The endocannabinoid system and its role in the pathogenesis and treatment of cardiovascular disturbances in cirrhosis

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Abstract

It has been known for over half a century that liver cirrhosis is associated with abnormal cardiovascular function. Although the mechanisms underlying the association of portal hypertension and hyperdynamic circulation have been intensively investigated during the past decades, the results are still inconclusive. This review focuses on the role that the endocannabinoids and their receptors could play in the pathogenesis of the cirrhotic cardiomyopathy, as well as on the treatment options that they offer. (Acta gastroenterol. belg., **2013**, 76, **195-199**).

Key words : endocannabinoid system, cirrhotic cardiomyopathy, receptor, treatment, hyperdynamic circulation.

Introduction

Heart diseases can affect the liver with development of, for instance, cardiac cirrhosis and liver diseases may affect the heart with development of cirrhotic cardiomyopathy. At present no specific treatment exists for this cardiomyopathy, as its pathogenic mechanisms are not fully understood. One of the molecular mediators of the impaired myocardial function in cirrhosis seems to be the endocannabinoid system. This review focuses on the potential this system may have in understanding and treating the cirrhotic cardiomyopathy.

Cardiovascular disturbances in cirrhosis

Circulatory function is severely impaired in cirrhotic patients with ascites due to a splanchnic arterial vasodilatation. An increased local release of nitric oxide and other vasodilators related to portal hypertension is the most likely explanation for this abnormality. Compensatory mechanisms such as an increased cardiac output and overactivity of the renin-angiotensin system, sympathetic nervous system and antidiuretic hormone, are essential in the maintenance of arterial pressure in decompensated cirrhotic patients (1).

Patients with end-stage liver disease manifest a hyperdynamic circulation characterized by a decrease in the systemic vascular resistance and arterial pressure, and an increase in the heart rate and cardiac output. In addition to the hyperdynamic circulation, impaired ventricular contractility in response to stimuli was also described in cirrhotic patients. Initially, this was thought to be a manifestation of latent alcoholic cardiomiopathy but later studies in non-alcoholic patients and in experimental animal models revealed the same pattern of blunted cardiac contractile responsiveness. Thus, these cardiovascular changes are now termed „cirrhotic cardiomyopathy" (2).

The prevalence of the cirrhotic cardiomyopathy remains unkown at present, mostly because the disease is generally latent and shows itself when the patient is subjected to stress such as exercise, drugs, hemorrhage and surgery. The main clinical features of cirrhotic cardiomyopathy include baseline increased cardiac output, attenuated systolic contraction or diastolic relaxation in response to physiologic, pharmacologic and surgical stress, and electrical conductance abnormalities (prolonged QT interval). In the majority of cases, diastolic dysfunction precedes systolic disfunction, which tends to manifest only under conditions of stress. Generally, cirrhotic cardiomyopathy with overt severe heart failure is rare. Major stress on the cardiovascular system such as liver transplantation, infections and insertion of transjugular intrahepatic portosystemic stent-shunts (TIPS) can unmask the presence of cirrhotic cardiomyopathy and thereby convert latent to overt heart failure (3,4).

The pathogenic mechanisms of cirrhotic cardiomyopathy include cardiomyocyte plasma membrane physicochemical changes, attenuated stimulatory pathways, and enhanced activity of inhibitory systems which includes the following : ß-adrenegic receptor function, muscarinic receptor activity, membrane fluidity, nitric oxide, carbon monoxide and endocannabinoids (2).

Myocardial endocannabinoid production may be increased in response to stress such as increased heart rate and hemodynamic overload ; these substances are known to have a negative inotropic effect in rats and humans (3).

The endocannabinoid system

Endogenous cannabinoids (EC) are ubiquitous lipid signalling molecules provided by a number of central and peripheral effects, which are mainly mediated by the specific cannabinoid receptors CB_1 and CB_2. Although the

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Submission date : 25/04/2012
Acceptance date : 14/12/2012

expression of these receptors is very low or even absent in the healthy liver, a considerable series of experimental studies and some clinical observations have recognised the EC system as an important player in the pathophysiology of liver diseases. The EC system is highly upregulated during chronic liver diseases and, to date, it has been implicated in the pathogenesis of non-alcoholic fatty liver disease, progression of fibrosis to cirrhosis and the development of the cardiovascular abnormalities of cirrhosis, such as the hyperdynamic circulatory syndrome and cirrhotic cardiomiopathy (5,6).

