In this issue of American Journal of Physiology-Heart and Circulatory Physiology, Pacher et al. (16) characterized the cardiovascular effects of anandamide (AEA) in mice deficient in fatty acid amide hydrolase (FAAH), an enzyme responsible for metabolizing AEA. There was no difference in baseline hemodynamics or baroreceptor reflex function in FAAH-deficient mice, which displayed elevated cardiac tissue levels of AEA. However, cardiovascular responses to exogenously administered AEA were enhanced as might be expected. Whereas these observations suggest a lack of involvement of endogenous cannabinoids in cardiovascular function, recent studies in hypertensive animals reveal tonic and even enhanced effects of FAAH blockade (1). Thus, under conditions of pathophysiological stress (hypertension, inflammation, and hemorrhagic shock) where an increase in synthesis and release of AEA might occur, FAAH deficiency would be a risk factor for cardiovascular perturbations (cardiodepression and hypotension). FAAH inhibitors are being explored as therapeutic agents for pain and anxiety (6, 7). Such agents would be predicted to exhibit low incidence of side effects in healthy individuals. However, in the event of sepsis or cardiovascular impairment, exacerbation of cardiodepression by exogenous or endogenous cannabinoids could become problematic.

Cannabinoids elicit neurobehavioral as well as cardiovascular effects through cannabinoid receptors, of which two types, CB1 and CB2, have, so far, been cloned (9, 10). CB1 receptors are expressed in the central nervous system, and CB1 and CB2 receptors are expressed in certain peripheral tissues, including the vasculature. AEA and 2-arachidonoylglycerol (2-AG) are the two lipid mediators, termed endocannabinoids because of their action at cannabinoid receptors, with AEA receiving more attention as a vasorelaxant in a myriad of vascular beds (13, 17). The cardiovascular effects of AEA appear to be mediated by the CB1 receptor. However, antagonism by SR-141716 of Ca2+-induced relaxation of isolated arteries from CB1 receptor-deficient mice suggests a role for non-CB1 receptors (2, 3). Similar observations of non-CB1 receptor-mediated vasodilation led to the suggestion that an “AEA receptor” distinct from CB1 or CB2 and coupled through Gq/11 to phosphatidylinositol-3 kinase-Akt signaling pathway plays a role in this process (14, 15).

One problem with increasing endogenously synthesized AEA as a therapeutic strategy is that AEA is a promiscuous agonist that interacts with multiple proteins, many of which have direct relevance to neuromuscular reactivity. These include not only agonist actions at CB1 receptors and vanilloid receptor TRPV1 ion channels on sensory nerves but also regulation of myoendothelial gap junctions, L-type channels, and unidentified processes involved in intracellular Ca2+ regulation (8, 9, 13). To the extent that the effects of AEA differ in potency and efficacy at these various receptors and proteins, pharmacological manipulations that decrease AEA metabolism would be expected to predominantly affect those mechanisms for which AEA has low potency but high efficacy. On the other hand, AEA at high concentrations could behave as a weak partial agonist to competitively antagonize effects of the more efficacious endogenous agonist 2-AG at CB2 receptors. This is particularly important in vascular regulation if one considers that the predominant source of endocannabinoids acting in vasculature may be macrophages and platelets that participate in an inflammatory response (21).

In developing pharmacological targets for modulation of endocannabinoids, proteins other than FAAH should be considered (7, 8). It might be expedient to separate the role of AEA as an autocrine versus paracrine regulator. Thus one could manipulate enzyme(s) that synthesize precursor N-acylphosphatidylethanolamines or the specific phospholipase D associated with the release of AEA as a mechanism to enhance effects of intracellular AEA. Agents that would limit transport of AEA out of cells would be expected to enhance autocrine regulation at intracellular targets within AEA synthesizing cells while limiting paracrine regulation of neighboring cells that react to released AEA, providing for selectivity that FAAH inhibitors would not exhibit.

