World Journal of Medical Sciences 1 (2): 119-123, 2006
ISSN 1817-3055

Nicotine Antinociception: Possible Role for Ca^{2+}

[1]G.F. Ibironke, [2]A.S. Oyadeyi and [1]K.I. Ajiboye

[1]Dept of Physiology, College of Medicine, University of Ibadan, Nigeria
[2]Department of Physiology, Ladoke Akintola,
University of Technology, P.M.B. 4000, Ogbomoso, Nigeria

Abstract: The present study was designed to determine the degree of participation of calcium ions in the antinociception produced by systemic nicotine. Adult male Wistar rats (180-220 g) pretreated with saline (10 mL kg^{-1}) or calcium channel blockers, verapamil or nifedipine (0.05-0.20 mg kg^{-1} each) were injected with nicotine (1 mg kg^{-1}) 15 min later. The animals were subjected to the hot plate test after another 30 min. Hot plate latencies (HPL) were measured before (base line) and at 15, 30, 45 and 60 min after nicotine injection. Nicotine produced antinociception for 15 to 45 min peaking 30 min after injection. Intraperitoneal (i.p) administration of graded doses of nifedipine and verpamil each antagonized in part, the antinociception produced by nicotine. Systemic administration of the vehicle (10 mL kg^{-1}) did not alter nicotine-induced antinociception. The data suggest that the antinociceptive responses produced by nicotine are mediated at least in part via the calcium ions.

Key words: Antinociception · calcium · verapamil · nifedipine · nicotine

INTRODUCTION

The management and treatment of pain is probably one of the most common and yet most difficult aspects of medical practice. Analgesic therapy is currently dominated by two major classes of analgesic drugs, namely opioids and the non-steroidal anti-inflammatory drugs (NSAIDs). Many improved synthetic variants, as well as techniques of administration have been developed but there is considerable opportunity for conceptual innovation. Both classes of analgesic drugs produce side effects, such as gastrointestinal disturbances and renal damage (with NSAIDs), respiratory depression and possibly dependence (with opioids). It is obvious that new models designed as analgesic agents are needed, hence research into nicotine antinociception

Nicotine is one of the active components in tobacco smoke and it appears to play a major role in tobacco addiction [1]. This compound affects different aspects of behaviour such as locomotion, nociception, anxiety, learning and memory and it produces several behavioural responses related to its addictive properties such as rewarding effects and physical dependence [2].

The pharmacological effects of nicotine are mediated by the activation of nicotine acetylcholine receptors (nAchR'S) which are located mainly at the presynaptic level and their activation produces antinociception mainly through the release of dopamine [3], noradrenaline [4], acetylcholine [5], glutamate [6] and GABA [7]. Although nicotine antinociception may not extend to all types of pain and it appears to be dependent on the mode of administration, recent observations suggest that cigarette smoking and nicotine reduce pain in humans indlicating a true analgesic component [8-11].

However the data in human clinical literature on the relationship between nicotine and pain are inconclusive at best. Nicotine antinociception has been shown to involve several systems and receptors, for example the cholinergic system [12-14] and the endogenous opioid system [15]. In view of the recent observations in our laboratory on the diverse pharmacological and physiological activities of nicotine, this study was designed to probe further into the receptor basis of nicotine antinociception using the calcium channel blockers, nifedipine and verapamil.

MATERIALS AND METHODS

Animals: Adult male albino Wistar rats (180-250 g) obtained from the central animal house, College of Medicine Univeristy of Ibadan were used throughout the study. The animals were housed in groups of six where they had free access to food and water.

Corresponding Author: Dr. G.F. Ibironke, Department of Physiology, College of Medicine, University of Ibadan, Ibadan, Nigeria

Drugs: Nicotine was obtained from DBH chemicals Ltd. (Poole, England). Nifedipine and verapamil were purchased from a local pharmaceutical outfit in the city of Ibadan, Nigeria.

Hot plate test: The original method of Eddy and Leimbach [16] as modified by Ibironke *et al*. [17] was employed. The hot plate temperature was maintained at 52 ± 2.0°C and a cut off time of 60 sec was imposed to avoid significant tissue damage. Pain sensitivity was evaluated by the response latency for paw licking on the hot plate.

For the purpose of the experiment, the animals were divided into 3 groups of 8 rats each and treated as follows.

