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Review article

Potential neurochemical links between cholesterol and suicidal behavior

Maria da Graça Cantarelli [a], Ana Carolina Tramontina [b], Marina C. Leite [c], Carlos-Alberto Gonçalves [a,c,*]

[a] Neuroscience Post-Graduation Program, Federal University of Rio Grande do Sul (UFRGS), Brazil
[b] State University of Rio Grande do Sul (UERGS), Brazil
[c] Biochemistry Department, UFRGS, Ramiro Barcelos, 2600-Anexo, 90035-003 Porto Alegre, Brazil

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ABSTRACT

The role of cholesterol in psychiatric diseases has aroused the interest of the medical community, particularly in association with violent and suicidal behavior. Herein, we discuss some aspects of brain cholesterol metabolism, exploring possible mechanisms underlying the findings and reviewing the available literature on the possible neurochemical link between suicide and low or reduced levels of serum cholesterol. Most of the current hypotheses suggest a decreased serotonergic activity due to a decrease in cholesterol in the lipid rafts of synaptic membranes. Some aspects and limitations of this assumption are emphasized. In addition to serotonin hypofunction, other mechanisms have been proposed to explain increased impulsivity in suicidal individuals, including steroid modulation and brain-derived neurotrophic factor decrease, which could also be related to changes in lipid rafts. Other putative markers of suicidal behavior (e.g. protein S100B) are discussed in connection with cholesterol metabolism in the brain tissue.

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1. Introduction

Suicidal behavior remains a major challenge for psychiatrists and other health care professionals. The suicide rate for the world as a whole is estimated at 11.6 per 100,000 inhabitants (Värnik, 2012). The WHO estimated that approximately 900,000 people die each year by suicide worldwide, mostly in countries of low and middle income (Patel et al., 2012) and predominantly in young (Hawton et al., 2012) and male individuals (Phillips and Cheng, 2012).

Suicide rates have increased in the young population, changing the risk profile, which is traditionally known as being directly proportional to the increase in age (Pitman et al., 2012). In fact, suicide is among the three most frequent causes of death in young people aged 10–24 or 15–44 years (Hawton et al., 2012; Yip et al., 2012). In Brazil, an epidemiological analysis of suicide rates performed by Lovisi and

* Corresponding author at: Department of Biochemistry, Universidade Federal do Rio Grande do Sul, Ramiro Barcelos, 2600-Anexo, 90035-003 Porto Alegre, RS, Brazil. Fax: +55 51 3308 5535.
E-mail address: casg@ufrgs.br (C.-A. Gonçalves).

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collaborators, from 1980 to 2006, showed a 30% increase in suicide rate during these 26 years, with higher average rates in the south and central-West regions. Teenagers and young adults of the Guarani-Kaiowá indigenous community represented a significant proportion of these deaths (Lovisi et al., 2009).

Suicidal behavior is a condition of high complexity, with different etiological factors and is still poorly understood. New approaches are needed to complement the fundamental vision of social influences, cultural and individual propensity to suicide. In particular, improved prevention strategies are required in addition to extensive scientific studies. Many researchers have focused on the search for biological markers that may be linked to suicidal behavior and can be used as an additional instrument for prevention and therapeutic actions.

The role of cholesterol in mental health has aroused the interest of the scientific community, due to its association with violent and suicidal behavior, as identified by a number of studies. As such, we discuss some aspects of brain cholesterol metabolism, exploring possible mechanisms underlying the findings and reviewing the available literature on the possible link between suicide and low or reduced levels of cholesterol.

2. Low serum cholesterol and suicidal behavior

A number of studies have investigated a possible link between low serum cholesterol and psychiatric symptoms, especially suicidal behavior (Troisi, 2009). These studies include cholesterol-lowering trials (e.g Nakamura et al., 2006), as well as cross-sectional (e.g. Zhang et al., 2005), case-control (e.g. Vuksan-Cusa et al., 2009) and cohort studies (e.g Boscarino et al., 2009). Among the few studies that differentiate the fractions of cholesterol, suicidal behavior and impulsivity have been associated with lower levels of low-density lipoprotein/cholesterol (Lee and Kim, 2003; Agargun et al., 2004; Garland et al., 2007; Marcinko et al., 2008), while low levels of high-density lipoprotein/cholesterol have been more strongly associated with depressive symptomatology (Troisi, 2009). The earliest mention of suicide in a clinical study designed to assess the influence of diet on cardiovascular disease risk probably occurred in the 1960s (Dayton and Pearce, 1969). Subsequently, deaths from injury were also recorded during a study with patients receiving cholestyramine (Manfredini et al., 2000), a cholesterol-lowering drug (Gupta et al., 2010), which may also decrease the concentration of essential polyunsaturated fatty acids (PUFA) (Hibbeln and Salem, 1996). It is important to mention that some authors claim that cholesterol is only a bystander for PUFA, which have been associated with depressive behavior (Liperoti et al., 2009). However, the association of brain PUFA levels in suicide cases is also not consistent (Lalovic et al., 2007).

