Evaluation of anti-arrhythmic potency of naltrexone in isolated ischaemic rat heart

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ABSTRACT The anti-arrhythmic properties of naltrexone were evaluated by an anti-arrhythmic screening test using the isolated ischaemic perfused rat heart preparation. The maximal anti-arrhythmic effect of naltrexone was attained 60 min after its administration and the potency based on cardiac anti-arrhythmic protection was 750 nmol/heart with 95% confidence limits of 674-836 nmol/heart. The time required to reach the maximal response and the anti-arrhythmic potency were much longer than that of naloxone, respectively.

KEY WORDS naltrexone; naloxone; isolated heart; myocardial ischaemia; anti-arrhythmic agents
There is substantial evidence suggesting that endogenous opioid peptides may be involved in cardiac arrhythmogenesis11. It is suggested therefore that opioid antagonists may or used as anti-arrhythmic agents. Naloxone, being the first pure opiate antagonist and most commonly used, was naturally the first one to be considered. Its anti-arrhythmic potency was determined with a screening test using the isolated ischaemic perfused rat heart preparation developed by us14. It was found to be comparable to those of the prototype anti-arrhythmic agents, namely, lidocaine, quinidine and propranolol15,16. However, naloxone is short-acting with a 1/2 in human of about 1 h17,18 and is easily degraded when administered orally. Naltrexone, another pure opiate antagonist with a much longer 1/2, 3.9-10.3 h, is more resistant to enzymes in the liver and is twice more potent than naloxone in stopping the development of heroin dependence in humans19,20. It is therefore of interest to determine the anti-arrhythmic potency of naltrexone and compare it with that of naloxone.

MATERIALS AND METHODS

The screening test using the Langendorff technique in the isolated rat heart preparation described previously by us10 was employed. Female Sprague-Dawley rats of 210-250 g were used. The rat was decapitaded and the heart mounted within 3 min. The heart was perfused with Krebs-Ringer solution at pH 7.4. The perfusion pressure and rate were about 15.3 kPa (110 mm Hg) and 6-8 ml/min respectively. The heart was kept at 31-32°C. Electrocardiograms were monitored throughout the experiment with a positive electrode hooked at the apex of the heart and a negative electrode at the aorta.

Immediately after mounting, perfusion was stopped for 10 min followed by reperfusion. Previous studies have shown that ventricular fibrillation (VF) usually occurred 2-15 min after reperfusion20. Naltrexone (DuP707) dissolved in Krebs-Ringer solution was injected via an aorta cannula within 1 min after VF had occurred. The volume and rate of injection were 20 μl and 1 min. respectively. In the control group 25 μl of Krebs-Ringer solution was injected. The doses of naltrexone were 525, 147, 3175 and 4762 nmol/hratet.

We have also employed the same method in evaluation of the anti-arrhythmic potency as described previously21. It was considered to have cardiac anti-arrhythmic protection (CAP) if VF was converted into sinus rhythm after drug administration. The time course of changes of CAP of the naltrexone at different doses were analysed and the times of maximal CAP determined. It was 60 min after medication (see Result). A regression line showing the relationship between maximal CAP and doses was also determined by the least square fit analysis with each dose on regression point representing data from 10 hearts.

RESULTS

![Figure 1: Time course of conversion of ventricular fibrillation to sinus rhythm after administration of naltrexone to the isolated heart, n=10 rat hearts for each dose,](image-url)
In this study, the anti-arrhythmic potency of naltrexone based on the CAP values was found to be comparable to that of naloxone of which the CAP was 818 nmol/heart with 95% confidence limits 616-985 nmol/heart(13). With receptor binding studies using rat brain membranes the affinity of naltrexone to μ and δ receptors were found to be much greater than that of naloxone whereas the affinity to κ sites of both opiate antagonists were similar(13). In the guinea pig ileum naltrexone is 3.5 - 5 times more potent than naloxone in antagonizing morphine, a μ-agonist, but they are equipotent in antagonizing ethylketazolam, a κ-agonist(11). The similar anti-arrhythmic potency of these two antagonists suggests that their anti-arrhythmic action may be due mainly to the occupation of κ receptors.

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纳曲酮对离体缺血大鼠心脏抗心律失常效能的评估

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摘要 用离体大鼠心室肌片，大鼠心脏预备纳曲酮对心室肌离体心脏左心室心电图在离体后30min内，出现电刺激阈值（CAP）值2.18 mmol/L，纳曲酮对心室肌最大电刺激作用时，

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