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Review article

Pharmacological inhibition of FAAH activity in rodents: A promising pharmacological approach for psychological—cardiac comorbidity?

Luca Carnevali[a], Silvia Rivara[b], Eugene Nalivaiko[c], Julian F. Thayer[d], Federica Vacondio[b], Marco Mor[b], Andrea Sgoifo[a,*]

[a] Department of Neuroscience, University of Parma, Italy
[b] Department of Pharmacy, University of Parma, Italy
[c] School of Biomedical Sciences, University of Newcastle, Australia
[d] Department of Psychology, The Ohio State University, Columbus, OH, USA

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ABSTRACT

Numerous studies have documented a link between psychological disorders and cardiac disease. Yet, no systematic attempts have been made to develop pharmacological approaches for mood and anxiety disorders that could also be beneficial for cardiac health. The endocannabinoid system has been implicated in the regulation of stress, emotional behavior and cardiovascular function. General preclinical findings indicate that the endocannabinoid anandamide modulates physiological and behavioral stress responses and may also protect the heart from arrhythmias. Moreover, recent experimental studies suggest that pharmacological enhancement of anandamide signaling *via* inhibition of its degrading enzyme fatty acid amide hydrolase (FAAH) exerts anxiolytic- and antidepressive-like effects and improves cardiac autonomic function and the electrical stability of the myocardium in rodent models that reproduce aspects of human psychological/cardiac comorbidity. Here we summarize and discuss such experimental findings, which might guide future preclinical studies towards a systematic evaluation of the therapeutic potential of pharmacological approaches that target FAAH activity for the treatment of the comorbidity between psychological disorders and cardiac disease.

Contents

1. Introduction

The high comorbidity between psychological disorders and cardiovascular disease has long been documented in the scientific literature. Mood and anxiety disorders in particular have been linked to heart disease, with research showing that individuals displaying symptoms of depression or anxiety are at higher risk for cardiovascular-related morbidity and mortality (Kawachi et al.,

* Corresponding author at: University of Parma, Department of Neuroscience, Stress Physiology Laboratory, Parco Area delle Scienze 11/a, 43123 Parma, Italy.
E-mail address: andrea.sgoifo@unipr.it (A. Sgoifo).

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1994; Musselman et al., 1998; Rozanski et al., 1999). A common precipitating factor for the onset and progression of both psychological and cardiovascular disorders in vulnerable individuals is represented by chronic stress exposure (Cohen et al., 2015). Underlying pathophysiological mechanisms may include a dysregulation of the autonomic neural control of cardiac function. Consistent with this model is evidence that both depressive and anxious subjects without known cardiac disease may display a predominance of sympathoadrenergic activation and/or reduced parasympathetic modulation, as evidenced by increases in resting-state heart rate (HR) and decreases in its variability (HRV) (Alvares et al., 2013; Chalmers et al., 2014; Kemp and Quintana, 2013; Udupa et al., 2007). These features of cardiac autonomic neural outflow are thought to bring about disturbances of myocardial electrical activity, thereby lowering the threshold for arrhythmias and sudden cardiac death (Carney et al., 2005). This raises the question of whether conventional treatments for psychological disorders are able to ameliorate autonomic function, thereby reducing cardiac risk. It is beyond the scope of this review to go into depth on the autonomic effects of conventional psychiatry medications, which have been addressed in depth by others (Kemp et al., 2014, 2010; Licht et al., 2010, 2008; Sgoifo et al., 2015; Wu et al., 2014). However, what emerges from this literature is that traditional medications for depression or anxiety (including tricyclic antidepressants, serotonin reuptake inhibitors and benzodiazepines) may not lead to a full normalization of resting HR or HRV, or may even worsen HRV indexes. In addition, conventional antidepressant drugs may have cardiotoxic side effects, such as vasoconstriction, QT prolongation, and promotion of arrhythmias (Glassman et al., 1998; Sheline et al., 1997). This warrants the search for alternative pharmacological approaches for depression and anxiety that could also be beneficial for cardiac health.

A large body of evidence supports a contribution of the endocannabinoid (eCB) system in the regulation of stress and emotional behavior (Gorzalka and Hill, 2011; Hill and Patel, 2013; Morena et al., 2016). General findings from this work indicate that eCB anandamide signaling is critical for buffering the physiological effects of the stress response, dampening anxiety and regulating mood. Moreover, anandamide has been reported to exhibit cardioprotective abilities, including potential anti-arrhythmic actions (Hiley, 2009). The present review summarizes the results of rodent studies that have explored the involvement of anandamide signaling in the regulation of stress-response physiology, emotional behavior and cardiac function. Moreover, recent promising findings on the effects of pharmacological enhancement of anandamide signaling in rodent models that reproduce aspects of human psychological/cardiac comorbidity are discussed.