Endogenous cannabinoids (EC) are mimicking the activity of Δ9-tetrahydrocannabinol, the main psychotropic constituent of marijuana. They are provided by a series of central and peripheral effects because they influence analgesia and motor function, energy balance and food intake, cardiovascular function, immune and inflammatory responses, and cell proliferation, which are mediated by the specific cannabinoid receptors CB_1 and CB_2. The CB_1 receptor is mainly expressed in brain, but also in several peripheral tissues including heart and vessels, whereas CB_2 is mostly found in immune system cells. However, some EC effects result from the interaction with other receptors, such as the vanilloid receptor (5).

The role and distribution of the CB_1 and CB_2 receptors are shown in tabel 1 :

Tabel 1. — **The CB_1 and CB_2 receptors (7,8)**

CB_1	CB_2
– coupled through G proteins to adenylyl cyclase and mitogen-activated protein kinase – also coupled through G proteins to several types of calcium and potassium channels	– coupled through G proteins to adenylyl cyclase and mitogen-activated protein kinase
– has been cloned from rat, mouse, and human tissues and exhibits 97 to 99% amino acid sequence identity across species	– exhibits 48% homology with the CB_1 cannabinoid receptor
– are found primarily in brain and neuronal tissue – were found to be particularly enriched in cerebral cortex, hippocampus, basal ganglia, and cerebellum; lower levels were found in hypothalamus and spinal cord – are widely expressed in the peripheral nervous system, both on sensory nerve fibers and in the autonomic nervous system – are also expressed in some immune cells, but their level of expression is considerably lower than that of CB_2 receptors – can be found to a lower extent in peripheral tissues, including the adrenal gland, bone marrow, heart, lung, prostate, testis, thymus, tonsils, and spleen	– found primarily in immune tissue and is notably absent from normal nervous tissue – is found in spleen , thymus, tonsils, bone marrow, pancreas, splenic macrophage/monocyte preparations, mast cells, peripheral blood leukocytes, and in a variety of cultured immune cell models, including the myeloid cell line U937 and undifferentiated and differentiated granulocyte-like or macrophage-like HL-60 cells
– they were shown to mediate metabolic steatogenesis in the liver, by central and peripheral hepatic effects; they might also affect lipolysis in the adipose tissue, thereby enhancing the influx of triglycerides in the liver	– it was found that their genetic inactivation reduces obesity and insulin resistance; their antagonism blunts hepatic steatosis, following inhibition of obesity-associated inflammation in the adipose tissue

2-Arachidonoylglycerol and arachidonoyl ethanolamide (anandamide) are the 2 best characterized endocannabinoids. Their effects are mediated by 2 G protein–coupled receptors, CB_1 and CB_2, as well as additional, as-yet unidentified ones. 2-Arachidonoylglycerol binds to both CB_2 and CB_1 receptors, whereas arachidonoyl ethanolamide has higher affinity for CB_1 receptors and may also bind to vanilloid VR_1 receptors. The tissue levels of endocannabinoids are determined by the balance between their biosynthesis (involving phospholipase D– and diacyl-glycerol lipase–dependent and other pathways), cellular uptake, and degradation by fatty acid amide hydrolase and/or monoacylglycerol lipases (9). The structures of the constituents of the cannabis can be seen in figure 1 :

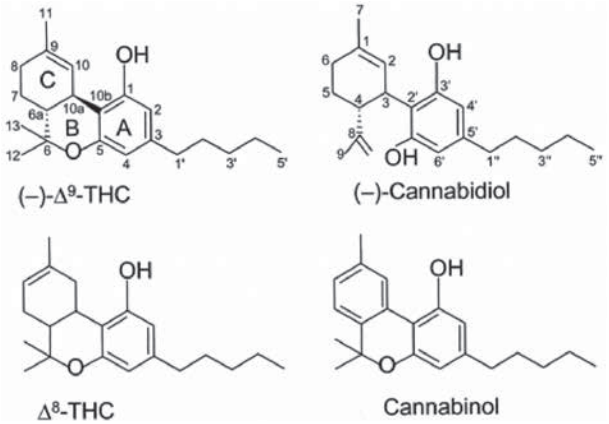

Fig. 1. — The structures of four constituents of cannabis : Δ^9-THC, Δ^8-THC, cannabinol, and cannabidiol (10).