A meta-analysis reported by Muldoon and collaborators in 1990 is often cited as a reference of critical importance with regard to demonstrating the association between low serum cholesterol, suicide and violent death. This study demonstrated a significant association between reductions in cholesterol and increases in death by suicide or accidental or violent death, regardless of how cholesterol levels were reduced (dietary or pharmacological use); although mortality from coronary heart disease has been reduced in the treated group, specifically those under pharmacologic action, total mortality was unchanged (Muldoon et al., 1990). It is important to point out that impulsive and aggressive behavior is a predisposing factor to accidents, trauma and suicidal behavior (Virkkunen et al., 1989; Muldoon et al., 1990; Romanov et al., 1994).

A prospective observational study in Chinese individuals with naturally low serum cholesterol levels found an inverse association between deaths not related to illness, including suicide, and serum cholesterol, although this was considered by the authors as "marginally significant" (Chen et al., 1991). Since then, a succession of studies have sought to determine whether low serum levels of cholesterol are a risk factor for suicidal behavior. Epidemiological, clinical and biochemical data have provided important information on this theme, although not conclusive, but these data may be important for understanding the mechanism at play. Many studies provide data to support the existence of this association (Lindberg et al., 1992; Neaton and Wentworth, 1992; Kunugi et al., 1997; Partonen et al., 1999; Almeida-Montes et al., 2000; Ellison and Morrison, 2001; Tamosiunas et al., 2005; Garland et al., 2007; Boscarino et al., 2009); however, other studies have found no relationship (Smith et al., 1992; Seneviratne et al., 1999; Steinert et al., 1999) and others have identified an increased risk of violent death by suicide in the presence of elevated serum cholesterol (Tanskanen et al., 2000).

Case-control studies developed in clinical populations have often shown that individuals with past suicide attempts had lower levels of serum cholesterol, compared to patients without the same history (Guillem et al., 2002; Kim et al., 2002; Atmaca et al., 2003; Lee and Kim, 2003; Favaro et al., 2004; Kim and Myint, 2004; Fiedorowicz and Coryell, 2007; Marcinko et al., 2008); again the findings are not unanimous, with negative results regarding this association reported (Apter et al., 1999; Almeida-Montes et al., 2000; Huang and Wu, 2000; Roy et al., 2001; Deisenhammer et al., 2004; Huang, 2005; De Leon et al., 2011. It is important to mention, at this time, that the low cholesterol referred to throughout this text does not necessarily constitute hypocholesterolemia, which is defined as total cholesterol and low density protein/cholesterol levels of below the 5th percentile of the general population, when adjusted for age, gender and race (Moutzouri et al., 2011). The 5th percentile of total cholesterol for adult men in USA ranges from 3.39 to 3.98 mmol/L and the 5th percentile of cholesterol in low density protein is approximately 2.33 nmol/L.

With regard to the genetic aspects of cholesterol homeostasis, some genes may be considered as candidates for the investigation of suicidal behavior (Gietl et al., 2007). Among the causes of hypocholesterolemia is the syndrome of Smith–Lemli–Opitz, an autossomal recessive disorder, where cholesterol synthesis is impaired due to 7-dehydrocholesterol reductase deficiency (DeBarber et al., 2011; Hayashi, 2011; Pfrieger and Ungerer, 2011). A family history of suicidal behavior is frequent among carriers of Smith–Lemli–Opitz syndrome (Lalovic et al., 2004), reinforcing the link between low cholesterol and suicidal behavior. Another candidate is ABCG1, a transporter of sterols across cell membranes (Schmitz et al., 2001). Five variants of ABCG1 gene were investigated in suicide attempters and completers, suggesting a connection of this gene with the aggression-related trait of these individuals (Gietl et al., 2007).

Two meta-analyses summarize our current knowledge about cholesterol and suicidal behavior; follow-up studies found that those individuals with lower cholesterol levels do have a slightly, but statistically significant, increased risk of completing suicide (Lester, 2002); however, there is no evidence indicating that non-illness mortality (including accidents, trauma and suicide) is increased significantly by cholesterol-lowering treatments (Muldoon et al., 2001).

Moreover, more recently other serum lipid changes beyond cholesterol have been associated with violent and non-violent suicide attempt suggesting the necessity of observing signals of altered adiposity in these individuals (Baek et al., 2014; Park et al., 2014). It is also noteworthy that serum cholesterol is affected by age, gender, nutritional status, and in the case of psychiatric patients (frequently linked with suicide risk), cholesterol levels are also affected by medication and lifestyle (e.g. smoking, alcohol use and sedentary). All these elements are confounder factors and demand a careful adjustment in statistical analyses. For example, a

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