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Review

Endogenous opioid peptides and cardiac arrhythmias

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Introduction

There is substantial evidence that cardiac opiate receptors are activated during arrhythmias induced by administration of opioid peptides or myocardial ischemia and reperfusion, supporting the hypothesis that endogenous opioid peptides are involved in cardiac arrhythmogenesis [1–10]. The occurrence of arrhythmias is accompanied by an increase in myocardial levels of cyclic adenosine monophosphate which suggests a possible functional relationship between the cyclic nucleotide and cardiac arrhythmias [11–14]. An obvious hypothesis is that myocardial ischemia and reperfusion activates the myocardial opiate receptors through an increased release of opioid peptides from the heart, which in turn leads to an increase in myocardial levels of cyclic adenosine monophosphate [15,16], thereby causing arrhythmias through alteration of the ionic channels [17–19]. In this review, I have discussed the possible roles of endogenous opioid peptides in cardiac arrhythmogenesis.

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Localization of endogenous opioid peptides in the cardiovascular system

The idea that there are endogenous morphine or opiate-like substances in our body was first initiated when Reynolds [20] observed that electrical stimulation of the periaqueductal grey of rats produced analgesia; and that naloxone, an opiate antagonist, antagonized this stimulation-produced analgesia [21,22]. Later, stereospecific binding sites for opiates – what came to be called the "opiate receptors" – were demonstrated in the brain [23,24], further suggesting the presence of endogenous opiate ligands. In 1975, Hughes and Kosterlitz [25] first identified and synthesized Met- and Leu-enkephalin from extracts of the brain and pituitary, which possessed opiate-like activity similar to the naturally-occurring opiates. These two pentapeptides were the first group of endogenous opioid peptides discovered. Subsequently, other groups of endogenous opioid peptides were also found, which in common practice, were classified into three different families: the enkephalins, endorphins and dynorphins [26–28].

Endogenous opioid peptides are widely distributed throughout the body. Studies by radioimmunoassay and by immunocytochemistry showed that there are immunoreactive beta-endorphin, dynorphins and enkephalins in the brain [29–32].

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Various kinds of endogenous opioid peptides are also found in peripheral organs such as the lung, intestine, liver, kidney, pancreas, muscles and testes [33,34]. This widespread distribution and localization of endogenous opioid system exerts biological activities as neurotransmitters [35,36], neuroendocrine regulators [37,38], blood borne hormones [39,40] and as local factors [41,42], which regulate a very extensive range of body functions.

Endogenous opioid peptides and opiate receptors are also abundantly distributed throughout the cardiovascular system of the body. Centrally, endogenous opioid peptides [33,43,44] and opiate receptors [45,46] have been found in brain regions where they could affect the cardiovascular functions, such as in the nucleus tractus solitari [47], the dorsal vagus nucleus and the nucleus ambiguus [48]. Peripherally, endogenous opioid peptides and/or opiate receptors have been identified in the vagus nerve [33,49], sympathetic ganglia [50], as well as in the heart [42,51–53] (especially in the cardiac ganglia, paraganglionic cells and amine precursor uptake and decarboxylation cells) [52]. This widespread distribution and localization of endogenous opioid peptides throughout the cardiovascular system exerts biological activities which influence and regulate the cardiovascular functions, both centrally and peripherally, including a direct action of endogenous opioid peptides on the heart.

Endogenous opioid peptides and cardiovascular functions

Changes in blood pressure and heart rate following administration of morphine [54–56] and endogenous opioid peptides [55,57,58] centrally or peripherally have been described. The interactions between endogenous opioid peptides and the catecholamine [59], dopamine [59], acetylcholine [60] and serotonin [57] systems have also been observed. It has been shown that beta-blockers attenuated the increases in blood pressure and heart rate due to intracerebroventricular administration of Leu-enkephalin [61]. Administration of beta-endorphin intracisternally increased plasma concentrations of epinephrine, norepinephrine and dopamine [59]. These findings suggest that endogenous opioid peptides may act centrally to stimulate the sympathetic outflows, thus affecting the cardiovascular functions. In another aspect, intracisternal administration of hemicholinium-3 (which interferes with cholinergic neurotransmission) [62], inhibited the plasma catecholamine responses to beta-endorphin [59], suggesting that cholinergic neurones may interact with endogenous opioid peptides. Moreover, administration of beta-endorphin intravenously induced hypotension which was facilitated by fluoxetine (a serotonin-uptake inhibitor), and antagonized upon depletion of brain serotonin or blocking the serotonin receptors by cyproheptadine, methergoline or mianserine [57]. This indicates that some cardiovascular effects of endogenous opioid peptides could be mediated via serotoninergic pathways.