Enzymatic mechanisms for biosynthesis and inactivation of AEA exist in both central and peripheral tissues and play significant roles in its disposition. As illustrated in Pacher’s study, AEA was elevated twofold in cardiac tissue. Previous reports support a greater role for FAAH in the brain, where FAAH-null mice exhibit 10- to 15-fold elevations in AEA (5). There exists a close correspondence in distribution of FAAH and CB1 receptors in the rat brain and their expression at the cellular level (7, 9). Thus FAAH may participate in cannabinoid signaling mechanisms of the brain. CB1 receptors are also localized in dorsal root ganglia, which contain cell bodies of many sensory neurons projecting into the spinal cord and the periphery. Bukoski and colleagues (2, 11) showed that the Ca2+-sensing receptor, found in the perivascular sensory network of rat mesenteric arteries, is linked to release of a hyperpolarizing vasodilator compound. Endocannabinoids acting via a non-CB1 receptor may participate in this mechanism (3, 13, 15). These key observations by Bukoski and colleagues provided an important link between neural and vascular mechanisms of action of endogenous cannabinoids. Since that time, activation of CB1 receptors was shown to mediate sympathoin-
hibitation as a consequence of presynaptic inhibition of norepinephrine release from nerve terminals of postganglionic sympathetic neurons producing hypotension, as well as enhancement of cardiac vagal tone producing bradycardia (13, 17). In the rat brain, activation of CB1 receptors depresses respiration and increases sympathetic tone and cardiac vagal tone. Modulation of brain autonomic pathways, particularly in areas involved in reflex regulation of blood pressure control, participate in the complex hemodynamic events in response to AEA. After intravenous administration, centrally mediated as well as direct vascular and cardiac effects are likely. The administration of AEA directly into the nucleus of the solitary tract (NTS), the site of the first synapse for baroreceptor input, increases sensitivity of the reflex control of renal sympathetic nerve activity via CB1 receptor actions involving presynaptic interactions with GABA or glutamate fiber terminals (19). Increases in blood pressure elevate AEA levels in NTS tissue demonstrating dynamic regulation of the system. Because brain AEA levels are not dependent on neuronal stores, metabolism is of major importance to regulate local tissue levels (7, 9). The diversity of effects illustrated above makes it difficult to interpret the individual mechanisms involved in cardiovascular regulation by the endocannabinoids.

Multiple enzymes (FAAH, cytochrome P-450 enzymes, cyclooxygenases, and lipoxygenases) are involved in degradation of endocannabinoids. Thus, like cytochrome P-450 metabolism of arachidonic acid to products that control cardiovascular function, AEA and 2-AG contain primary hydroxyl groups subject to oxidative metabolism to unique signal mediators with potent activities distinct from their cannabimimetic precursors (4, 12, 18). It can therefore be argued that, whereas FAAH may play a predominant role in the brain, other biotransformation pathways may have prominence in the vasculature. Because endocannabinoids are also susceptible to oxidative metabolism, products from these pathways may confound effects of FAAH inhibition or knockdown in the cardiovascular system. Reductions in FAAH activity may uncover compensatory mechanisms of AEA metabolism leading to formation of other vasoactive compounds (22).

The inevitability of cardiovascular effects due to derivatives or metabolites of AEA and 2-AG cannot be ignored. 2-AG has several pharmacological effects; however, it is not clear whether these effects are due to 2-AG itself or arachidonic acid and other metabolites derived from it. For example, 2-AG-induced contraction of the isolated rat aorta is attributed to its uptake and conversion to the prostanooid thromboxane in vascular smooth muscle cells (20). In coronary arteries, 2-AG may be an intermediate in vasodilation, eicosanoid release, and regulation of coronary tone (9, 17). 2-AG, like AEA, induces hypotension in rats, and its production in the rat aorta is enhanced by muscarinic M1 receptor stimulation (17). Thus the biological effects of such products must be considered not only for exogenously administered endocannabinoids but also for endogenously produced AEA and 2-AG. Oxidative metabolites (e.g., cytochrome P-450 products) or prostanooid ethanalamides synthesized by COX2 probably work through pharmacological targets other than those acted on by AEA. These novel additional pathways may go beyond physiological regulatory mechanisms into the realm of toxicological reactions, depending on the cell types involved and their sensitivity to these novel AEA derivatives.

REFERENCES


AJP-Heart Circ Physiol • VOL 289 • AUGUST 2005 • www.ajpheart.org