Presence of so-called "CB_3" at excitatory synapses was proposed based on the electrophysiological data showing the persisting effects of cannabinoid agonists on hippocampal excitatory transmission in CB_1-knockout mice . Previous immunohistochemical results showing the absence of CB_1 receptors on hippocampal excitatory presynaptic terminals were apparently in line with the "CB_3" hypothesis, but several studies support that the CB_1 receptor is the major, if not exclusive, cannabinoid receptor at excitatory synapses in these brain regions and indicate that there is no evidence for the presence of "CB_3" receptor (11).

The endocannabinoids and the liver

The most likely sources of CB_2 receptors in the normal liver are the resident macrophages (Kupffer cells), endothelial and hepatic stellate cells, while under pathological conditions overexpression of CB_2 receptors may also be prominent in hepatocytes and originate from infiltrating inflammatory cells. While CB_2 receptor activation in hepatic stellate cells mediates apoptosis and antifibrotic effects, its activation in Kupffer, endothelial and inflammatory cells most likely attenuates inflammation and reactive oxygen and nitrogen species generation associated with hepatic ischemia-reperfusion (I/R) as well as other liver pathologies (12).

In patients with cirrhosis of various etiologies, the activation of vascular and cardiac CB_1 receptors by macrophage-derived and platelet-derived endocannabinoids contributes to the vasodilated state and cardiomyopathy, which can be reversed by CB_1 blockade (13).

In a rat model of bile duct ligated cirrhosis, increased endocannabinoid signaling blunted the ventricular responsiveness to ß-adrenergic stimuli by the CB_1 receptor. A study in a rat model of carbon tetrachloride-induced cirrhosis showed that increased activity of the endocannabinoid/CB_1 receptor blockade restored the normal contractile function. The negative inotropic effect of CB_1 receptor might be the result of L-type calcium channel inhibition and cAMP reduction (14).

Furthermore, the EC system influences the mechanisms responsible for cell damage and the inflammatory response during acute liver injury, such as that resulting from ischaemia-reperfusion. At present, the CB_1 antagonists represent the most attractive pharmaceutical tool to resolve fat accumulation in patients with non-alcoholic fatty liver disease and to treat patients with cirrhosis, as they may slow the progression of fibrosis and attenuate the cardiovascular alterations associated with the advanced stage of the disease (5).

Also, the CB_2 receptor has been identified to as a possible target for the management of the liver diseases based on the ability of CB_2 agonists to reduce experimental fibrosis and exert curative effects in cirrhotic rats (15).

The cardiovascular effects of the endocannabinoids

Cardiovascular effects of endocannabinoids *in vivo* are complex and may involve the modulation of autonomic flow of central and peripheral nervous systems, as well as the direct effects of myocardium and vasculature. However, its peripheral actions appear to play a dominant role, at least after systemic administration of doses used by most researchers (16).

The endocannabinoid system appears to play limited role in normal cardiovascular regulation under physiological conditions, which is supported by the normal blood pressure and myocardial contractility and /or baroreflex sensitivity of CB_1, CB_2 and fatty acid amine hydrolase knockout mice. But in many pathological conditions, such as heart failure, shock, advanced liver cirrhosis, the endocannabinoid system may become overactivated and may contribute to hypotension/cardiodepression through cardiovascular CB_1 receptors (12).

So, besides their well known neurobehavioral and immunological actions, cannabinoids and their endogenous and synthetic analogs exert important cardiovascular effects. The underlying mechanisms are complex, involving direct effects on the vasculature and myocardium , as well as modulation of autonomic outflow through sites of action in the central and the peripheral nervous systems. As for endogenous cannabinoids, their effects are also complicated by their rapid metabolism, which liberates arachidonic acid that can be further metabolized into vasoactive prostanoids (17).

Studies to date indicate that CB_1 receptors are much more important than CB_2 receptors in cardiovascular regulation, the latter so far being implicated only in ischemic preconditioning and ischemia/reperfusion (I/R) injury of the myocardium. CB_1 receptors have been detected in the human, rat, and mouse myocardium where they mediate negative inotropy and also in vascular tissues, where their activation leads to vasodilation, and both of these effects appear to be involved in the hypotensive effect of anandamide in anesthetized rodents. Sympathetic nerve terminals contain presynaptic CB_1 receptors, stimulation of which inhibits norepinephrine release, which contributes to the bradycardic effects of anandamide in vivo. Anandamide-induced cardiovascular depressor effects are devoid of a centrally mediated component, in contrast to the effects of certain synthetic cannabinoids, which cause centrally mediated sympathoexcitation (17).

