lewis et al., 2011). Higher blood levels of n-6 PUFAs also have been reported in association with higher suicide risk and depression in a study of 234 pregnant women (Vaz et al., 2014).

Lower n-3 PUFA levels are also observed in depressed patients compared with healthy controls, in plasma (Dinan et al., 2009; Féart et al., 2008; Frasure-Smith et al., 2004; Rees et al., 2009; Tiemeier et al., 2003) and serum phospholipids (Conklin et al., 2007; Maes et al., 1999; Riemer et al., 2010; Schins et al., 2007), red blood cell membranes (Adams et al., 1996; Amin et al., 2008; Edwards et al., 1998; McNamara et al., 2010b; Peet et al., 1998), and adipose tissue (Mamalakis, 2002; Mamalakis et al., 2006a, 2006b; Papandreou et al., 2011; Sarri et al., 2008), and confirmed by meta-analytic findings (Lin et al., 2010). These relationships are relevant since depression is one of the main risk factors associated with suicidal behavior (Teti et al., 2014).

Another suicide risk factor, the presence of impulsive/aggressive traits (van Heeringen and Mann, 2014), also has been observed to associate with lower n-3 PUFAs. In patients with deliberate self-harm, correlations were seen between low plasma levels of n-3 PUFAs and higher impulsivity scores (Garland et al., 2007). In context of substance use disorders, another risk factor for suicide (Tondo et al., 1999), low plasma EPA was associated with aggression and impulsivity in adults with MDD and comorbid substance use disorders (Beier et al., 2014); and lower plasma levels of docosapentaenoic acid (DPA, 22:5n-6), DHA, and total n-3 PUFAs were found in aggressive cocaine addicts (Buydens-Branchey et al., 2003). Of note, a low cholesterol diet in nonhuman primates also is associated with serotonin neurotransmitter system deficits and greater aggressive behavior (Kaplan et al., 1994).

Meta-analyses provide variable conclusions concerning the therapeutic benefits of n-3 PUFAs in depression (Appleton et al., 2006, 2010, 2015; Bloch and Hannestad, 2012; Grosso et al., 2014; Martins, 2009; Martins et al., 2012; Mocking et al., 2016; Sublette et al., 2011; Yang et al., 2015); disparities appear to stem from differences with regard to depression severity, selection of outcome measures, composition of n-3 PUFA supplements, and estimates of negative publication bias. There is considerable support for the finding that n-3 PUFA supplements have greatest efficacy in patients who have a diagnosis of