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Do B-Blockers Decrease Pain Sensation by Activating Opium Receptors?

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Abstract: Propranolol competitively blocks response to beta1- and beta 2-adrenergic Receptors which results in decreases in heart rate, myocardial contractility, blood pressure and myocardial oxygen demand. Nowadays it is used for Management of many cardiovascular disorders, pheochromocytoma, essential tremor, migraine headache prophylaxis. In this investigation an experimental trial study was conducted to evaluate the anti-nociceptive effect of propranolol on formalin induced chronic pain in rats. Thirty five male rats randomly divided into 7 groups and administered Normal Saline, Propranolol (20mg/kg b. wt.), morphine (1,2, 4mg /kg b. wt.), Propranolol along with Morphine, Propranolol pretreated with Naloxone (2mg/kg b. wt.) respectively. Formalin test was conducted to each animal 20 minutes after intra peritoneal injection and pain scores were recorded for 60 minutes.The results indicated that Propranolol decreased pain throughout the Formalin test which was significantly lesser than control group in 2nd phase of formalin induced pain (1.52±.060 vs. 1.93±.039, p<001). The anti-nociceptive effect of Propranolol was the same as all three doses of morphine sulfate and was reversed by Naloxone. Pretreatment with Propranolol before administration of morphine decreased pain sensation but it was not significant to Morphine (2mg/kg) group. It is concluded that Propranolol attenuates chronic pain induced in 2nd phase of formalin test. Seems this action has been reversed by Naloxone pretreatment is probably due to the activation of Opioid receptors by Propranolol.

Key words: Propranolol · Aspirin · Pain · Formalin test

INTRODUCTION

The physiologic effects of catecholamine are represented by activation of specific alpha and beta adrenergic receptors. There are three types of beta receptors; Beta-1, which are found in heart muscle. Activation of them results in increases in heart rate, contractility and atrioventricular (AV) conduction and a decline in AV node refractoriness. Beta-2, which is more prominent in bronchial and peripheral vascular smooth muscle. Activation of them results in vasodilatation and bronchodilatation.Beta-3, which are found in adipose tissue and the heart. Activation of them may mediate catecholamine-induced thermogenesis and may reduce cardiac contractility [1-3].

The beta blockers can be categorized into two broad categories; Those eliminated by hepatic metabolism and Those excreted unchanged by the kidney. Drugs in the first part such as Propranolol are lipid-soluble, almost absorbed by the small intestine and metabolized by the liver. They enter the central nervous system (CNS) in high concentrations, possibly resulting in an increased incidence of CNS side effects. They tend to have highly variable bioavailability and relatively short plasma half-lives. In contrast, drugs in the second category are more water soluble, incompletely absorbed through the gut, eliminated unchanged by the kidney and do not as readily enter the central nervous system [4, 5].

Several clinical studies in adults have found that chronic therapy with Propranolol reduces the frequency and severity of migraine in 60 to 80 percent of patients [6, 7].

Some studies with nonselective beta blockers in patients with severe peripheral vascular disease showed a variety of complications including worsening claudicating, cold extremities, pulselesness and, in some patients, cyanosis and impending gangrene [8]. It was supposed that both the reduction in cardiac output and blockade of beta-2-receptor-mediated skeletal muscle vasodilatation contribute to the vascular insufficiency [9].

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In this investigation an experimental trial study was conducted to evaluate the anti-nociceptive effect of Propranolol on formalin induced chronic pain in rats.

MATERIALS AND METHODS

Animals: Thirty five male Wistar rats weighing 150-220 g were used. The animal were housed in 7 groups per cage at room temperature (25±1°C) under a regular light/dark schedule (light 8:00 am_8:00 pm) and testing took place during the light phase. Food and water were given unlimited. Before formalin injections rats were placed in an open transplant Plexiglas chamber (30×20×20 cm) for 30 minutes to accommodate to the surrounding environment.

All protocols were approved by Animal lab of medicine, School of Shahid Sadoughi Medical University.

Animal Grouping
Rats Were Divided into 7 Groups:

- Control group (group 1)was administered normal saline(IP).
- Test group 2 was administered Propranolol (20mg/kg b.wt.) (IP).
- Test group 3 was administered morphine (1mg/kg b.wt.) (IP).
- Test group 4 administered by morphine (2mg/kg b.wt.) (IP).
- Test group 5 administered by morphine (4mg/kg b.wt.) (IP).
- Test group 6 administered by propranolol(20 mg/kg) along with morphine (2mg/kg b.wt.) (IP).
- Test group 7 administered by Test propranolol(20 mg/kg) pretreated with naloxone(2mg/kg b.wt.) (IP).

Formalin Test: Formalin test was carried out between 8:00 a.m to 5:00 pm as a standard pain rating model in rodents. 20 minutes after the IP injection of vehicle or drugs, a solution of formalin (50µl) at 2.5% concentration was injected subcutaneously into plantar surface of the left hind paw.

After the injection, the rat was immediately placed in a Plexiglas box (40×30×25 cm) with a mirror mounted underneath at 45° to facilitate observation of paws. One rat was observed at once.

The pain scores were collected by the observation of injected paw over a period of 60 minutes every 15 seconds as follow:

0 : The injected paw is completely on the ground;
1 : The injected paw has little or no weight placed on it; (not lifted but underweighted)
2 : The injected paw is raised; (lifted without shaking)
3 : The injected paw is licked, bitten or flicked.

Statistical Analysis: Mean pain scores for each animal were calculated in each 5 minutes and the Mean ± SEM of pain scores for different groups were statistically compared, using independent T-student test. In this study $P<0.05$ was considered as the level of significance.

