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Short communication

Adrenergic Component of Nicotine Antinociception in Rats

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ABSTRACT: It has been widely established that nicotine, the active pharmacological agent in tobacco has antinociceptive effects, but the mechanism of this activity is yet to be fully investigated. The present study examined the effects of two adrenergic receptor antagonists, propranolol and prazosin, on nicotine antinociception using the hot plate (HP) paradigm in adult male Wistar rats (180-220gm). Three groups of rats received respectively, first, saline (10ml/kg) intraperitoneally (ip) plus intravenous (iv) nicotine (1ml/kg), second, propranolol (10-30mg/kg, ip) plus nicotine and the last group had prazosin (0.2- 1.0mg/kg, ip) followed by the same dose of nicotine. Nociception was measured at 15 mins intervals for one hour. While the administration of normal saline had no effect on the supraspinally mediated hot plate latencies, both propranolol and prazosin reduced the hot plate responses (significant at 15, 30, 45 and 60 mins, post injection). These findings suggest the involvement of the adrenergic system in nicotine induced antinociception.

Keywords: propranolol, prazosin, antinociception, hot plate

INTRODUCTION

Nicotine is a naturally occurring alkaloid from the leaves of tobacco plant. It is one of the pharmacologically active substances in tobacco smoke. It has been observed that activation of cholinergic pathways by nicotine elicit an antinociceptive effect in a variety of species (Aceto et al, 1986). Although nicotine effect may not extend to all types of pain and appears to be dependent on the route of administration, recent observations suggest that cigarette smoking and nicotine reduce pain in humans (Lane et al, 1995, Perkins et al, 1994, Rau et al, 1993). However, Matilla et al, (1968), reported that nicotine can reduce pain responses to thermal stimuli in the

mouse and rabbit after relatively low doses of nicotine and Davis et al, (1932) observed that nicotine as low as 1.1mg/kg can profoundly suppress reactions to visceral pain without altering sensitivity to somatic pain.

These findings, together with previous failures to obtain nicotine induced analgesia in other pain tests (Pert 1975) raise the possibility that nicotine may selectively alter sensitivity only to certain classes of pain stimuli. Since the mechanism through which nicotine produces antinociception has received relatively little attention, the objectives of this study are to determine whether this action is mediated via the central nervous system and to characterize antinociception using adrenergic antagonists.

MATERIALS AND METHODS

Animals

Adult male rats (180-220g) obtained from the pre-clinical animal house of the College of Medicine University of Ibadan were used throughout the study. The rats were housed in groups of six and had free access to food and water.

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Drugs

Nicotine was obtained from BDH chemicals Ltd (Poole , England) .Propranolol and prazosin were obtained from a local pharmaceutical outfit in Ibadan , Nigeria .

Hot plate test: The original method of Eddy and Leimbach (1953) as modified by Ibironke et al , (2004) was used . The hot plate temperature was maintained at $52 \pm 2.0^{\circ}\text{C}$ and a cut off time of 60 seconds was imposed to avoid significant tissue damage . Pain sensitivity was evaluated by the response latency for paw licking on the hot plate. The latency was measured twice at 15 minutes intervals and the average calculated. For the purpose of the study , the animals were divided into three groups and treated as follows

- Group 1 - ip normal saline (10ml/kg) + iv nicotine (1mg/kg) 15 minutes later
 Group 2 - ip propranolol (10- 30mg/kg) + iv nicotine (1mg/kg) 15 minutes later
 Group 3 - ip prazosin (0.2- 1mg/kg) + iv nicotine (1mg/kg) 15 minutes later

About thirty minutes after the administration of nicotine , the animals were placed on the hot plate and latencies measured at 15 minutes intervals for the next one hour .

Statistical Analysis

Values are expressed as means \pm SEM. Statistical significance was determined using the student's *t*-test. Values with $p < 0.05$ were considered significant.

RESULTS

The results of pre - treatment with saline and adrenergic receptor blockers on nicotine antinociception are as shown in figs 1 , 2 , and 3.

Effects of pre - treatment with saline on nicotine antinociception: Fig. 1 shows that normal saline administered before nicotine had no effect on its antinociceptive activity as the two curves [nicotine alone and nicotine + saline] were almost superimposed on each other.

