Cholesterol in mood and anxiety disorders: review of the literature and new hypotheses

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Received 3 December 2002; received in revised form 17 June 2003; accepted 17 June 2003

Abstract

Cholesterol plays an integral role in the structure and function of the cell membrane and may also affect neurotransmission in the central nervous system. Previous work has identified abnormalities in serum cholesterol levels in patients with mood and anxiety disorders as well as in suicidal patients. However, the biological significance of these abnormalities remains to be clarified. An understanding of how serum cholesterol relates to the pathophysiology of mood disorders may generate biological markers that predict treatment response as well as targets for novel therapeutic strategies. In this article, we review the literature studying the significance of cholesterol in mood and anxiety disorders, with an emphasis on new studies focusing on the adverse impact of hypercholesterolemia on the treatment of major depressive disorder (MDD). We then propose possible mechanisms that would account for the relationship between elevated cholesterol and treatment non-response in MDD.

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Keywords: Cholesterol; Depression; Anxiety; Suicide; Membrane; Fluidity

1. Cholesterol levels in mood and anxiety disorders

1.1. Cholesterol and depression

Research suggests that patients with major depressive disorder (MDD) may have significant differences in cholesterol levels compared to healthy controls (Fava et al., 1996). A number of studies report an association between low cholesterol levels and major depression (Morgan et al., 1993; Lindberg et al., 1994; Maes et al., 1994; Cadeddu et al., 1995; Olusi and Fido, 1996; Horsten et al., 1997; Suarez, 1999; Rabe-Jablonska and Poprawska, 2000; Steegmans et al., 2000; Rafter, 2001), including a large Finnish study involving over 29,000 men (Partonen et al., 1989). Ghaemi and colleagues assessed cholesterol levels in patients with various mood disorders including bipolar disorder, MDD and schizoaffective disorder, and found significantly lower cholesterol levels in patients experiencing manic or depressive episodes compared to patients experiencing mixed episodes (Ghaemi et al., 2000). Low cholesterol levels have also been found to confer an increased risk of MDD (Partonen et al., 1989), and to correlate with the severity of depressive symptoms in a sample of elderly men (Morgan et al., 1993), middle-aged women (Horsten et al., 1997), and depressed patients (Rabe-Jablonska and Poprawska, 2000; Steegmans et al., 2000; Rafter, 2001). Furthermore, a cholesterol-lowering diet with increased fish intake was found to result in a decrease in depressive symptoms (Weidner et al., 1992). In addition, esterified cholesterol levels have been found in euthymic relatives of depressed patients (Maes et al., 1994), suggesting a possible genetic component for this phenomenon. Other abnormalities related to lipid homeostasis described in depressed patients include an increase in the activity of enzymes involved in lipid oxidation and peroxidation (Bilici et al., 2001), lower vitamin E concentrations (Maes et al., 2000), and lower serum high-density lipoprotein-cholesterol (HDL-C) levels (Maes et al., 1997). However, it is important to note that not all studies suggest a relationship between cholesterol and depression. Freedman et al. (1995), for instance, did not find any relationship between cholesterol...
and depression in an epidemiologic study involving 3490 men who had served in the US army. In a similar fashion, McCallum et al. (1994) also found no relationship between depressive symptoms and low cholesterol in a community study of over 2800 men and women aged 60 and older.

