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ACUTE NICOTINE INDUCED PRESSOR RESPONSE IS IN PART DUE TO INTERACTION WITH BARO REFLEX PATHWAY

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ABSTRACT
Arterial baro-reception is regarded as one of the most powerful rapidly acting homeostatic mechanism regulating blood pressure. Investigation had suggested that nicotine may interact with aortic baro-receptors to produce its sustained presser response, an effect that had received little attention. Anaesthetized Wister albino rats were used. Bilateral carotid occlusion (BCO) method was used to introduce a predominantly sympathetically mediated cardiovascular reflex. Baroreceptor sensitivity (BS) test was assessed as gain in baroreflex function. Others BCO led to increases in mean arterial pressure (MAP) in normal rats (Δ Map 27 + 3.6mm HG) and increases in MAP induced by BCO was less after nicotine pretreatment (P<0.001). BCO also led to significant increases in heart rate in both normal and in nicotine treated rats but the increases shows no significant differences. Acute nicotine pretreatment reduced BS evoked by presser stimulus (phenylephrine) from 0.789, 0.039 and 0.004 beats per min mm HG-1 (P<0.001). The significant decreases in BCO reduced presser response by nicotine may be an indication of strong pre-existing sympathetic activation. Reduction of BS by nicotine may be an indication that nicotine do interact with beroreflex pathway either peripherally at the receptors or centrally to reset the system. Thus nicotine action on baro-reflex system could contribute to the sustained presser response it produced.

Key words: Baroreceptors, Means Arterial Pressure (MAP), Baroreflex, Baro - reception

INTRODUCTION

Although, nicotine was found to decrease the risk of pre-eclampsia in pregnant women by reduction of production of cytokines by the placenta (Oonagh Dowling *et al.,* 2010). Acute nicotine administration whether by smoking or intravenous injection is generally accepted to increase blood pressure and heart rate in most animals and in human subjects (Squire *et al.,* 1984; Aceto *et al.,* 1981; Benowich *et al.,* 1986; Gropelli *et al.,* 1990). The effects are also associated with pregnant women, thus; smoking during pregnancy was found to cause adverse effects including: spontaneous abortion (George *et al.,* 2006), placenta previa (Chelmow *et al.,* 1996), placental abruption (Ananth *et al.,* 1999), preterm birth (Fantuzzi et al., 2007), stillbirth (Hogberg and Cnattingius, 2007), fetal growth restriction (Hammoud *et al.,* 2005; Nordentoft *et al.,* 1996), low birthweight (Jaddoe *et al.,* 2008), and sudden infant death syndrome (SIDS) (Mitchell and Milerad, 2006). Stoppage of was found to reduce the damage to the developing fetus (Pickett *et al.,* 2003). Smoking cessation therapy was found to reduce the incidence of low birth weight and preterm birth (Lumley *et al.,* 2004).

Cigarette smoking in animal models exposed to nicotine during gestation and lactation leads to defective; metabolic (Bruin *et al.,* 2008), reproductive (Anzar *et al.,* 2006; Lagunov *et al.,* 2009), cardiovascular (Gao *et al.,* 2005, 2008), pulmonary (Petre *et al.,* 2008) outcomes in the offspring.

These effects of cardiovascular associated symptoms are primarily mediated through the activation of sympathetic nervous system (Cryer *et al.,* 1976; Mancia, 1990; Winnifford *et al.,* 1990), leading to increases in sympathetic tone with resultant increases in blood pressure, heart rate and coronary vasoconstriction similar to various cardiovascular reflex like cold presser test, isometric and dynamic exercise Mudge *et al.,* 1976; Brown *et al.,* 1984; Berkenboom *et al.,* 1986). The extent of the haemodynamic changes that induced those cardiovascular reflexes depend mainly on the integrity of the baroreceptor reflex system. Arterial baroreflex system is regarded as one of the most powerfully rapidly acting homeostatic mechanism for regulating blood pressure (Abdul-Rahman *et al.,* 1987).

Mendel *et al.* (1973) had shown that, nicotine, in conscious dogs induces bradycardia after the initial tachycardia and suggested that it is probably due to baroreceptor stimulation. It had also been reported that since the heart rate increases due to nicotine become normal in the presence of persistent increases in blood pressure, this may suggest some baroreceptor accommodation (Mendel *et al.,* 1973). Robert *et al.* (1988) suggested that nicotine may interact with aortic baroreceptor system in producing its sustained presser response, an effect which had received very little attention. Hence the effect of acute nicotine on baroreflex sensitivity and on bilateral carotid occlusion test was investigated.

MATERIALS AND METHODS

The experiments were performed on Wister albino rats, weighing from 150-200g (Animal Centre, College of Medicine Lagos). The animals were anaesthetized with a mixture of alpha chloralose (1% W/V) and urethane (25% W/V) at a dose level of 5ml/kg, injected intraperitioneally. Femoral artery and vein were isolated and cannulated with Luer polyethylene cannula filled with 150mmol/kg NaCI solution. Heparin (Upjhon U.S.A.) 100 l.U/l00g I/V was injected. The arterial cannula was used for recording arterial blood pressure and heart rate, while the venous cannula was used for injecting drugs and saline. The carotid arteries were isolated for bilateral carotid occlusion tests. Body temperature was maintained at 36-38 ^{o}C using overhead tamp when necessary. The rats were fasted 24 hours prior any experimentation. The drugs used were Nicotine (Waco pure chem. Japan) and phenylephrine (Sigma chem. Co) all dissolved in 150 mmol/L saline.

