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Review

Cholesterol overload impairing cerebellar function: The promise of natural products

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ABSTRACT

The cerebellum is the part of the brain most involved in controlling motor and cognitive function. The surface becomes convoluted, forming folia that have a characteristic internal structure of three layers including molecular, Purkinje cell, and granular layer. This complex neural network gives rise to a massive signal processing capability. Cholesterol is a major constituent, derived by de novo synthesis and the blood brain barrier. Cholesterol is tightly regulated between neurons and glia that is, astrocytes, microglia, and oligodendrocytes and is essential for normal brain development. The axon is wrapped by myelin (cholesterol, phospholipids, and glycosphingolipids) and made up of membranes of oligodendrocytes, separated by periodic gaps in the myelin sheath, called nodes of Ranvier. Hypercholesterolemia is associated with increased oxidative stress and the development of neurotoxicity and Alzheimer's disease. Treatment with natural products has been found to support improved brain function and reduce low density lipoprotein cholesterol level. Fish oil is one such product; among the many plant products are: *Morus alba* leaves, fruit, and bark; pomegranate fruit and peel; Barley β glucans; date palm; and *Allium sativum*. The therapeutic potential was discussed in relation with the antilipidemic drugs, statins (HMG CoA reductase inhibitors).

Anatomy of cerebellum

The cerebellum is a structure attached to the bottom of the cerebral hemispheres of the brain that plays an important role in motor and cognitive functions [1]. Its surface is covered with finely spaced parallel grooves, in striking contrast to the broad irregular convolutions of the cerebral cortex. Within this, there are thin layers of several types of neurons with a highly regular arrangement, the most important being Purkinje cells and granule cells. The cerebellar cortex is divided into three layers from distal to proximal; the molecular layer, containing the flattened dendritic trees of Purkinje cells; the Purkinje layer, which occupied the medium zone and thick granular layer, which has densely grouped granular, stellate, and basket cells [2].

Purkinje cells are the main computational units of the cerebellum, each integrating a staggering 150 000 synaptic inputs which exhibit firing rates that increase and decrease from their baseline intrinsic spontaneous rate in correlation with different aspects of movement (Fig. 1).

Cholesterol metabolism

The adult human brain contains about 35 grams of cholesterol [3], about 20% of the body's total cholesterol [4], making cholesterol a major constituent of the human brain. Numerous lipoprotein receptors and apolipoproteins are expressed throughout the brain. Brain cholesterol is primarily derived by de novo synthesis, and the blood brain barrier prevents the uptake of lipoprotein cholesterol from circulation [5].

Cholesterol is tightly regulated between the major brain cells (astrocytes, microglia, and oligodendrocytes) and is essential to normal development. It is required for synapse and dendrite formation [6], and for axonal guidance [7]. Cholesterol is a pivotal constituent of cell membranes, steroid hormones, and for the function of hedgehog proteins [8]. In mammals, Purkinje cells actively synthesize progesterone de novo from cholesterol during cerebellar cortical formation in neonatal life. Both progesterone and estradiol promote dendritic growth, spinogenesis, and synaptogenesis via each cognate nuclear receptor in Purkinje neurons. Allopregnanolone is also involved in Purkinje and granule cell survival [9]. Niemann Pick disease type C (NPC) is a neurodegenerative disease often caused by mutation in a gene

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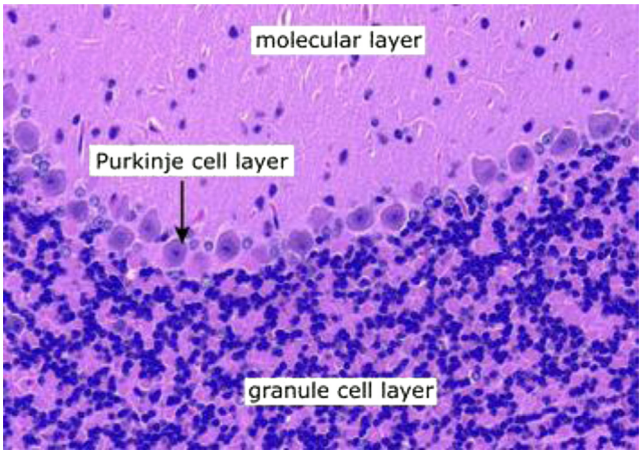

Fig. 1. Cerebellum (delta base histology atlas).

called NPC1, which results in the accumulation of unesterified cholesterol and glycosphingolipids in the endosomal lysosomal system. Astrocyte dysfunction contributes to the neuro degeneration of NPC, and estradiol treatment may be useful in ameliorating progression of the disease [10].

