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Serum Cholesterol level – a suitable biomarker of suicide and suicidal tendency

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ABSTRACT
Suicide and suicidal tendencies have become a global public health problem. It is reported that more than 700 000 deaths are due to suicide. Suicide is the fourth leading cause of death among 15-29 year olds.Therefore, there are many studies conducted to find suitable solutions to prevent or reduce suicidal deaths. Many epidemiological surveys are conducted to delineate and discuss the present status of suicide and human behavior. Apart from the routine surveys it has been postulated there is a link between serum cholesterol level and suicide. Cholesterol being an important constituent of plasma membrane its concentration will influence membrane structure and its function. It has been shown that in patients who have attempted or committed suicide the serum cholesterol level is low compared to the normal population. In this short review the role of cholesterol in suicide is analyzed taking into account its role in serotonin receptor and its function.

Key words: Suicide, cholesterol, serotonin, serotonin receptor, aggression

INTRODUCTION:

Cholesterol is a molecule which plays a very important role in human metabolism. It has a cyclopentanoperhydrophenanthrene ring system (steroid nucleus) with two methyl groups (carbon 18 and 19), a hydroxyl group at carbon 3 and with a side chain at carbon number 17.

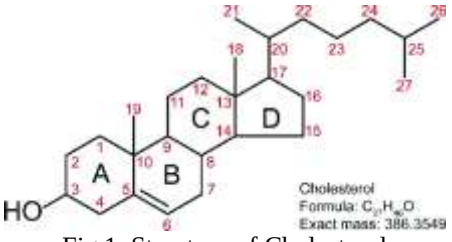

Fig.1. Structure of Cholesterol

Cholesterol biosynthesis takes place by two pathways, namely, the Kandutsch-Russell and Bloch pathways. These pathways have common initial steps starting from acetate and branch out after lanosterol. [1]

The biosynthesis of cholesterol can be divided into four stages: (I) Synthesis of mevalonate (MVA); (II) Production of isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP); (III) Synthesis of squalene; (IV) Squalene cyclizes to form lanosterol and subsequently to synthesize cholesterol. The process is regulated by a negative feedback mechanism with the downstream products. [2-3]

Cholesterol in the CNS is almost entirely synthesized within the brain since the Blood Brain Barrier (BBB) prevents any direct transfer of sterols from the blood to the brain, especially when they are contained in lipoprotein particles. Cholesterol biosynthesis follows Kandutsch-Russel pathway in neurons and Bloch's pathway in astrocytes . The enzyme 24-hydroxylase participates in the homeostasis of cholesterol in the CNS. [4-5]

Cholesterol is therefore a very important molecule which is required for the synthesis of steroid hormones, bile acids, vitamin D (7-dehydro cholesterol in the skin) and the maintenance of plasma membrane fluidity. [6-7]

Cholesterol and plasma membrane:

Cholesterol helps maintain the integrity of plasma membranes, and plays a role in facilitating cell signaling and receptor binding. Cholesterol is an amphipathic molecule; it contains a hydrophilic and a hydrophobic portion. Cholesterol's hydroxyl (OH) group aligns with the phosphate heads of the phospholipids. The remaining portion of it tucks into the fatty acid portion of the membrane. Because of the way cholesterol is shaped, part of the steroid ring (the four hydrocarbon rings in between the hydroxyl group and the hydrocarbon "tail") is closely attracted to part of the fatty acid chain on the nearest phospholipid. This helps slightly immobilize the outer surface of the membrane and make it less soluble to very small water-soluble molecules that could otherwise pass through more

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easily. Without cholesterol, cell membranes would be too fluid, not firm enough, and too permeable to some molecules. [8]