Involvement of endogenous opioid peptides in cardiac arrhythmogenesis

It was first demonstrated in 1976 that high doses of morphine induced cardiac arrhythmias, including atrial fibrillation and atrioventricular block, in the conscious rat [63]. This observation has led to the speculation that endogenous opioid peptides may be involved in cardiac arrhythmogenesis. Moreover, if endogenous opioid peptides indeed cause cardiac arrhythmias as morphine does, the opiate antagonists may naturally have antiarrhythmic effects against those arrhythmias induced by endogenous opioid peptides. Subsequent investigation has, however, found no direct action of leucine-enkephalin on the heart in the heart-lung preparation [64]. In 1984, however, Lee et al. [3] demonstrated that, when administered directly into the heart, both beta-endorphin and dynorphin caused cardiac arrhythmias in the isolated perfused rat heart preparation. Beta-endorphin caused only atrial arrhythmias (such as atrioventricular block and atrial fibrillation similar to that caused by morphine) [3], whereas dynorphin caused both atrial and ventricular arrhythmias including ventricular premature contraction, ventricular tachycardia and ventricular fibrillation [16]. These findings suggest that endogenous opioid peptides may act directly on the heart causing cardiac arrhythmias.

That the opiate antagonists may naturally have

antiarrhythmic effects has been verified in several experimental models when arrhythmias are induced by various procedures. In the unanaesthetized young rat induced by theophylline and chloroform to exhibit respiratory arrest and ventricular fibrillation, naloxone (an opiate antagonist) reduced the incidence of ventricular fibrillation. In the anaesthetized guinea pig subject to ouabain intoxication [4], naloxone increased the dosage of ouabain required to induce ventricular arrhythmias and cardiac arrest [7,8]. In the anaesthetized dog subject to acute coronary arterial occlusion and reperfusion, moreover, naloxone reduced both the ischemia- and reperfusion-induced arrhythmias [6]. The above findings indicate that naloxone possesses antiarrhythmic property. The results are in agreement with that of Fagbemi et al. [1], who reported that naloxone blocked the cardiac arrhythmias resulting from acute coronary ligation in both anaesthetized and conscious rats. They are not compatible with the findings of Bergey and Beil [65], who observed no antiarrhythmic action of naloxone in the anaesthetized pig subject to coronary arterial ligation. The discrepancy may be due to differences between species. Benfey et al. [66] also found that, during acute coronary occlusion and reperfusion, both prazosin and propranolol had antiarrhythmic effects in the dog, but not in the pig. Moreover, the inefficacy in the pig may be due to a different anatomy of the coronary circulation, with less collateral flow in the pig [67].

To test further the hypothesis that endogenous opioid peptides are indeed involved in cardiac arrhythmogenesis, the antiarrhythmic properties of the stereoisomers of two different opiate antagonists have been studied [9]. It was demonstrated that the active isomer inhibited ventricular arrhythmias due to acute coronary arterial ligation in anaesthetized rats. The isomer which possesses no opiate antagonistic activity was without any antiarrhythmic property. Moreover, tolerance to the arrhythmogenic effects of endogenous opioid peptides or myocardial ischemia and reperfusion after chronic morphine treatment has also been studied. It is reasoned that, if chronic morphine treatment resulted in an attenuating effect against either one of the two stimulations in induction of arrhythmias, it suggests that the arrythmogenic effects are due to activation of opiate receptors. It was found that hearts from morphine-treated rats were less vulnerable to the arrhythmogenic effects of dynorphin or myocardial ischemia and reperfusion [10]. This is in agreement with the findings of Chan et al. [68], who also reported that rats receiving chronic morphine treatment were less susceptible to myocardial ischemia in induction of arrhythmias. The results indicate that desensitisation of the opiate receptors of the heart by chronic morphine treatment reduces the vulnerability of the heart to develop cardiac arrhythmias.

