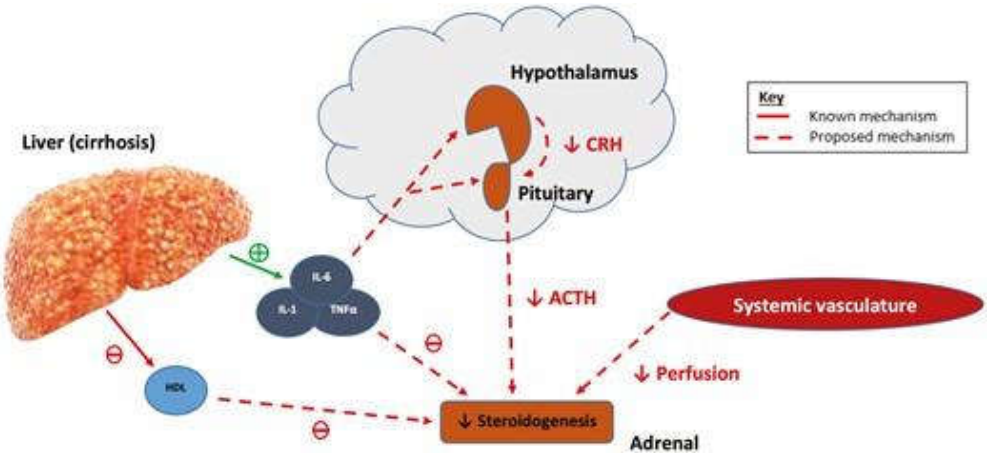

Figure 2. Pathogenesis of adrenal insufficiency in cirrhosis.

Conclusions. Assessment of AI in cirrhosis is difficult and requires careful attention to many patient-related variables. Traditional endocrinology approaches to the diagnosis and management of AI do not account for the physiology in the cirrhotic state. Importantly, the majority of AI in cirrhosis is "relative" but represents an independent predictor of short- to medium-term mortality. More research is needed to fully understand the mechanisms underlying AI in cirrhosis. Given the lack of clear benefit of glucocorticoid replacement in many common clinical scenarios, low TC levels in the absence of consistent signs and symptoms of AI do not warrant empiric treatment. Additionally, clinicians should consider the risks of exogenous glucocorticoids, including exacerbating baseline immunodeficiency and/or induction of an iatrogenic Cushing syndrome.

INFLUENCE OF PHOSPHOLIPASE A2 ENZYME ACTIVITY ON THE DEVELOPMENT OF ATHEROSCLEROSIS

Hussni Ya., Beri Z.
Scientific supervisor: Seniuk I. V.
National University of Pharmacy, Kharkiv, Ukraine
citochrom@gmail.com

Introduction. Circulating levels and enzymatic activity of two families of phospholipase A2 enzymes, secretory phospholipase A2 (sPLA2) and lipoprotein-associated phospholipase A2 (Lp-PLA2), have been evaluated as biomarkers of cardiovascular risk in population-based studies inclusive of apparently healthy individuals, and patients with established coronary heart disease (CHD). In the EPIC (European Prospective Investigation of Cancer) Norfolk study, the increased CHD risk associated with the oxidation specific biomarker, oxidized phospholipids on apolipoprotein B (apoB) or lipoprotein(a), was enhanced further among individuals with high sPLA2 concentration and activity than Lp-PLA2 activity. This study and other observational studies have shown that both enzyme concentration and activity predict incident cardiovascular events. The evidence that these phospholipase A2 enzymes retain their importance as biomarkers of risk in statin-treated patients is less certain; however, in one trial, LpPLA2 concentration was associated with future CVD events in models that adjusted for baseline covariants and apolipoprotein concentrations. The importance of this phospholipase A2 enzyme biomarker data should not be overemphasized, as circulating levels of these two groups of PLA2 enzymes and their various members may not encompass their multifarious downstream pro-atherosclerotic effects

in the vessel wall. Recently, the non-functional (null) V279F allele within the PLA2G7 gene, a common loss of function mutation of Lp-PLA2 in Asians, was associated with reduced CHD risk. This Mendelian randomization study provides support for the hypothesis that marked reduction Lp-PLA2 enzymatic activity may be an effective strategy for CVD prevention.

Recently, selective inhibitors of sPLA216 and LpPLA217 have been targeted as potential candidates to reduce incident atherosclerotic cardiovascular events. The completion of clinical outcomes trials with selective inhibitors of these phospholipase A2 enzymes will provide important information on the future role of these crucial enzymes in CVD prevention and treatment.

The aim. To study the biological function of two groups of phospholipase A 2 enzymes in atherosclerosis.

Materials and methods. Scientific publications based on experimental data on the biological activity of the phospholipase A2 enzyme were used.