Group I: Normal saline (i.p, 10 mL kg^{-1}) + Nicotine (i.v, 1 mg lkg^{-1}) 15min later.
Group II: Nifedipine (i.p, 0.05-0.20 mg kg^{-1}) + Nicotine (i.v, 1 mg kg^{-1}) 15 min later.
Group III: Verapamil (i.p, 0.05-0.20 mg kg^{-1}) + Nicotine (i.v, 1 mg kg^{-1}) 15 min later.

About 30 min after the administration of nicotine, the animals were placed on the hot plate and latencies were measured at 15 min intervals for the next one hour.

Statistical analysis: Values were expressed, as means ± S.E.M. Statistical significance was determined using the students' t-test. Values with $p<0.05$ were considered significant.

RESULTS

Effect of saline pre-treatment on nicotine antinociception: Figure 1 shows that normal saline administered 15 min before nicotine had no significant effect on nicotine antinociceptive activity as the two curves, nicotine alone and nicotine with saline were almost superimposed on each other.

Effect of nifedipine pre-treatment on nicotine antinociception: It was observed that graded doses of nifedipine produced a dose-dependent inhibition of nicotine antinociception (Fig. 2).

Effect of verapamil pre-treatment on nicotine antinociception: The results were similar to that of nifedipine as verapamil, also dose dependently inhibited antinociceptive acitivity of nicotine (Fig. 3).

DISCUSSION

The results presented herein support previous findings from our laboratory (unpublished observations) that nicotine has potent antinociceptive properties. A similar profile has been reported by other investigators using other nicotine agents [18-20]. The mechanism of nicotine antinociception has been a subject of investigation by various authors. For example, mecamylamine a tertiary nicotinic blocker known to block the central and peripheral effects of nicotine antagonized the antinociceptive effect completely [21] indicating the involvement of nicotinic receptors. Phan *et al*. [14] found

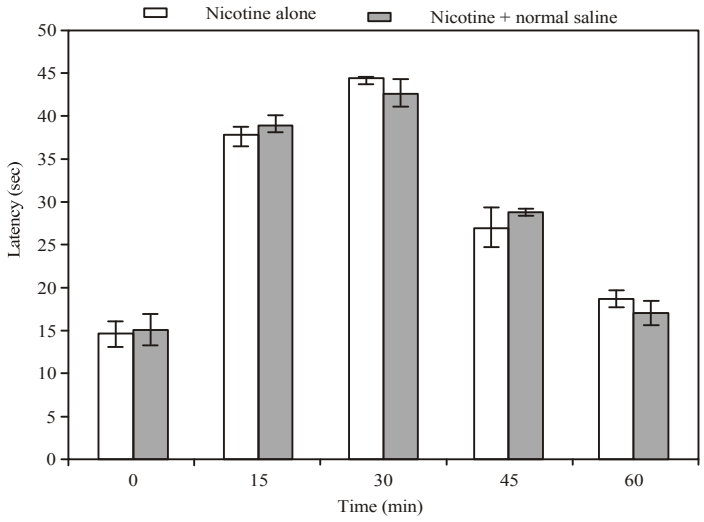

Fig. 1: Antinociceptive effects of nicotine with or without normal saline. Each data point represents the mean ± S.E.M of nine rats

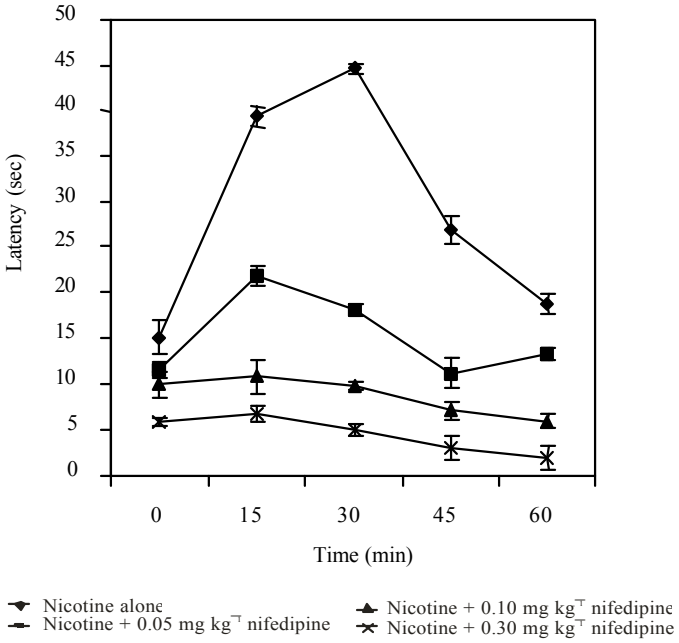

Fig. 2: Effects of graded doses of nifedipine on nicotine antinociception. Each point represents the mean ± the S.E.M of ten rats