2. The endocannabinoid system

Endocannabinoids (eCBs) are endogenous lipid mediators generated by almost all cell types both in the brain and in the peripheral tissues that mimic most of the effects of Δ^9-tetrahydrocannabinol (THC), the active ingredient of the marijuana plant *Cannabis sativa*. The two best characterized eCBs are arachidonoyl ethanolamide (anandamide, AEA) and 2-arachidonoyl glycerol (2-AG), although this family of bioactive lipids includes other fatty arachidonic acid derivatives with putative cannabimimetic properties (*e.g.*, virodhamine, noladin ether, N-acyl dopamines). ECBs exert biological actions predominantly *via* activation of two $G_{i/o}$ protein-coupled cannabinoid receptors, the type-1 (CB_1) and type-2 (CB_2) (Fig. 1) (Howlett, 2002). The CB_1 receptor is highly expressed in the brain (Moldrich and Wenger, 2000) but also present at much lower yet functionally relevant concentrations in various peripheral districts, including the cardiovascular system (Batkai et al., 2004; Bonz et al., 2003; Pertwee et al., 2010). The CB_2 receptor was initially thought to be expressed only in immune and hematopoietic cells (Howlett, 2002), but subsequent studies have established its presence also

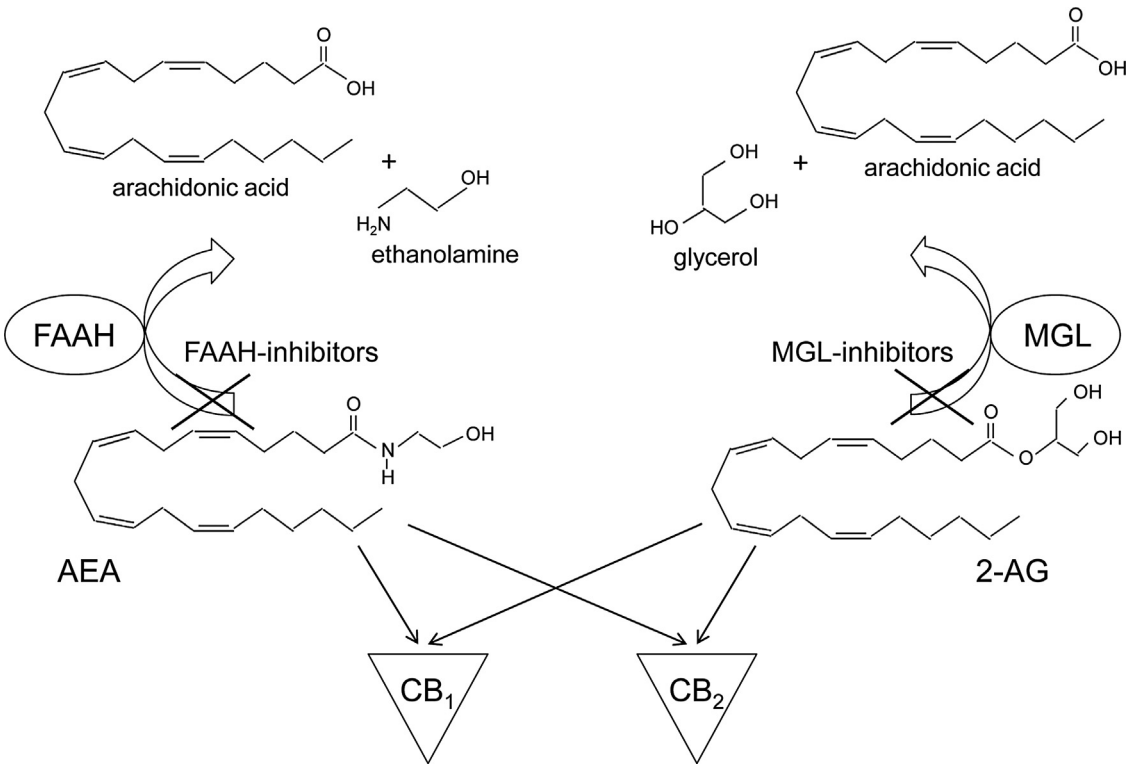

Fig. 1. Schematic illustration of the endocannabinoid system targets and catabolism. The main endocannabinoids, arachidonoyl ethanolamide (anandamide, AEA) and 2-arachidonoyl glycerol (2-AG), bind to CB_1 and CB_2 receptors and are preferentially degraded *in vivo* by the enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MGL), respectively.