1.2. Cholesterol and suicide

A number of studies have also associated low cholesterol levels, especially below 160 mg/dl, with an increased risk of death from suicide (Parton et al., 1989; Boston et al., 1996; Rabe-Jablonska and Poprawska, 2000; Sarchiapone et al., 2001). Maes et al. (1997) reported lower serum high-density lipoprotein cholesterol (HDL-C) in depressed men with a history of serious suicide attempts. Ama et al. (2002) more recently found that patients with suicide attempts had significantly lower cholesterol levels than controls. Patients admitted to an emergency room following a suicide attempt were found to have lower cholesterol levels than controls (Kunugi et al., 1997), while in a separate study, the severity of a suicide attempt was inversely correlated with serum cholesterol levels (Kim et al., 2002). A retrospective chart review of 783 psychiatric outpatient revealed that the proportion of men with a personal lifetime history of attempted suicide, especially if violent, or the proportion of patients with a first degree relative who completed suicide, was higher among the group with cholesterol levels in the lowest quartile (Bocchetta et al., 2001). In a similar fashion, a retrospective chart review of 584 psychiatric inpatients revealed that patients who had attempted suicide had lower serum cholesterol levels than non-suicidal patients (Modai et al., 1994). Patients with low cholesterol levels were found to be twice as likely to have ever made a medically serious suicide attempt than men with levels above the 25th percentile (Golier et al., 1995), while patients who survived a violent suicide attempt were found to have lower cholesterol levels than patients who survived a non-violent suicide attempt (Alvarez et al., 2000) or controls (Alvarez et al., 1999). This relationship between low cholesterol and suicide was further confirmed in two epidemiologic studies (Zureik et al., 1996; Ellison and Morrison, 2001). A number of reports also suggest a relationship between the degree of suicidal ideation and the degree of hypercholesterolemia. Papassotiro-poulos et al. (1999), for instance, reported that the degree of suicidal ideation in psychiatric inpatients was inversely related to their cholesterol levels, while Sullivan et al. (1994) reported a similar finding in outpatients with major depressive disorder (Sullivan et al., 1994). Finally, there are also reports of low cholesterol levels among parasuicidal patients (Gallneri et al., 1995; Garland et al., 2000).

1.3. Low cholesterol and depression: possible mechanisms

Earlier studies suggested that very low cholesterol levels (i.e. 160 mg/dl) may adversely effect mood result-
1.4. Cholesterol and anxiety

While a number of studies report low cholesterol in patients with major depressive disorder, particularly in suicidal patients, several studies report high cholesterol levels in patients with anxiety disorders, or with co-morbid depression and anxiety. Patients suffering from panic disorder (PD), generalized anxiety disorder (GAD), obsessive compulsive disorder (OCD) and post-traumatic stress disorder (PTSD), all have been found to have higher cholesterol levels than patients with anxiety disorders and co-morbid MDD or healthy subjects (Hayward et al., 1989; Bajwa et al., 1992; Kuczmiczky et al., 1996; Agargun et al., 1998; Kagan et al., 1999; Sevincok et al., 2001; Yamada et al., 2001; Peter et al., 2002). Also, patients with co-morbid depression and anger attacks were found to have elevated cholesterol levels, even following adjustment for age, body mass index (BMI) and gender (Fava et al., 1996). The effects of anxiety on cholesterol may perhaps be mediated through an increase in the activity of lipoprotein lipase (Hayward et al., 1989), secondary to an increase in noradrenergic tone seen in GAD (Charney and Redmond, 1983) and PD (Villacres et al., 1987), resulting in an increase of free fatty acids (Hayward et al., 1989). As we will discuss in more detail in a latter section of this review, elevated cholesterol may also directly contribute to anxiety by altering the sensitivity of the γ-aminobutyric acid (GABA) receptors (Sooksawate and Simmonds, 1998, 2001a,b).

2. Serum cholesterol in the treatment of major depressive disorder

Despite the body of evidence showing that patients with anxiety disorders or co-morbid depression and anxiety have high serum cholesterol levels while patients with MDD, particularly suicidal patients, have low serum cholesterol levels, studies exploring cholesterol in the treatment of depression have been lacking. Studying cholesterol in depression may help identify a factor that places these patients at risk for non-response to treatment. Our group recently tested whether cholesterol can serve as a marker of treatment non-responders may be that an excess of cholesterol is present even after controlling for age and gender. In our studies, however, the relationship between elevated cholesterol and treatment non-response: possible mechanisms

