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NALOXONE AS AN ANTIARRHYTHMIC AGENT

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Aside from its traditional use in the therapy of morphine-induced respiratory depression, the discovery of the endogenous opioid system has led to the utility of naloxone in other medical conditions. Naloxone is now tried in the treatment of septic and hypovolemic shock, spinal cord injury, stroke, respiratory depression, drug overdose and a number of other diseases, Recently substantial evidence has shown that endogenous opioid peptides are involved in cardiac arrhythmogenesis. That the opiate antagonists may naturally have antiarrhythmic effects has been verified in several experimental models. Naloxone is classified as a Class III antiarrhythmic agent, based on electrophysiological studies. Its determined antiarrhythmic potency is comparable to that of the prototype of antiarrhythmic drugs (propranolol, quinidine and lidocaine). In human studies, it was found that beta-endorphin induced angina pectoris, and that naloxone reversed electrical-mechanical dissociation from cardiac arrest. More clinical studies are required to define the therapeutic value of naloxone as an antiarrhythmic agent.

Key words: Endogenous opioid peptides, Naloxone, Cardiac arrhythmias, Antiarrhythmic effect.

The opiate antagonist naloxone, the n-allyl derivative of oxymorphine, is employed widely to reverse opiate-induced respiratory depression.[1] Since the discovery of endogenous opioid peptides (EOP)[2,3] and the identification of multiple opiate receptors in the central nervous system and other tissues,[4-7] the possibility has been raised that naloxone may have wider therapeutic uses. Possible uses of naloxone now include the treatment of septic and hypovolemic shock, spinal cord injury, stroke, respiratory depression, drug overdose and a number of other diseases.[8-13] EOP are involved in cardiovascular functions. Administration of morphine or EOP or their derivatives has been shown to reduce blood pressure and heart rate in experimental animals and man, as well as demonstrated that these depressant effects are most pronounced when the cardiovascular system is already compromised.[14,15] Recently, there has been substantial evidence that cardiac opiate receptors are activated during arrhythmias induced by administration of EOP or myocardial ischemia and reperfusion. This supports the hypothesis that EOP are involved in cardiac arrhythmogenesis.[16-23] A logical, natural step following demonstration of possible involvement of EOP in cardiac arrhythmias is the search for use of opiate antagonists as antiarrhythmic agents. Following is a review of the clinical implications of antiarrhythmic effects of naloxone, as well as considerations for use of naloxone as a likely antiarrhythmic agent.

EOP AND CARDIAC ARRHYTHMIAS

The discovery of specific opiate receptors (designated as "mu", "kappa" and "sigma") in the brain,[4] pituitary,[5] sympathetic ganglia,[6] kidney,[7] liver,[7] gastrointestinal tract[5] and heart[5,6] suggested that there may be endogenous substances which interact specifically with these receptors. In 1975 Hughes and Kosterlitz[2] identified and synthesized the first endo-

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genous opioid peptides---met- and leu-enkephalin-from extracts of the brain and pituitary which possessed opiate-like activity and exhibited specific binding to the opiate receptors. Subsequently, other major families of EOP have been found: the enkephalins, endorphins and dynorphins.[2,3]

EOP are widely distributed throughout the body. EOP and opiate receptors, of which multiple forms have been defined, are present in the brain, lung, intestine, liver, kidney, pancreas, autonomic ganglia, adrenal gland and the heart (especially in the cardiac ganglia, paraganglionic cells and amine precursor uptake and decarboxylation (APUD) cells[5-6, 27-29].

Although little is known to date about the regulatory mechanisms of EOP in normal cardiovascular function, it is clear that cardiovascular stress situations such as shock[8,9] and stroke[13] substantially modify the activity of the endogenous opioid system. In 1976, morphine-induced cardiac arrhythmias, including atrio-ventricular block and atrial fibrillation, were first demonstrated in the conscious rat.[24] This has led to the speculation that EOP may likewise be involved in cardiac arrhythmogenesis. In 1984, Lee et al. first discovered that administration of beta-endorphin[17] and dynorphin[25] directly into the isolated rat heart could cause cardiac arrhythmias. Beta-endorphin caused atrial arrhythmias such as atrio-ventricular block and atrial fibrillation similar to that caused by morphine; dynorphin caused both atrial and ventricular arrhythmias such as ventricular premature contraction, ventricular tachycardia and ventricular fibrillation. Since met-enkephalin,[26] dynorphin and pro-dynorphin-derived opioid peptides[27-29] have been demonstrated to be present in the heart, beta-endorphin and dynorphin administered into the isolated heart may reach the opiate receptors by non-specific diffusion and mimic an intracardiac neurotransmitter, thereby causing arrhythmias.

ANTIARRHYTHMIC EFFECT OF NALOXONE

That EOPs are involved in cardiac arrhythmogenesis has led to the speculation that opiate antagonists may naturally have antiarrhythmic effects, an idea verified in several experimental models. In the ***in vivo*** preparations, naloxone has been demonstrated to reduce both the ischemia and reperfusion-induced arrhythmias in the anesthetized dog.[20] In the unanesthetized young rat subjected to theophylline and chloroform to induce ventricular fibrillation, naloxone lowered the incidence of ventricular arrhythmias.[18] In the anesthetized guinea pig with ouabain intoxication, naloxone increased the dosage of ouabain required to induce ventricular arrhythmias and cardiac arrest.[21] The above findings indicate that naloxone is antiarrhythmic, results in agreement with those of Fagbemi et. al.[16], who demonstrated that naloxone blocked cardiac arrhythmias caused by acute coronary artery ligation in the rat. The findings are not, however, compatible to the findings of Bergey and Beil,[30] who observed no antiarrhythmic effects of naloxone in the anesthetized pig subjected to coronary ligation. The discrepancy may be due to species difference. It has also been found that during acute coronary occlusion and reperfusion, both prazosin and propranolol had antiarrhythmic properties in the dog, but not in the pig.[31] Moreover, the inefficacy of naloxone in the pig may result from differences in the anatomy of the coronary circulatory system, with fewer collateral vessels in the pig than in the dog.[32] In the ***in vitro*** preparations, naloxone also reduced the arrhythmias caused by myocardial ischemia and reperfusion in the isolated rat heart.[19] Results support the antiarrhythmic effect of naloxone in rat isolated atria.[33]