It is generally believed that the blocking effect of naloxone is an indication of opiate antagonism. To provide more conclusive evidence to support the involvement of endogenous opioid peptides in a particular physiological process, however, a number of other criteria has been suggested [69]. These include the demonstration of, first, cross tolerance with morphine; second, similar responses with other opiate antagonists; third, the lack of an effect with non-antagonist isomers; fourth, that agents which inhibit the breakdown of endogenous opioid peptides potentiate the response and, fifth, a direct release of endogenous opioid peptides [69]. Thus, from the evidence cited above, it is obvious that endogenous opioid peptides indeed cause cardiac arrhythmias through activation of opiate receptors in the heart. An obvious explanation is that arrhythmogenic stimulations such as myocardial ischemia and reperfusion increase the release of opioid peptides from the heart, which in turn activate the opiate receptors thereby causing cardiac arrhythmias. The most convincing piece of evidence needed to confirm this suggestion is the demonstration of a direct release of endogenous opioid peptides during myocardial ischemia and reperfusion. This awaits further study.

Cellular and biochemical mechanisms of endogenous opioid peptides – induced arrhythmias

In the rabbit papillary muscle preparation, Saxon et al. [70] have shown that morphine or Met-enkephalin induced a naloxone-reversible

shortening of cardiac action potential duration, rendering the heart more vulnerable to cardiac arrhythmias. On the other hand, Brasch [19] has shown that naloxone increased the cardiac action potential duration and the functional refractory period of guinea-pig papillary muscle. This may in the same manner render the heart less vulnerable to cardiac arrhythmias.

It is well-established that most amines, peptides and protein hormones act by interacting with receptor sites upon the plasma membrane with the resultant generation of intracellular messengers (cyclic adenosine monophosphate) which regulate a number of cellular processes [71,72]. Since endogenous opioid peptides are peptides which have been shown to cause an increase in cyclic adenosine monophosphate in the beating heart cell culture [73], it is highly possible that the mode of action of endogenous opioid peptides in cardiac arrhythmogenesis may be via the adenyl cyclase – cyclic adenosine monophosphate system.

The relationship between myocardial cyclic adenosine monophosphate and arrhythmogenesis remains controversial. Cardiac arrhythmias due to myocardial ischemia with or without reperfusion has been shown to be preceded by or associated with an increase in myocardial cyclic adenosine monophosphate levels in the cat [11], dog [12], pig [13] and in the isolated working rat heart [14], suggesting that increased levels of myocardial cyclic adenosine monophosphate may predispose the heart to arrhythmias. Other studies do not support such a relationship between increased levels of cyclic adenosine monophosphate and arrhythmogenesis [74,75]. In a recent study, Lee and Wong [15] have found that myocardial ischemia and reperfusion induced arrhythmias which were accompanied by corresponding increases in cyclic adenosine monophosphate levels. Attenuation of these arrhythmias by naloxone was accompanied by a corresponding reduction in myocardial cyclic adenosine monophosphate levels. These results support the notion that myocardial cyclic adenosine monophosphate may be related to cardiac arrhythmias. Moreover, both dynorphin- and reperfusion-induced arrhythmias were found to be associated with an increase in myocardial cyclic adenosine monophosphate levels [16]. The above findings indicate that both the arrhythmogenic action of endogenous opioid peptides and the antiarrhythmic action of naloxone involve cyclic adenosine monophosphate. That myocardial ischemia and reperfusion lead to the simultaneous occurrence of cardiac arrhythmias and elevation in myocardial cyclic adenosine monophosphate also suggests that myocardial cyclic adenosine monophosphate may mediate cardiac arrhythmias induced by dynorphin or myocardial ischemia and reperfusion, with the further possibility that the latter process acts via the release of endogenous opioid peptides. Whether the increase in cyclic adenosine monophosphate levels is a result of activation of adenyl cyclase or inactivation of phosphodiesterase (an enzyme responsible for degradation of cyclic adenosine monophosphate), or both, awaits further study. Since cyclic adenosine monophosphate has been shown to increase the slow inward current in ventricular myocardial preparation [17,18] and that the antiarrhythmic action of naloxone has been explained by an inhibition of the time-dependent membrane potassium ion outward current [19], it is likely that activation of opiate receptors may lead to an increase in myocardial cyclic adenosine monophosphate, which is turn may mediate arrhythmias via its effects on the calcium and potassium ion channels, as proposed and illustrated in Fig. 1.