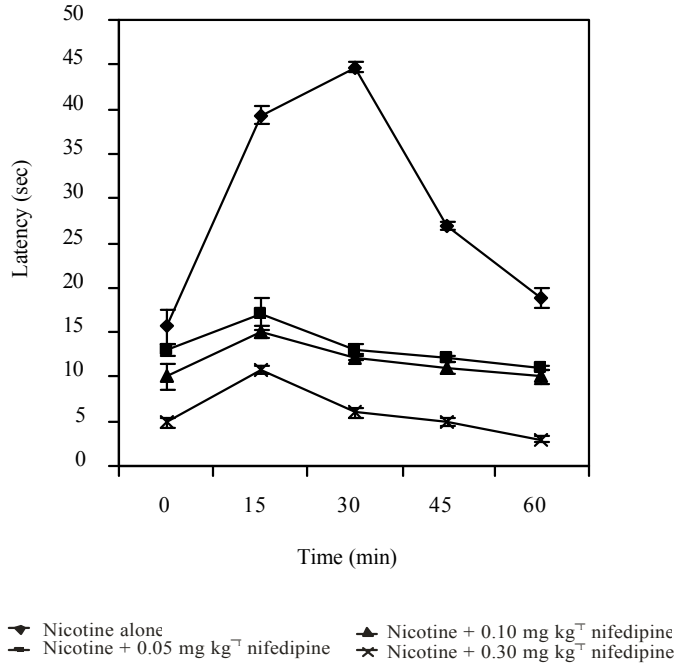

Fig. 3: Effects of graded doses of verapamil on nicotine antinociception. Each point represents the mean ± the S.E.M of seven rats

out that atropine did not interfere with antinociceptive activity of nicotine thus ruling out the involvement of muscarinic receptors.

Also nicotine, apparently does not interfere with opiate receptors in rats because naloxone failed to block its antinociceptive effect in the tail flick test [22]. While nicotine antinociception has been attributed to its facilitation of glycine release [23]. Glycine is a major inhibitory neurotransmitter in the spinal cord. Nicotine exerts its antinociceptive effects by interacting with nicotine acetylcholine receptors (nAchR's) which are present throughout neuronal pathways involved in neural processing of pain [24-26].

In the present study we observed that the calcium channel blockers, verapamil and nifedipine inhibited nicotine antinociception dose dependently strongly implying the involvement of Ca^{2+}. What then is the mode of action of calcium (Ca^{2+}) ions? Rathouz *et al*. [27] observed that neuronal nAchR's particularly those containing the α-7 sub units display a high permeability to calcium and sodium ions. The resulting calcium influx may cause a facilitation of neurotransmitter release. Activation of presynaptic nAchR's depolarizes the nerve terminals and activates the voltage dependent Ca^{2+} channels to facilitate the release of glycine [28]. Therefore Ca^{2+} influx has been found to contribute to the nicotine-induced facilitation of glycine release, which has been implicated in nicotine antinociception. Therefore, our use of calcium channels blockers in this study prevented Ca^{2+} influx which is critical to the release of glycine by exocytosis.

Since glycine release is essential in nicotine antinociception, it therefore follows theoretically that nicotine antinociception, would be seriously affected by its absence and this partly explains our observation in this study i.e., inhibition of nicotine antinociception by calcium channel blockers. As stated earlier on we came across very few reports that have demonstrated the role of calcium ions in nicotine antinocieption using other calcium channel blockers. This therefore makes it impossible to compare our work with similar studies on a wider basis. This study therefore serves as a reference point for other investigators in this area.

In summary we demonstrated the antinociceptive activity of nicotine and contributed to the literature on the mechanism of its antinociception by establishing the involvement of calcium ions.

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