Effects of propranolol on nicotine antinociception: The graph showed that graded doses of propranolol produced a graded inhibition of hot plate latencies. Significant inhibitions were obtained at 15,30, 45,and60 minutes post injection with a maximum at 30 minutes. (Fig 2)

Effects of prazosin on nicotine antinociception: A dose dependent inhibition of nicotine antinociception was obtained. These inhibitions which were also significant at 15 , 30 , 45 and 60 minutes also peaked at 30 minutes post injection (Fig. 3)

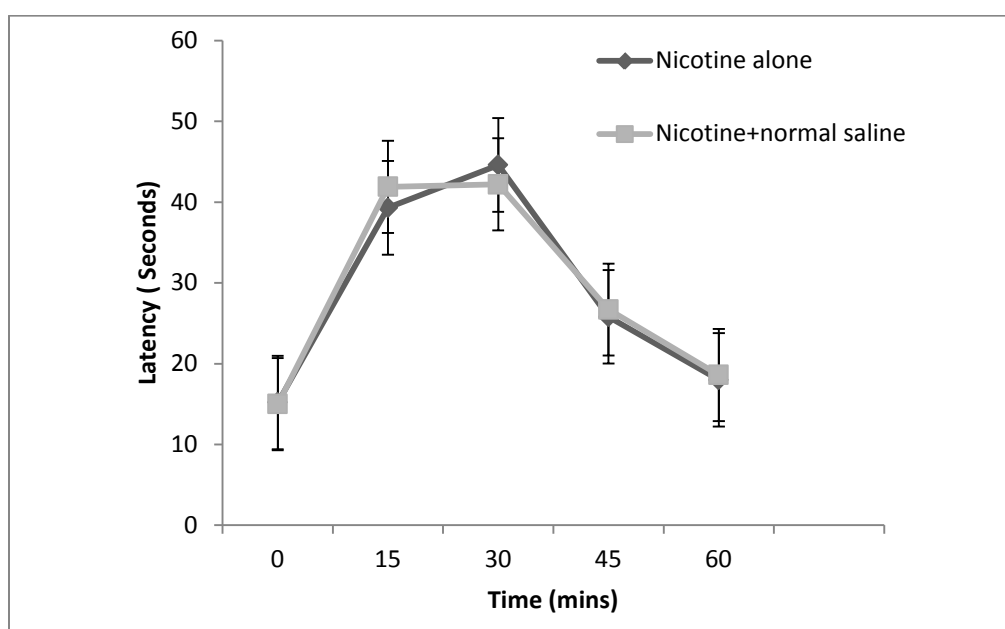


Fig. 1 Antinociceptive effects of nicotine with or without normal saline. Each point represents Mean+SEM of 6 animals in each group.

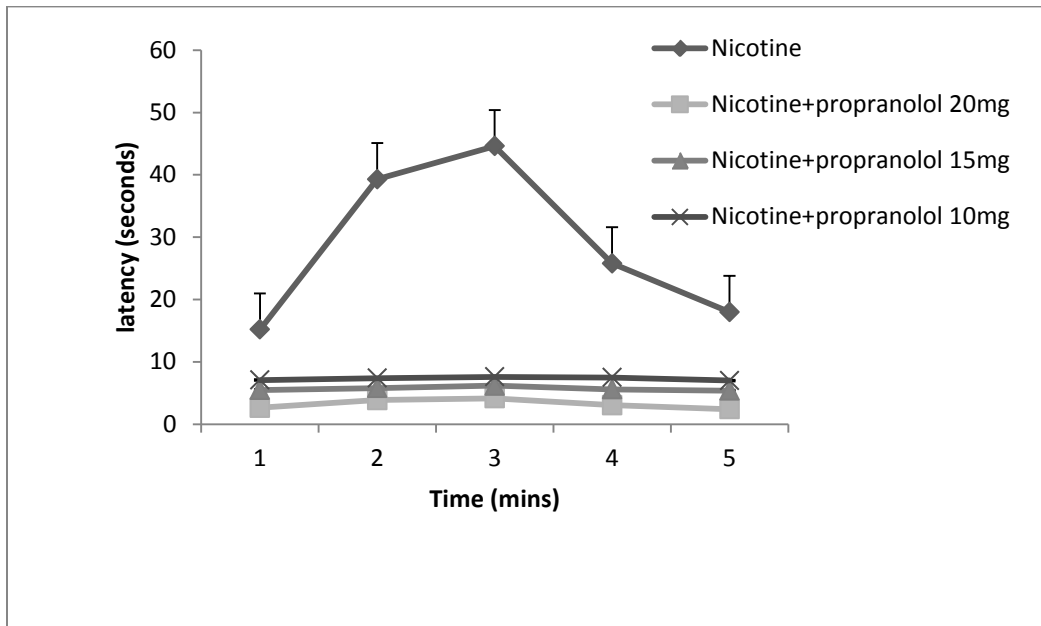


Fig. 2
Effect of graded doses of propranolol on nicotine antinociception Each point represents Mean+SEM of 6 animals in each group