Research results. Phospholipase A2 enzymatic activity generates lipid products with biological properties and functions (Fig. 1). Secretory phospholipase A2 (sPLA2) acts to hydrolyze phospholipids from the surface of cell membranes, native lipoproteins and oxidatively-modified lipoproteins to generate multiple bioactive lipids that include arachidonic acid, non-esterified fatty acids (NEFA), lysophospholipids (Lyso-PL), lyso-platelet acting factor (LYSO-PAF), and oxidized non-esterified fatty acids (Ox-NEFA). In contrast, lipoprotein-associated phospholipase A2 (Lp-PLA2) or platelet acting factor (PAF) requires oxidized phospholipids as a substrate (oxidized phosphotidylcholine).

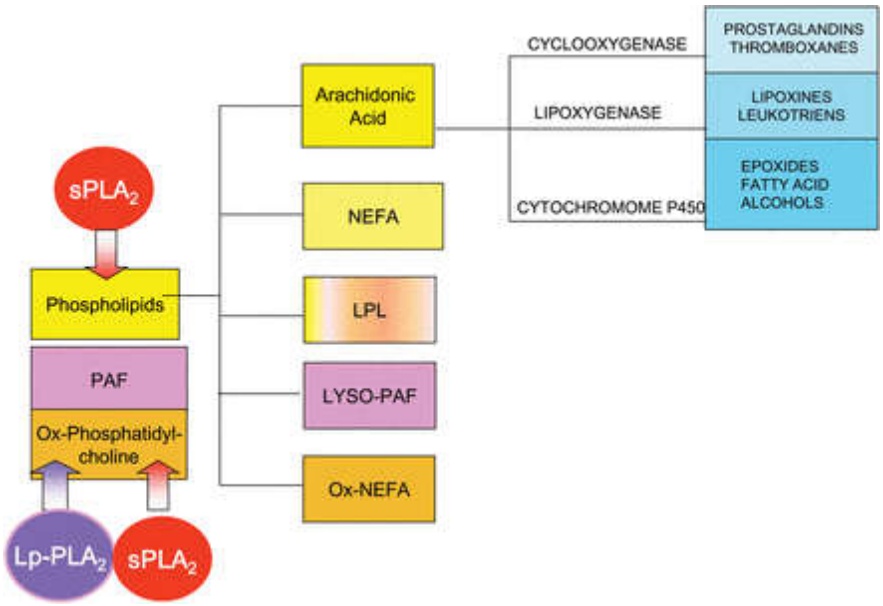

Figure 1. Phospholipase A2 enzymatic activity.

sPLA2 hydrolyzes the sn-2 ester bond in the glyceroacyl phospholipids presents in lipoproteins and cell membranes, inducing structural and functional changes and forming lysopholipids and non-esterified fatty acids (NEFAs) with direct proinflammatory effects. The homology between these sPLA2 enzymes varies, but they share a calcium-dependent catalytic mechanism, presence of several disulphide bridges, and a well-conserved overall three-dimensional structure. In addition to their role in atherogenesis, sPLA2 enzymes are implicated in various physiological and pathophysiological functions, including lipid absorption, cell proliferation,

myocardial injury, tumour formation, and inflammation. Interestingly, sPLA2 activity is involved in cholesterol homeostasis. Specifically, GX sPLA2 generates lipolytic products that suppress LXR activation, which negatively regulates ABCA1 and ABCG1 expression and cholesterol efflux from macrophages.

Secretory PLA2 activity can be proatherogenic in the circulation, and at sites of atherosclerotic plaque development **(Fig. 2)**. In plasma, sPLA2 activity hydrolyzes surface phospholipids on lipoproteins, resulting in structural alteration in these particles. GV sPLA2 and GX sPLA2 enzymes hydrolyze phosphatidylcholine on the surface of VLDL and LDL at least 20-fold more efficient than GIIA sPLA2.

Secretory phospholipase A2 (sPLA2) hydrolyzes phospholipids from the surface of native lipoproteins and oxidatively-modified lipoproteins, whereas lipoportein-associated phospholipase A2 acts only on oxidatively-modified lipoproteins. Phosphoatidylcholine hydrolysis by sPLA2 results in small VLDL and LDL particles with altered confirmation of apolipoprotein B (apoB). The conformational change in apoB reduces binding and internalization of apoB-containing lipoproteins by the apoB/E (LDL) receptor resulting in prolonged residence time in the circulation. This prolonged circulation time of LDL particles increases exposure to reactive oxygen species (ROS) resulting in an oxidized LDL particle (Ox-LDL) that may serve as a substrate for group IIA sPLA2 (GIIA sPLA2) and Lp-PLA2. Phospholipid hydrolysis of Ox-LDL particles generates oxidized non-esterified fatty acids (Ox-NEFA) and lysophophotidylcholine (Lyso-PC). sPLA2 acts on cellular membranes resulting in elaboration of arachidonic acid that serves as the substrate for eicosanoids, thromboxanes and leukotrienes.