There are two major pools of central nervous system (CNS) cholesterol: One pool (containing up to 70% of the CNS choles terol) consists of the myelin sheaths of oligodendroglia; the other is made up of plasma membranes of astrocytes and neurons. The lipid protein composition of myelin differs from that of other cell membranes; myelin dry weight consists of about 70% lipids and 30% proteins. In other cell membranes, the distribution is about 30% lipids and 70% proteins [3]. Major lipid constituents of myelin are cholesterol, phospholipids, and glycosphingolipids in molar ratios of about 4:4:2. In neurons (which are composed of the cell body and the axon), electrical impulses are transmitted rapidly along the axon. The axon is wrapped by myelin made up from the membranes of oligodendrocytes, separated by periodic gaps in the myelin sheath, called nodes of Ranvier [11].

Astrocytes are the main source of apolipoprotein E (apoE) followed, by oligodendrocytes, microglia, and ependymal layer cells [12]. The significance of apoE expression in neurons, to our/ my knowledge, has not been determined yet. ApoE expression was observed in primary cultures of human hippocampal neu rons [13]. The low density lipoproteins (LDL) receptor and LDL receptor related protein 1 are the main receptors for the uptake of apoE containing lipoprotein particles in the brain. LDL receptor knockout mice have increased levels of apoE in brain parenchyma and in cerebrospinal fluid, which suggests impaired metabolism of apoE [14]. The lipocalin apolipoprotein D is upregulated in peripheral nerves after injury, and in the cerebral cortex, hippocampus, and cerebellum during aging and pro gression of certain neurologic diseases [15] (Fig. 2).

The integrity of central and peripheral nervous system myelin is affected in numerous lipid metabolism disorders. The rapid saltatory conduction of action potentials along axons is depen dent on myelination. The myelin membrane is an extended and highly specialized plasma membrane synthesized by myelinat ing glial cells: oligodendrocytes in the CNS, and Schwann cells in the peripheral nervous system. The wrapping of myelin around an axonal segment increases axonal resistance and enables

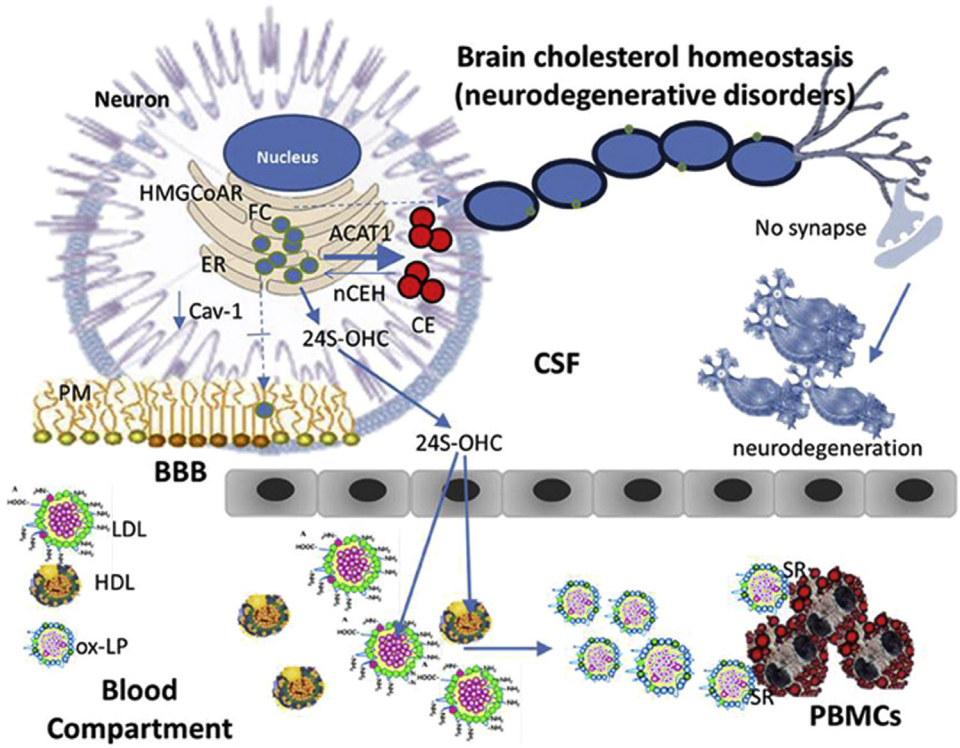

Fig. 2. Cholesterol homeostasis. Cholesterol uptake from blood circulating through the low density lipoprotein receptor (LDLR), by the blood–brain barrier (BBB). The brain meets its cholesterol needs through de novo synthesis mainly in glial cells. Glial cells neo-synthesize cholesterol into apoE-containing lipoprotein particles, which in turn are secreted into the cerebrospinal fluid through the ATP-binding cassette transporter 1 (ABCA1). Cholesterol synthesized in the endoplasmic reticulum (ER), as well as that released by apoE-containing lipoprotein catabolism, moves to PMs, by interacting with Cav-1. Excess cholesterol is transported to the ER, where it is esterified by ACAT and accumulates as lipid droplets. The large part of excess cholesterol, however, is converted into 24 S-OHC, which then crosses the BBB, enters the plasma, and is delivered to the liver for excretion into bile [16].