RESULTS

According to our information, Propranolol decreased pain sensation in rats (pain scores in rats in all time blocks) and the scores were significantly lesser than saline group specially in second phase of formalin test (time block 5 to 12) significantly that can represent Propranolol decrease chronic pain.

Our results indicated that Propranolol decreased pain throughout the Formalin test which was significantly lesser than control group in 2nd phase of formalin induced pain (1.52±.060 vs. 1.93±.039, p<001).

Other results showed that Propranolol can be compared with morphine as an anti-inflammatory pain sensation, but the result expressed that it has not significant anti-nociceptive effects.

The anti-nociceptive effect of Propranolol was the same as all three doses of morphine sulfate (it means that may be Propranolol can play the same role of morphine in inflammatory pain).

For determining the mechanisms of propranolol in reducing pain sensation, we decided to administer Naloxone before administration of propranolol, our theory was naloxone can block (fill) morphine receptors. it means just like morphine that its antagonist for its receptor is naloxone, it can be the same for propranolol and with this plan we may be can clear the pathway that propranolol can affect morphine receptors just as morphine do.

Pretreatment with propranolol before administration of morphine decreased pain sensation but it was not significant to morphine (2mg/kg b.wt) group.

DISCUSSION

According to our data, propranolol attenuates chronic pain induced with formalin specially in 2nd phase of formalin test and because of the way that formalin test

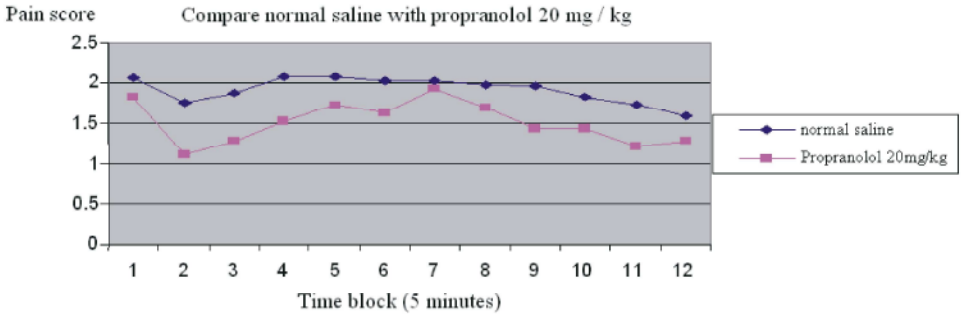

Fig. 1: Comparing normal saline with Propranolol

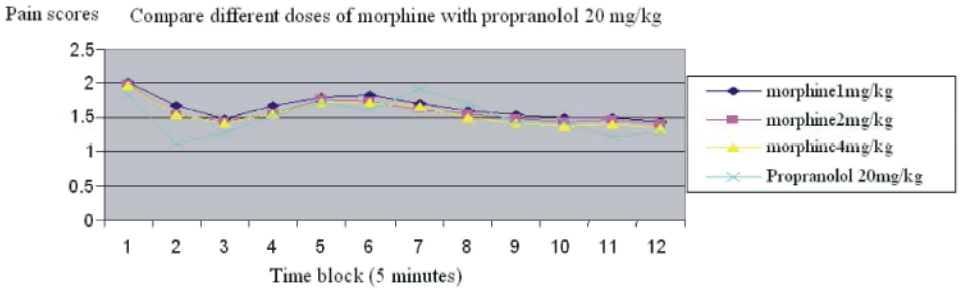

Fig. 2: Comparing different doses of morphine with propranolol

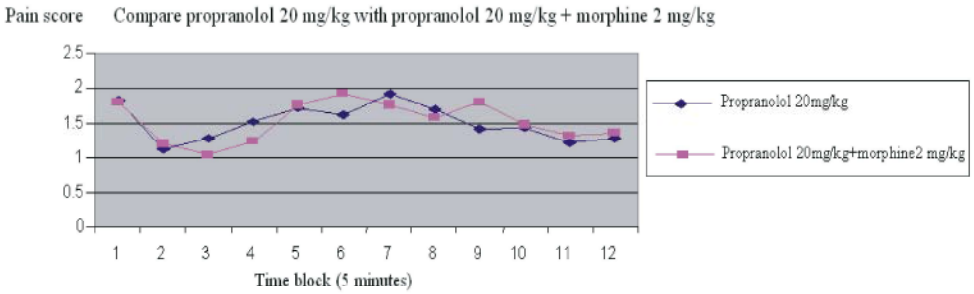

Fig. 3: Comparing propranolol with/ or without morphine

can represent inflammatory pain in both acute and chronic pain we can conclude that propranolol potentially can reduce pain, some researches can confirm this effect, for example researches that proved propranolol can be used as a prevention therapy in migraine headaches (seems this action has been reversed by naloxone pretreatment is probably due to the activation of opioid receptors by propranolol: Following transmission in the caudal brain stem and high cervical spinal cord information is relayed in a group of fibers (the quintothalamic tract) to the thalamus. Processing of vascular pain in the thalamus occurs in the ventroposteromedial thalamus, medial nucleus of the posterior complex and in the intralaminar thalamus (Zagami and Goadsby, 1991). Zagami and Lambert, 1991 has shown by application of capsaicin to the superior sagittal sinus that trigeminal projections with a high degree of nociceptive input are processed in neurons particularly in the ventroposteromedial thalamus and in its ventral periphery. These neurons may be a target for preventive treatments; certainly they are inhibited by β-adrenoceptor blockers, such as propranolol.

CONCLUSION

According to our data, Propranolol attenuates chronic pain induced in 2nd phase of formalin test. Seems this action has been reversed by Naloxone pretreatment is probably due to the activation of Opioid receptors by Propranolol.

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