3. Elevated cholesterol levels and antidepressant non-response: possible mechanisms

If depressed patients have lower cholesterol levels on average, why should elevated cholesterol levels be linked to treatment resistance? One reason may be that elevated cholesterol levels are a marker of vascular disease which may be associated with poor response to antidepressants. Several reports in the literature have suggested that vascular risk factors—such as smoking, hypertension, and increased serum cholesterol—play a putative role in the etiology of depression. There is also neuropathological evidence for an excess of atheromatous disease in the aortic and cerebral vessels in late life depression (Thomas et al., 2001). On the basis of such findings, several researchers have postulated a ‘vascular depression’ hypothesis (Alexopoulos et al., 1997; Krishnan et al., 1997). This hypothesis argues that for a subset of patients, depression may be caused by cerebrovascular disease manifesting as small lacunes in the subcortical gray and the white matter. These lesions would then disrupt the prefrontal systems related to mood regulation or the white matter pathways connecting these areas with other parts of the brain (Alexopoulos et al., 1997). As our studies suggest, the presence of high cholesterol levels (a cardiovascular risk factor) is characterized by lower rates of response to usual antidepressant therapies. While it is very likely that vascular disease plays a key role in contributing to antidepressant resistance in elderly hypercholesterolemic patients, it is probably far less likely to contribute to this phenomenon in younger patients, particularly younger women, given the lower incidence of vascular disease in these populations. In our studies, however, the relationship between elevated cholesterol and treatment non-response was present even after controlling for age and gender.

Another possibility that would explain why depressed patients with high cholesterol levels are more likely to be treatment non-responders may be that an excess of cholesterol in cell membranes serves to inhibit neuronal growth. A number of studies suggest that enhanced activity of the enzyme γ-secretase in CNS neurons inhibits neuronal and dendritic outgrowth and promotes the formation of β-amyloid, implicated in the pathophysiology of Alzheimer’s dementia (Wahrle et al., 2002). In contrast, inhibition of γ-secretase activity in human CNS neurons has been shown to promote neuritic and dendritic outgrowth (Figueroa et al., 2002). Enriching the neuronal membrane with cholesterol has been found to stimulate the activity of the enzyme γ-secretase, while depletion of membrane cholesterol has been found that patients with TRD presented with higher triglyceride levels and a trend towards higher cholesterol level at baseline compared to depressed patients without TRD. In the same study, high cholesterol levels also predicted poor response to a 6-week open trial of nortriptyline (NT) in patients with TRD.
shown to have opposite effects (Wahrlé et al., 2002). In fact, reducing serum cholesterol has been shown to result in a decrease in neuronal formation of β-amyloid (Refolo et al., 2001), while inducing hypercholesteremia has been shown to have opposite effects (Shie et al., 2002). Similar to the vascular depression hypothesis, however, one would also expect any contribution of β-amyloid formation on antidepressant response to feature more prominently in the elderly.

A third possible explanation stems from research focusing on the connection between cholesterol and the serotonergic system. *meta*-Chlorophenylpiperazine (*m*-CPP), a metabolite of the antidepressant trazodone, binds to a number of 5HT receptors, primarily the 5HT-2a and -2c receptors (Kahn and Wetzler, 1991; Terao et al., 2000b). In humans, administration of *m*-CPP results in stimulation of the hypothalamic–pituitary–adrenal (HPA)-axis and cortisol secretion, while a greater of *m*-CPP-induced cortisol secretion is thought to reflect the sensitivity of these 5HT receptors (Terao et al., 2000b). Two studies of young healthy controls revealed serum cholesterol levels to be positively correlated with the degree of cortisol secretion after *m*-CPP administration, suggesting that a greater degree of sensitivity of these receptors is associated with higher cholesterol levels and vice versa (Terao et al., 1997, 2000b). In humans, administration of *d,l*-fenfluramine also results in an increase in plasma cortisol and prolactin (Cowen, 1993), presumably through the activation of the 5HT-1a (Meltzer and Maes, 1995) and 5HT-2a and -2c (Coccaro et al., 1996) receptors, respectively. Studies of humans where both *m*-CPP and *d,l*-fenfluramine were used as probes of serotonergic function revealed a positive correlation between the prolactin response to *d,l*-fenfluramine and *m*-CPP (Coccaro et al., 1997).