The mechanisms of cardiac arrhythmogenesis are complex. Likewise, there may be a variety of mechanisms for the endogenous opioid peptides–induced arrhythmogenesis. One of the possible mechanisms (as proposed) by which endogenous opioid peptides cause arrhythmias is via the adenyl cyclase–cyclic adenosine monophosphate system. Further studies are needed to define the extent of involvement of endogenous opioid peptides, and the other mechanisms of action of endogenous opioid peptides involved in cardiac arrhythmogenesis.

Clinical relevance

The hypothesis that endogenous opioid peptides are involved in cardiac arrhythmogenesis may open a new area of research, concerning both the mech-

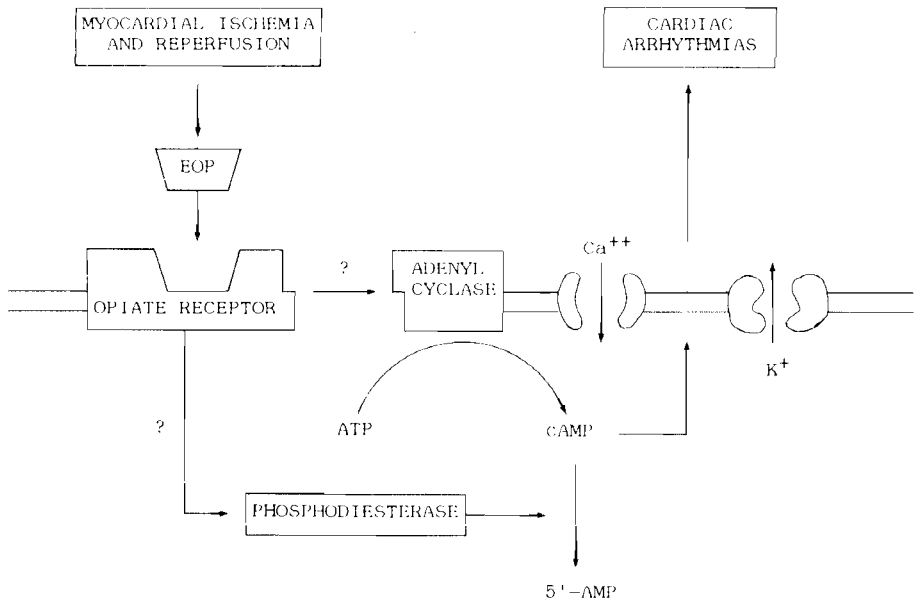

Fig. 1. A proposed hypothesis for the mechanisms of endogenous opioid peptides–induced cardiac arrhythmias. EOP = endogenous opioid peptides; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; 5′-AMP = adenosine 5′-monophosphate; Ca^{++} = calcium ions; K^{+} = potassium ions.

anisms of cardiac arrhythmias as well as the pathophysiology of myocardial ischemia and/or reperfusion. Since morphine is commonly prescribed for the relief of pain in patients with coronary arterial disease, great care must be taken, especially when high doses of morphine are required. It has been shown that morphine [76,77] and naloxone [78] increased and decreased the size of infarction respectively following myocardial ischemia in experimental animals. The occurrence of sudden death when morphine was injected in patients with acute myocardial infarction has also been reported [79]. Finally, since naloxone is antiarrhythmic, its therapeutic value as a new antiarrhythmic agent deserves further evaluation. The above basic and clinical information may be important in the field of cardiac medicine, especially in the prevention and treatment of cardiac arrhythmias as well as ischemic heart disease.

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