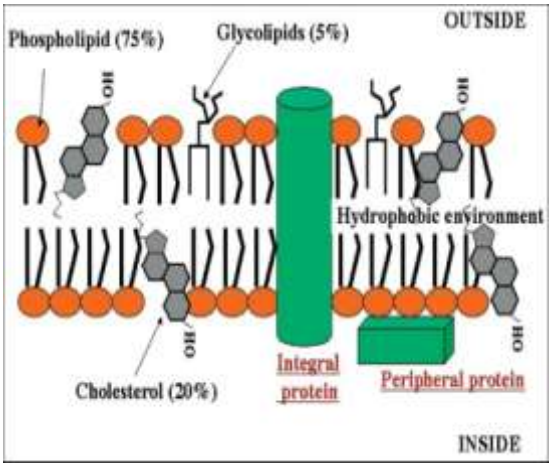

Fig.1. Plasma membrane and cholesterol

In the plasma membrane there are specific domains called lipid rafts. Lipid rafts (also known as lipid micro-domains) are small platforms, composed of sphingolipids and cholesterol in the outer exoplasmic leaflet, connected to phospholipids and cholesterol in the inner cytoplasmic leaflet of the lipid bilayer. These assemblies are fluid but more ordered and tightly packed than the surrounding bilayer. The difference in packing is due to the saturation of the hydrocarbon chains in raft sphingolipids and phospholipids as compared with the unsaturated state of fatty acids of phospholipids in the liquid-disordered phase. Cholesterol is thought to serve as a spacer between the hydrocarbon chains of the sphingolipids and to function as a dynamic glue that keeps the raft assembly together . Cholesterol partitions between the raft and the nonraftphase, having higher affinity to raft sphingolipids than to unsaturated phospholipids. Removal of raft cholesterol leads to dissociation of most proteins from rafts and renders them nonfunctional.[7-8]

Therefore, cholesterol helps prevent extremes - whether too fluid or too firm in the consistency of the cell membrane. Alterations in membrane composition and viscosity can affect the activity of the membrane transporters that control drug uptake and efflux and inactivate apoptotic signaling. Lipids are involved in various signaling processes as they modulate the conformation and dynamics of membrane receptors, control receptor partitioning, and they can also act as second messengers in signal transduction pathways.

All the constituents of the lipid bilayer phosphatidylcholine, sphingomyelin, cholesterol, unsaturated fatty acids may contribute to cell signaling pathways that promote cancer cell growth and survival. [9] It is to be noted that phospholipids/cholesterol molar ratio play a vital role plasma membrane function.

Cholesterol have a major impact on the physical properties of the membrane lipid bilayer, such as ordering of the phospholipids, changes in membrane fluidity and membrane viscosity. [10]

G-protein coupled Receptors and Membrane Lipids

The organization of molecules such as receptors and G-proteins in the membrane represents an important determinant in G-protein coupled receptors (GPCR) signaling. In this regard, the observation that GPCRs are not uniformly present on the plasma membrane but are concentrated in specific membrane domains that are enriched in cholesterol assumes significance. [11-12] Therefore, plasma Membrane fluidity is influenced by temperature, cholesterol and the presence of saturated or unsaturated fatty acid composition of membrane phospholipids.

Viscosity of Membranes and Cholesterol

Whenever the unsaturated fatty acid presence is increased the membrane become more fluid and vice versa. The optimal activity of expression of lipid desaturases helps to maintain the balance between saturated and unsaturated membrane lipids. This process of adaptation found in bacteria is called homeoviscous adaptation (HVA). Cholesterol modulates changes in the fluidity, thickness, compressibility, water penetration and inbuilt curvature of lipid bilayers. Therefore, an increase or decrease in cholesterol level influence membrane function and possibly viscosity. Serum cholesterol level and its regulation need careful consideration and scientific enquiry. Viscosity is a highly important parameter within the plasma membrane, controlling the rate of diffusion of small molecules and proteins.

Cholesterol and Central Nervous System:

The CNS contains one-fourth of the body's free cholesterol, which is synthesized primarily in situ. Cholesterol improves membrane stability, reduces permeability, and may influence serotonergic function. Cholesterol depletion may

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impair function of serotonin receptors 5-HT1A and 5-HT7. [13-23]

There is considerable body of evidence to suggest that cholesterol level regulates emotions and aggressive behavior through serotonin.

Serotonin formation and its receptors

Serotonin is formed from tryptophan

1. Conversion of L-tryptophan to l-5 hydroxy tryptophan is catalyzed by the enzyme Tryptophan hydroxylase, coenzymes Tetrahydrobiopterin, NADPH.
2. 5-hydroxy tryptophan is converted 5-hydroxy tryptamine by the action of Aromatic aminoacid decarboxylase which requires pyridoxal phosphate as coenzyme.[24-25]

Serotonin receptors are present at the post synaptic membrane or at the presynaptic terminal. There are about 14 human serotonin receptors encoded by different genes. These receptors segregated into seven families. Most of the receptors belong to G protein-coupled receptors (GPCRs). GPCR span the plasma membrane seven times with the N-terminal end at the extracellular site and carboxy terminal end intracellular side of the membrane. Most of GPCR coupled 5-HT receptors are localized on post synaptic membranes.[25]

Tonic increase of the 5-HT2 family expression may cause escalated aggression, whereas the phasic increase of 5-HT2 receptors inhibits aggressive behaviors. Polymorphisms in the genes of 5-HT transporters or rate-limiting synthetic and metabolic enzymes of 5-HT modulate aggression, often requiring interaction with the rearing environment.5-HT in the synaptic cleft interacts with cell-surface receptors localized at the postsynaptic membrane or on the presynaptic terminal. The 14 human serotonin receptors are each encoded by different genes and segregate into seven families.