In a recent study our group reported that MDD patients with elevated cholesterol levels at baseline (>200 mg/dl) were more likely to demonstrate an attenuated cortisol response to *d,l*-fenfluramine (Papakostas et al., 2003b). There was also a trend toward significance for patients with elevated cholesterol levels to demonstrate a blunted prolactin response to *d,l*-fenfluramine. These results are in accordance with two prior clinical reports that suggest the degree of 5HT-receptor sensitivity, as evidenced by an elevated secretion of cortisol or prolactin after administration of *d,l*-fenfluramine, to confer a good prognosis to treatment (Malone et al., 1993; Cleare et al., 1998). These results are also in accordance with a study published by our group reporting high cholesterol levels in depressed patients with anger attacks (Fava et al., 1996), a population that also shows evidence of attenuated serotonergic function by way of a blunted prolactin response to *d,l*-fenfluramine (Fava et al., 2000). In summary, while the former studies involving non-depressed subjects suggest a positive relationship between serotonergic function and serum cholesterol levels (Terao et al., 1997, 2000b), the present findings shed light on the reciprocal relationship in patients with MDD, namely that subjects with elevated cholesterol levels are more likely to demonstrate attenuated serotonergic function.

4. Elevated cholesterol, attenuated serotonergic function and treatment non-response in depression: are changes in neuronal membrane fluidity responsible?

The above discussion suggests that the relationship between cholesterol levels, treatment non-response, and serotonergic function in depression are probably complex. One possible explanation for this relationship may be that high cholesterol levels are somehow directly responsible for changes in serotonergic function in MDD. Incorporating cholesterol into the neuronal phospholipid bilayer leads to a reduction in membrane fluidity and an increase in membrane mechanical strength (Barenholz, 2002), which may serve to ‘insulate’ neurons by reducing proton and sodium leaks through the lipid bilayer and, thereby, the amount of energy required by each cell to maintain the transmembrane potential. Cholesterol is also integral to the formation of specialized microdomains within the cellular membrane called lipid rafts (Simons and Ikonen, 1997). Neurotransmitter receptors are concentrated and precisely localized in specific areas of the neuronal membrane, and this precise localization is critical for neurotransmission (Becher et al., 2001). These lipid rafts have been suggested to serve as assembly and sorting platforms for signaling complexes necessary for the activation of signal cascades (Becher et al., 2001). To date, a number of neurotransmitter receptors have been found to operate within such rafts, including GABA-B receptor (Becher et al., 2001), the α-7-subunit acetylcholine receptor (Bruses et al., 2001) and the ionotropic AMPA-type glutamate receptor (Suzuki et al., 2001). Excessive cholesterol may indirectly manipulate the conformation and function of membrane-bound proteins and receptors by reducing neuronal membrane fluidity and, thereby, altering or disrupting the function of lipid rafts (Ohvo-Reikka et al., 2002). Cholesterol also binds tightly to a number of these transmembrane ion channels, enzymes and receptors (Haines, 2002), and, as a result, may directly affect the function these structures (Ohvo-Reikka et al., 2002). These effects have already been described for the GABA-A receptor. Specifically, it has been shown that both enriching and depleting hippocampal neuronal membranes of cholesterol results in alterations in GABA-A receptor sensitivity that are thought to occur both indirectly, (i.e. as a result of altered neuronal membrane fluidity; Sooksawate and Simmonds, 2001a,b), and directly (i.e. by way of direct binding to the GABA-A receptor itself; Sooksawate and Simmonds, 1998).
While there is no direct evidence to suggest that elevated cholesterol may have an adverse impact on the sensitivity of the 5HT receptors or 5HTT transporter (5HTT) in the central nervous system (CNS), a number of studies focusing on the interactions between cholesterol, membrane fluidity, and 5HT in the peripheral vasculature of hypercholesterolemic humans and animals provide preliminary support for such an argument. Dilation of small arterioles in response to 5HT administration has been described in animals, and is thought to occur by way of a 5HT1-receptor mediated increase in the production of nitric oxide at the level of the endothelium (Mylecharane, 1990; Verbeuren et al., 1991; Whiting and Cambridge, 1995; Lamping et al., 1999; McDuffie et al., 1999). Studies involving genetic and diet-induced animal models of hypercholesterolemia reveal that high cholesterol levels result in blunted 5HT-mediated coronary arterial vasodilation (Cohen et al., 1988; Shimokawa and Vanhoute, 1989; Lamping et al., 1999). In a similar fashion, patients with high cholesterol levels secondary to familial combined hyperlipidemia (FCH) also showed blunted 5HT-mediated vasodilation in forearm arteries that improved significantly with lipid-lowering therapy (Stroes et al., 1997). Finally, further evidence of suppression of the 5HT system in hypercholesterolemic states in humans comes from a study by Smith and Betteridge (1997), who demonstrated that patients with familial hypercholesterolemia had lower platelet 5HT concentrations than controls, and lower collagen-mediated 5HT release in their platelets. Interestingly enough, a number of studies suggest that this impairment in vasodilation is functional rather than anatomical, as reversal of hypercholesterolemia during short-term treatment with cholesterol-lowering medications results in normalization of 5HT-mediated vasodilation in humans (Stroes et al., 1995; O’Driscoll et al., 1997; Perticone et al., 2000).

