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Editorial

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Serotonin and Atherosclerotic Cardiovascular Disease

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Serotonin and Atherosclerotic Cardiovascular Disease (ASCVD)

Platelets in blood stream secrete serotonin (5-hydroxytryptamine, 5-HT), which has hazardous effects on the vascular wall and promotes thrombogenesis, mitogenesis, and proliferation of smooth muscle cells[1]. Therefore, serotonin may be one of the factors involved in the development of ASCVD. In 1999, Vikenes et all reported that high serotonin levels in platelet rich plasma is associated with coronary artery disease and occurrence of cardiac events, particularly in younger age groups (<60 years of age), suggesting that this association seems to persist after adjustment for conventional risk factors.

Serotonin and 5-HT$_{2A}$ Receptor in Atherosclerosis

In the current issue, Ma *et al.*[2] evaluated the activity of 5-HT system, including synthesis and degradation of 5-HT and involvement of its receptor (5-HT$_{2A}$ receptor) in the macrophages and endothelial cells. They found that 5-HT is activated in oxidized low-density lipoprotein (LDL)- or saturated fatty acid-induced foam cells of THP-1 cell derived macrophages. Interestingly, they found that a combination of sarpogrelate hydrochloride, a 5-HT$_{2A}$ inhibitor, and carbidopa, an inhibitor of serotonin synthesis enzyme aromatic L-amino acid decarboxylase, dramatically decreases atherosclerotic formation of aortae in high-fat-diet-fed ApoE knockout mice. They assumed that oxidized LDL or saturated fatty acids activate PKCε via 5-HT$_{2A}$ receptors of macrophages and endothelia cells, leading to upregulation of the triglyceride synthetase glycerol-3-phosphate acyltransferase 1 (GPAT1) and uptake of oxidized LDL, which finally results in accumulation of lipid droplet in both cells.

Hence, possible underlying mechanisms of serotonin and 5-HT$_{2A}$ receptor system as a promoting and/or pathogenetic factor of ASCVD are discussed (Fig. 1)[3]. Oxidized LDL or saturated fatty acids activate and/or transudate to platelets and macrophages via CD36, TLR4, or others, and then stimulate intracellular lipid-mediated signaling. However, overaccumulated lipids or overactivated signals may produce cytotoxic molecules such as PKCε and then cause mitochondrial toxicity. This process may be linked to lipotoxicity in macrophages[4]. Signals of serotonin and 5-HT$_{2A}$ receptor can enhance the oxidized LDL or saturated fatty acids induced cell activation. Then, activated platelets and macrophages stimulate endothelium and cause plaque formation, plaque rupture and thrombosis, and finally cause onsets of ASCVD.

Therefore, suppression of serotonin and 5-HT$_{2A}$ receptor signaling may be effective in preventing the onset of ASCVD. In addition, the development of drugs targeting these receptors may be effective. However, there are many problems regarding this. The cells that produce serotonin and the dynamics of serotonin are completely unknown. Moreover, the interaction of serotonin and 5-HT$_{2A}$ receptors with oxidized LDL or saturated fatty acids is unknown. Furthermore, how macrophages or platelets play roles in the process of atherosclerotic consequences such as vasospasm, formation of lipid droplet, plaque rapture and thrombosis (Fig. 1). Future studies are warranted to clarify these points.

Conflict of Interest

None.

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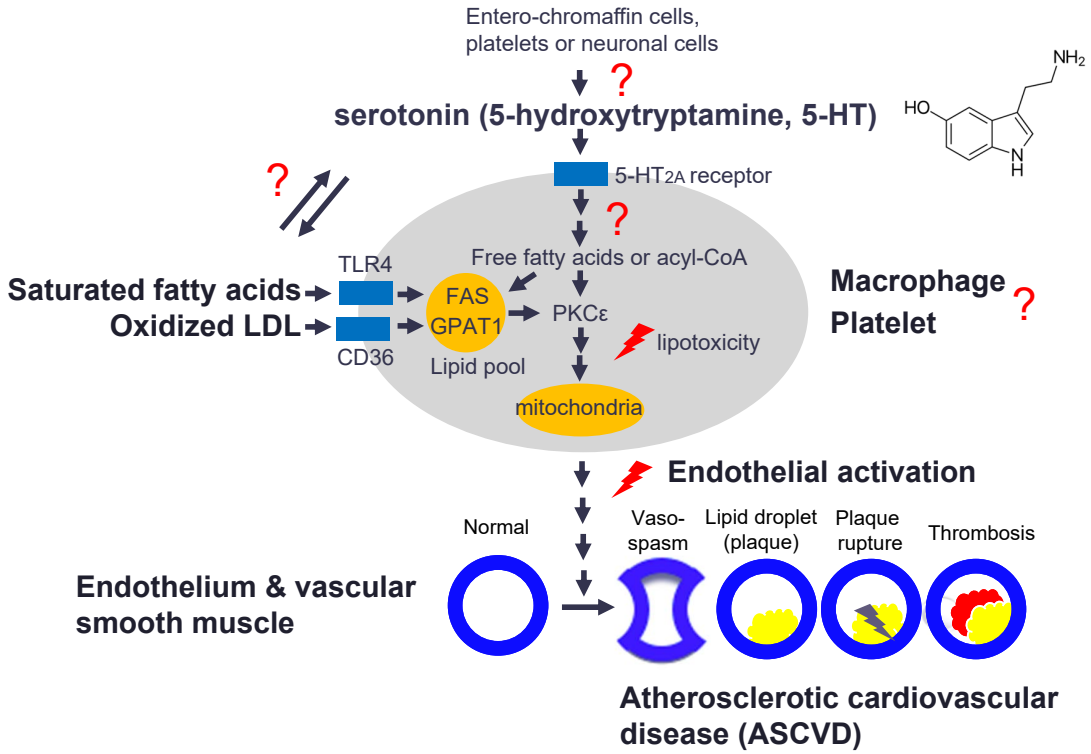

Fig. 1. Possible underlying mechanisms of serotonin and 5-HT2A receptor system in ASCVD

5-HT, 5-hydroxytryptamine; TLR4, Toll-like receptor 4; LDL, low-density lipoprotein; FAS, fatty acid synthase; GPAT1, glycerol-3-phosphate acyltransferase 1; ASCVD, Atherosclerotic cardiovascular disease

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