To test further that naloxone exerts its antiarrhythmic effect by opiate antagonism rather than via its membrane stabilizing action, the antiarrhythmic property of the stereoisomers of two different opiate anta-

gonists were studied.[22] It was observed that the active isomer inhibited arrhythmias induced by acute coronary ligation in the rat. The isomer without opiate antagonistic action had no antiarrhythmic effects. In another study, chronic morphine treatment was employed.[23] It is well known that animals so treated may develop tolerance to morphine, or cross-tolerance to other opiates in opiate receptor-mediated effects. It was therefore reasoned that, the finding that chronic morphine treatment resulted in reduction of arrhythmias against the arrhythmogenic stimulations of EOP or myocardial ischemia and reperfusion would suggest that the arrhythmogenic and antiarrhythmic effects of EOP and naloxone respectively involve the cardiac opiate receptors. It was found that hearts from morphine-treated rats were indeed less vulnerable to the arrhythmogenic effects of the above two stimulations. The results are also in agreement with that of Chan et. al.[34], who observed that morphine-treated rats were less susceptible to coronary artery ligation in induction of arrhythmias.

The evidence cited above suggests that arrhythmogenic stimulations such as myocardial ischemia and reperfusion increase the release of EOPs from the heart, in turn activating cardiac opiate receptors, thereby causing arrhythmias. Naloxone, by virtue of its antagonistic action against opiates, rectifies this irregular cardiac rhythm.

How naloxone exerts its antiarrhythmic action via opiate antagonism in the heart is not known. Saxon et. al.[35] have shown that in rabbit papillary muscle, morphine or met-enkephalin induced a naloxone-reversible shortening of the cardiac action potential duration. This may lead to shortening of the effective refractory period of the cardiac cycle, and hence render the heart more susceptible to cardiac arrhythmias. On the other hand, in the guinea-pig papillary muscle, Brasch[36] has demonstrated that naloxone increased the cardiac action potential duration as well as the functional refractory period, thus rendering the heart less vulnerable to cardiac arrhythmias. He further demonstrated that the antiarrhythmic action of naloxone could be explained by an inhibition of the time-dependent membrane K^+ outward current.[36] He therefore classified naloxone as a Class III antiarrhythmic agent, according to Vaughan Williams.[37]

ANTIARRHYTHMIC POTENCY OF NALOXONE

For the assessment of the antiarrhythmic potency of naloxone, a cardiac antiarrhythmic screening test using the isolated ischemic rat heart was developed.[38] The isolated heart preparation was used because extracardiac (neural or hormonal) influences could be eliminated and the quantitative assessment of antiarrhythmic agents, analyzed in a much simplified system. With this test, the relative antiarrhythmic potency of propranolol, quinidine and lidocaine was found to be 1:0.51:0.35 from the ED_{50} values, respectively.[38] The relative antiarrhythmic potency of naloxone was subsequently determined to be 0.22.[39] These results suggest that the antiarrhythmic potency of naloxone is comparable to that of the three prototype antiarrhythmic drugs, an important consideration of naloxone in the prevention and treatment of disease related to cardiac arrhythmias.

CONCLUSION

Naloxone has been shown to have therapeutic utility in a variety of medical conditons. However at present it must be noted that most of the findings with naloxone in these pathophysiological states are based on animal studies, and there is a marked paucity of human clinical data. It has been reported that administration of beta-endorphin to patients with coronary artery disease caused angina pectoris.[40] Naloxone has been shown to improve survival from fibrillatory cardiac arrest in the dog.[41] In humans, naloxone has

been reported to reverse cardiac arrest when an electrocardiogram showed an extreme bradycardia, with abnormally enlarged ventricular complex (electrical-mechanical dissociation).[42] More human studies will be required to assess the validity of animal experiments performed using naloxone. The potential clinical role of naloxone as an antiarrhythmic agent remains to be elucidated.

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抗心律不整劑——納洛酮

李應紹

自從體內之內源性鴉片樣胜系統(ENDOGENOUS OPIOID SYSTEM)發現以來，納洛酮(NALOXONE)除了傳統上用於抗嗎啡引起之呼吸衰竭外，亦應用於其他疾病。現今納洛酮在治療休克、脊椎傷害、腦中風、呼吸衰竭、嗎啡過量及其他疾病方面，均有試用。近年來已有文獻報導，內源性鴉片樣胜導致心律不整。而其對抗劑納洛酮具有抗心律不整之作用，亦有相當證實。從電生理學研究中，發現納洛酮屬第三類抗心律不整劑。其抗心律不整功能，具有一般常用抗心律不整藥物(PROPRANOLOL、QUINIDINE、LIDOCAINE)之效果。臨床上亦有報告指出：鴉片樣胜導致心絞痛；而納洛酮能恢復心臟停止時之電力機械分離(ELECTRICAL-MECHANICAL DISSOCIATION)。至於納洛酮之抗心律不整在臨床上之治療價值，仍需進一步研究探討。