All but one are members of the superfamily of G protein-coupled receptors (GPCRs), which span the plasma membrane seven times with the N-terminus on the outside of the cell and the C-terminus on the intracellular side of the membrane. The intracellular loops and C-terminal tail interact directly with G proteins .Within the nervous system, most of the G protein-coupled 5-HT receptors are localized on postsynaptic membranes and modulate neurotransmission via second messenger pathways.[26]

Cholesterol and human behavior:

Low levels of cholesterol in the CNS are associated with a decrease in synaptic function [27][17]. Some studies mention that serum cholesterol levels lower than 160 mg/dL (4.14 mmol/L) may affect human behavior through the serotonin system [28][18], which is related to a number of suicide attempts and violent deaths, in contrast with individuals who show higher serum cholesterol levels [29][19].

Cholesterol a biomarker of Suicide?

Suicides and suicidal behavior are major causes of mortality and morbidity in public health and are a global problem. Various authors have proposed changes in lipid metabolism (total cholesterol decrease) as a possible biological marker for suicidal behavior. The term suicide encompasses ideation, intent, and actions. Suicidal ideation is defined as thinking about or considering suicide; ranging from passive death wishes to active thoughts of committing suicide. In this sense, suicide is listed by the World Health Organization as one of the leading causes of deaths worldwide.[30]

Changes in cholesterol concentrations in brain alter the CNS functions, a decrease of cholesterol at neuronal level produces alterations in neurotransmission and synaptic degeneration. Several studies have investigated a possible link between low serum cholesterol and suicide.[31-32]

These findings and other studies support the hypothesis that lower serum concentrations of Cholesterol and LDL-Cholesterol are associated with even in patients who attempted to commit suicide.

There is a report that shows that low levels of total serum cholesterol (TC), LDL cholesterol, and C-reactive protein were significantly associated with suicide retries.[33] The authors propose that dyslipidemias contribute to changes in the membranes of serotonergic neurons and may contribute to suicidal behavior.[33] A possible explanation that suggests that a decrease in LDL levels in the CNS causes a decrease in the viscosity of the cell membrane; this leads to a decrease in 5-HT1A (serotonin) receptors, which in turn leads to impulsivity and violent suicidal behavior, secondary to low cholesterol levels.[34-36]The importance can be observed in the Smith-LemliOpitz syndrome, an innate error of cholesterol metabolism, characterized by severe alterations in the central nervous system.[36] This alteration is caused by a blockage of the

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dehydrocholesterol 7-alpha-reductase enzyme, which produces a significant decrease in cholesterol. Some research suggests an increase in suicidal behavior in patients affected by this genetic disease.[37]

Serotonin also **regulates the pre-frontal cortex**; therefore, lower levels of serotonin affect our response to external stimuli, meaning the person becomes aggressive easily and can't control their responses in a 'normal' way. They can't anticipate risk and therefore impulsively engage in aggressive behavior.Research indicates that, in general, the neurotransmitter serotonin has an inhibitory action in the brain and that it is deeply involved in the regulation of emotion and behavior, including the **inhibition of aggression**.[26]

The **5-HT_{2B} Receptor** in Aggressive and Depressive Behavior.

It has been generally assumed that 5-HT_{2B} receptor dysfunction or deficiency resulted in increased impulsivity and aggression.Aggression is associated with dysregulation in a cortico-limbic network.[38] Specifically, a deficient regulation of the amygdala via prefrontal cortex (PFC) areas has been described as a risk factor for aggressive behavior .[39] In healthy individuals, enhanced amygdala activation is a neural substrate of state anger after provocation [40], whereas lateral PFC activation counteracts aggressive reactions in such situations .[41] In summary, functioning of the PFC-amygdala regulation system seems to be central to successful emotion regulation [42], thus preventing impulsive aggression.On the transmitter level, aggression has frequently been associated with alterations of serotonergic neural activity.[43]

The role of cholesterol as a friend of human health more than its role as a foe. The attention that is given to higher cholesterol pales into insignificance to its lower levels. There is a need to balance and maintain an optimal level of cholesterol that will help to maintain health and well-being of humans.

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