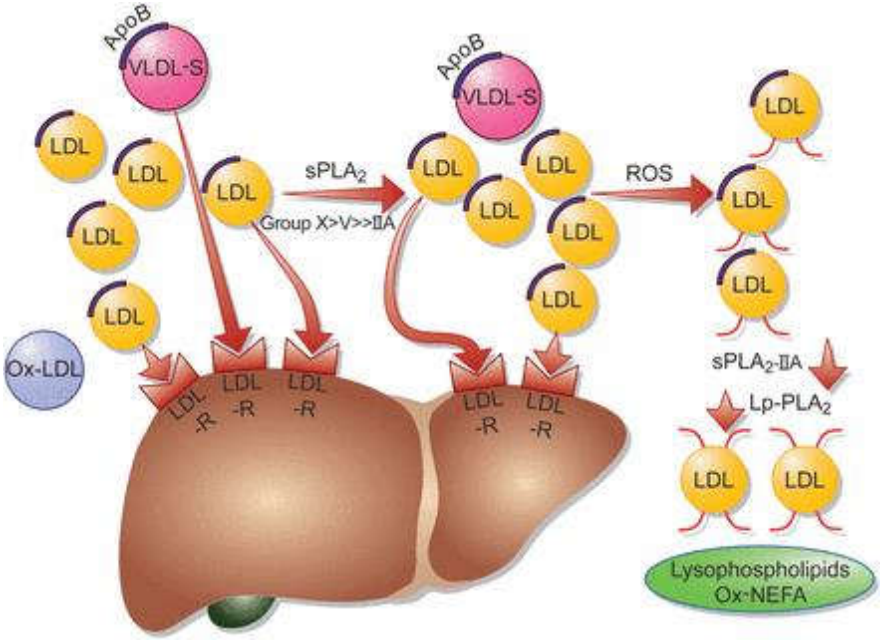

Figure 2. Effects of phospholipase A2 enzymatic activity on circulating lipoproteins.

Conclusions. The two major phospholipase A2 enzymes that have been studied as biomarkers of cardiovascular risk and targets of pharmacological intervention differ in several important aspects. Secretory phospholipase A2 groups IIA, V, and X hydrolyze native lipoproteins resulting in smaller, denser, and more electronegative lipoprotein particles that are less avidly internalized by the hepatic apoB/E receptor resulting in increased residence time in the circulation that allows for further

physicochemical alterations, increased intimal proteoglycan binding, and incorporation by macrophage scavenger receptors and specific PLA2R. Lp-PLA2 requires oxidized LDL as a substrate, and it has no effect on native lipoproteins. The hydrolysis of phospholipids on lipoproteins and cell membranes results in bioactive lipids (NEFAs, lysophospholipids, and eicosanoids) that activate pro-inflammatory redox-sensitive transcription factors and enhance proapoptotic effects.

BRAIN ADENOSINE RECEPTORS AS TARGETS FOR MEDICATIONS

Kabbaj A.
Scientific supervisor: Kravchenko G. B.
National University of Pharmacy, Kharkiv, Ukraine
abdelmounaaim@hotmail.fr

Introduction. Adenosine as a neuromodulator of the central nervous system has specific receptors, which have been the target of medical therapy for many years. Such compounds that have high affinity to adenosine receptors (ARs) can act both like antagonists and agonists. Despite this, there are still only a limited number of adenosinergic medications on the market.

The aim of our work was to review publications devoted to study medications, which mechanism of action is mediated by interaction with ARs in brain.

Materials and methods. Search for scientific publications was conducted in PubMed and ScienceDirect textual databases until December 2022. The following search terms were used: adenosine receptors, modulators of adenosine receptor activity, adenosine receptors antagonists, pharmacology of adenosine receptors.

Research results. Currently, four ARs are found in different tissues to be expressed, they named A1, A2A, A2B, and A3. All these receptors are metabotropic, particularly, G protein-coupled receptors. AR density is very high in the brain. Thus, A1AR and A2AAR are mainly localized at excitatory synapses, although they are also present in glial cells.

Both activation and blockade of ARs are important mechanisms in the correction of such brain conditions as ischemia and epilepsy. For example, in ischemic stroke, the dual and opposite control of A1 activation and A2A blockade provide reliable neuroprotection with abnormally increased load, which is also characteristic of epileptic conditions. This suggests that combined A1AR activation and A2A blockade may be more effective in limiting acute brain injury. The prospect of treating neurodegenerative diseases such as Parkinson's disease (PD) is also important. The particularly high density of A2A in the basal ganglia and their close antagonistic interaction with dopamine D2 receptors has prompted the targeting of A2A to alleviate the dopaminergic depletion characteristic of PD. Selective A2A antagonists also attenuate other motor conditions such as catalepsy and tremor, and others. In experiments, A2A blockade prevents memory deficits in models of Alzheimer's disease. Antagonism of A2A also prevents memory dysfunction associated with other states of cognitive dysfunction such as seizures, demyelination states.

Conclusions. Over the past several decades were generated a number of highly specific agonists and antagonists of ARs, which are important modulators of physiological and pathological processes.