In parallel to these reports of blunted 5HT-mediated vasodilatory responses in the peripheral vasculature of hypercholesterolemic animals and humans, a number of studies report a link between changes in membrane fluidity leading to alterations in 5HTT-uptake by pulmonary-artery endothelial cells (Block et al., 1986; Patel and Block, 1986; Block and Edwards, 1987; Sheridan and Block, 1988). A non-toxic decrease in the cholesterol content of the plasma membrane, for instance, resulting in an increase in membrane fluidity has been shown to decrease the rate ($V_m$) and affinity ($K_m$) of the 5HTT for 5HT (Scanlon et al., 2001). Based on this evidence, it is quite possible that high cholesterol levels may have a direct adverse impact on 5HT receptor function in the CNS by way of altered membrane fluidity, as in the peripheral vasculature.

5. Conclusion

The studies reviewed here indicate an interesting relationship between cholesterol levels and the presentation and treatment of major depressive disorder: while depressed patients with low cholesterol levels (defined as less than 160 mg/dl) appear to be at higher risk of suicide, those with elevated levels (defined as greater than 200 mg/dl) appear more likely to be treatment-resistant, to present with a co-morbid anxiety disorder, or to exhibit anger attacks. Elevated as well as low cholesterol levels may be associated with serotonergic dysfunction. A primary decrease in cholesterol levels may directly lead to decreased brain 5HT activity through a variety of mechanisms, ranging from an alteration in 5HT levels, to 5HT receptor concentration or 5HTT transporter activity. Alternatively, the decrease in cholesterol levels seen in depression and suicide may be secondary to decreased esterification of free cholesterol. In contrast, elevated cholesterol levels may lead to lower 5HT receptor sensitivity or 5HTT transporter activity in depressed patients compared to normal controls, either directly by binding to the various membrane-bound 5HT receptors or transporter or indirectly by altering the fluidity of the neuronal membrane and thereby the conformation of these structures. If additional evidence were to further strengthen this hypothesis, studies focusing on the use of agents that principally operate beyond the plasma membrane in treating depressed or anxious patients with cholesterol levels in either extreme would be warranted. Such agents include S-adenosyl methionine (SAMe; Baldessarini, 1987), ω-3 fatty acids, and possibly hypericum perforatum (Thiele et al., 2002). Other possible explanations for the relationship between elevated cholesterol levels in depressed patients and treatment non-response may be that elevated cholesterol levels lead to inhibition of dendritic outgrowth, the promotion of β-amyloid, or serve as a marker for co-morbid vascular disease. Further studies are needed to clarify the cellular mechanisms through which this relationship operates.

Acknowledgements

Financial support was provided by an American College of Neuropsychopharmacology/GlaxoSmithKline Fellowship in Clinical Neuropsychopharmacology (G.I.P.), a Harvard Medical School/Kaplen Fellowship in Depression Research (G.I.P.) and a Young Investigator Award from the American Foundation for Suicide Prevention (G.I.P.).

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