Treatment with endocannabinoid receptor antagonists

Several studies showed that the cardiac dysfunction in cirrhosis could be corrected by CB_1 blockade, highlighting the therapeutic potential of CB_1 antagonists in this disease condition. The first indication that CB_1 receptors are involved in some aspects of abnormal myocardial contractility in liver cirrhosis came from an in vitro study

using isolated left ventricular papillary muscle from bile duct-ligated cirrhotic rats, in which CB_1 blockade reversed the decreased β-adrenergic responsiveness (18).

Chronic CB_1 treatment was found to promote cardiac remodeling while cardiac function, but not the survival, was improved (17).

Two CB_1 receptor antagonists have been predominantly used to explore cannabinoid physiology in cirrhosis, AM 251 and SR 141716A (rimonabant). Although both are mainly active on the CB_1 receptor, the latter drug also partially inhibits at least two incompletely clarified cannabinoid receptors distinct from CB_1 and CB_2 (19). The structures of the cannabinoid receptor antagonists/inverse agonists, can be seen in figure 2 :

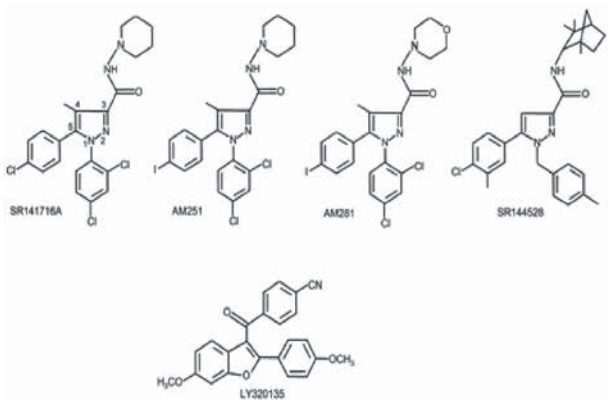

Fig. 2. — The structures of the cannabinoid receptor antagonists/inverse agonists, SR141716A, AM251, AM281, SR144528, and LY320135 (20).

Several studies reported normalization of hyperdynamic circulation by SR 141716A in cirrhotic rat models (19).

The clinical use of rimonabant for the treatment of obesity marked the first manipulation of the endocannabinoid system for therapeutic purposes (21). It was the first selective CB_1 receptor blocker to be approved for use anywhere in the world and was used as an anorectic anti-obesity drug, but it has now been withdrawn from the market due to its important side-effects : severe depression and suicidal thoughts.

On the other hand, there is evidence that endocannabinoids acting via CB_2 protect against hepatic ischemia/reperfusion (I/R) injury, highlighting the therapeutic potential of the CB_2 agonists, like HU-308. As the increased CB_1 activity contributes to the hemodynamic abnormalities and promotes fibrosis in liver cirrhosis, CB_1 blockade attenuates and delays these changes. CB_1 receptor blockade also protects the liver from I/R injury and superimposed endotoxemia (13).

Conclusions

Several conditions are associated with overactivation of the endocannabinoid system. Such conditions may include impaired cardiac function in various forms of cardiomyopathies and heart failure. Based on several studies, there is growing evidence that CB_1 receptor antagonism may be beneficial and, therefore can be therapeutically exploited in these conditions. One possible therapeutic strategy may involve the acute administration of a CB_1 antagonist to abrogate the undesirable hemodynamic and other effects of pathologically overproduced endocannabinoids (18).

Despite the setback with the first class of CB_1 antagonists, a better understanding of the role of the endocannabinoid system in various cardiovascular pathologies should lead to the developement of better therapeutic approaches. The recent emergence of second-generation, peripherally restricted CB_1 antagonists, may offer a solution : TM38837 is a first in class, second generation CB_1 receptor antagonist. It was designed to circumvent the risk of psychiatric side effects displayed by the first generation CB_1 receptor antagonists, through its restriction to peripherally located CB_1 receptors in the body.

Acknowledgements

„Research done within POSDRU/6/1.5/S/26 project, co financed by the European Social Funds by means of the Sectoral Operational Program for the Development of the Human Resources 2007-2013".

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