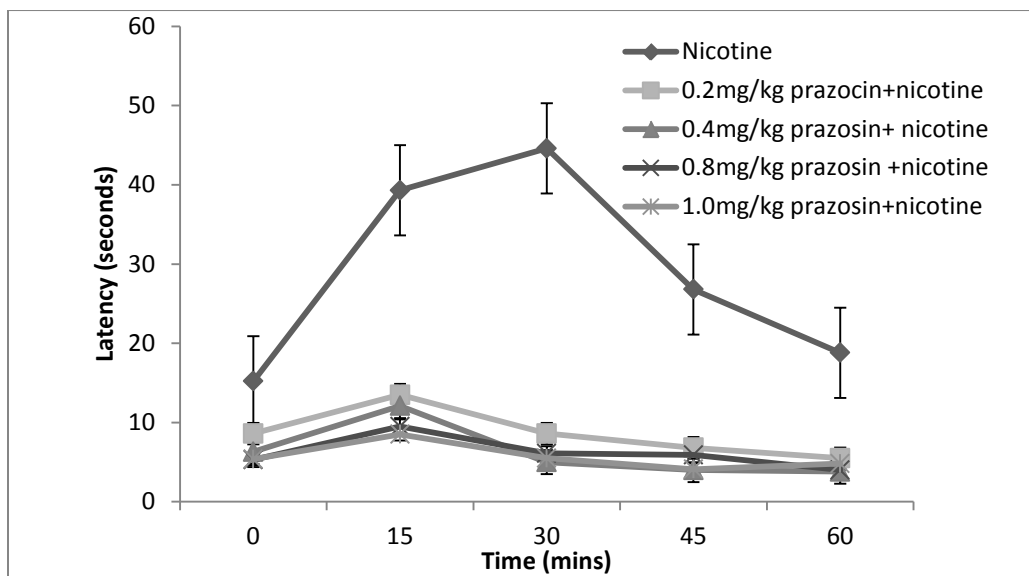


Fig. 3
Effects of graded doses of prazosin on nicotine antinociception. Each point represents Mean+SEM of 6 animals in each group.

DISCUSSION

Consistent with previous reports [Martin et al, 1983, Tripathy et al 1982], systemic nicotine administration exerted a potent antinociceptive action on thermal sensitivity as measured by hot plate test. The objective of this study was to characterise nicotine antinociception with adrenergic antagonist. Both propranolol and prazosin

antagonized the antinociceptive effect of nicotine in a dose related manner.

Several studies have reported the notion that nicotine blocks painful stimuli at the central level (Mansner 1972, Phan et al.1973, Shaley and Bernston 1979) and in addition suggested a positive correlation between brain levels of nicotine and antinociception. This report tallies with our own observation in that we have also established a central action of nicotine though we have not

measured brain nicotine levels due to lack of facilities. Our assertion of the central activity of nicotine is based on the fact that it is well established in pain research that agents that cause a prolongation of the hot plate latency must be acting centrally, since the hot plate test is supraspinally mediated, therefore the prolongation of the HP latency in this study is a confirmation of the central action of nicotine.

The time – course of nicotine antinociception in rats studied between zero and 60 minutes revealed that nicotine had a slow onset of action as the activity which was not noticed until about 15 minutes post injection peaked at 30 minutes and thereafter tailed to near basal level in about 60 minutes.

These results are consistent with those reported by Sahley and Bernston (1979) who also found a slower onset and a longer duration of action, but contradicted the report of Phan et al [1973] who observed little antinociceptive action of nicotine even 30 minutes after an i.p administration of nicotine. The difference might be due to the route of administration as the action of nicotine is known to be route dependent. The intravenous route employed in this study is expected to produce a faster results compared with the i.p. route employed by Phan et al (1973).

The results of the receptor blocking studies in the recent work shed light on the receptors basis of the antinociceptive properties of nicotine. The antinociceptive effect of nicotine was dose dependently inhibited by pre-treatment with propranolol and prazosin, indicating that the antinociceptive effects of nicotine is mediated at least in part through its action on the adrenergic receptors.

Prazosin was found to be more effective than propranolol as the longest latency recorded for its action was 12.5 seconds while that of propranolol was just about 8.6 seconds which means that prazosin caused a more prolongation of the hot plate latency compared with propranolol which translates to more antinociceptive activity.

The reason[s] for this difference cannot be accounted for as at now but it might not be unconnected with a higher density of the alpha adrenergic receptors in the systemic circulation.

Alternative explanation(s) for these results are possible. However, the resolution of this problems will require further experimentation.

In summary the present study established the antinociceptive activity of nicotine and that it is

medicated at least in part via the adrenergic pathway.

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