MEASUREMENT AND SPECIAL PROCEDURES

The arterial blood pressure was continuously recorded from cannulated artery, with a pressure transducer (P23 D Hato Rey Inc) placed at heart level. Heart rate was obtained from blood pressure recording and confirmed with a tachometer. The measurements were recorded on Grass polygraph model 7D (Grass Instrument Ltd. Quincy Mass U.S.A.).

Baroreceptor sensitivity was assessed as the gain in baroreflex function using methods previously described by others (Korner *et al.,* 1972 and Rothbaum *et al.,* 1974). Graded increase in arterial blood pressure was induced by injecting serial bolus doses of Phenylephrine. The peak changes in MAP (ΔMAP) together with reflex changes in heart rate (Δ HR) were used to calculate baroreceptor reflex sensitivity (BS). This was done by plotting a curve of changes in heart rate (Y-axis) against MAP changes (X-axis). The BS was expressed in beats min/mmHg-1, was obtained from the slope of the curve (Goldstein, 1983).

Bilateral carotid occlusion (BCO) method was used to introduce a predominantly sympathetic mediated cardiovascular reflex (Ledsome and Linden 1964; Adigun *et al.,* 1984 and 1991). The occlusion clips were applied below the carotid sinus for 30 seconds.

Experimental Protocol

1. The effect of graded intravenous infection of nicotine (50-800 µg/kg) on blood pressure and heart rate was done. Maximal changes was seen at 500 ug/kg dosage, thus the dose level used for subsequent experiments.
2. BCO: Normal rats were exposed to BCO 3 time at 20 minutes intervals, after which they were given nicotine (500 µg/kg I/V) then followed by 3 exposure to BCO at 20 minutes interval. Each exposure lasted 30 seconds. (n=8).
3. BS: Barorefiex sensitivity was tested using a vasopressor stimulus (phenylephrine 0.5 -5 µg/kg) as previously described above. The test was carried out in normal rats and in nicotine treated rats (500 µg/kg). (n=8).

Statistical Analysis

Mean arterial pressure (MAP) was calculated as MAP = diastolic pressure +1/3 pulse pressure mmHg. The results are presented as mean SEM. Paired and unpaired student T test was used to assess statistical significance (P<0.001).

RESULTS

Intravenous injection or nicotine, 500-800 µg/kg led to transient bradycardia and hypotension followed by sustained pressor and tachycardiac response (P<0.001). Maximal changes in pressor and tachycardia response was seen at 500 µg/kg dose level (Δ MAX MAP 52.5 ± 1 .2mmHg, (Δ MAX HR 71.67 ± 12.2 beats/min).

BCO led to increases in MAP in both normal rats (Δ MAX 27.8 ± 2.1 mmHg, P<0.001) and in nicotine treated rats (Δ MAX 14.6 ± 1.8mmHg, p<0.001. The increases in MAP was smaller after nicotine treatment (p<0.00l). BCO also led to significant increases in heart rate in both normal and in nicotine treated rats, but the increases shows no significant differences (Table 1). Acute nicotine administration also reduced baroreflex sensitivity evoke with a pressure stimulus from 0.789 + 0.039 to 0.332 + 0.04 beats min-1 mmHg-1 (p<0.001), (Table 2).

Table 1: Maximal Changes MAP and HR Induced by Bilateral Carotid Occlusion before and after Nicotine Treatment (MEAN ± SEM) n=s.

	Δ MAP mmhg	Δ HR beats min^{-1}
Before Nicotine	27.8 ± 2.1	26.6 ± 23
After Nicotine	14.6 ± 1.8 ^{S}	303 ± 3.2 ^{S}

Table 2: Baroreflex Sensitivity (BS) in Normal Rats and in Nicotine Treated Rats (MEAN + SEM).

	BS = Heart rate beats min-1 mmHg $^{-1}$ Mean (MAP)
Normal rats	0.789 ± 0.039
Nicotine treated rats	0.322 ± 0.04 ^{S}

Key: Not Significant = NS, Significant = S (P<0.001).

DISCUSSION

Cigarette smoking an as endemic hobby that traverses across the world population is associated with various diseases ranging from cardiovascular and respiratory, to the ones affecting pregnant mothers and their children in stillbirth (Hogberg and Cnattingius, 2007), fetal growth restriction (Hammoud *et al.,* 2005; Nordentoft *et al.,* 1996), low birthweight (Jaddoe *et al.,* 2008), and sudden infant death syndrome (SIDS) (Mitchell and Milerad, 2006). This resulted in governments intervention in the field of laws curtailing smoking and research.

Some researchers found that BCO to produce a predominantly sympathetic mediated reflex. A reduction of BCO-induced pressure response, will hence implied a decrease in sympathetic activation (Adigun *et al.,* 1984 and 1991). Thus, it was found that the paradoxical decreases in pressure response due to BCO by nicotine pretreatment may be due a strong preexisting sympathetic activation since both nicotine and BCO-induced presser responses is predominantly mediated by activation of the system. The dose level of nicotine used in treating the rats prior to BCO is the level that produces maximal presser response, thus indicating maximal nicotinic activation of the sympathetic system. This is in agreement with prior report showing of nicotine-induced homodynamic changes and some cardiovascular tests that increases sympathetic changes and some cardiovascular tests that increases sympathetic tone, occur at low nicotine dosage level only (Perkin *et al.,* 1990).

A decline in baroreflex function is due to two major possibilities. First, pathological arterial changes that reduce the distensibility of the vessel wall with miss match increases in compensatory receptor sensitivity (Sapru and Wang, 1976; Anderson *et al.,* 1980; Anderson and Brown, 1980). Secondly, the functional derangement in autonomic nervous tone (Volpe *et al.,* 1982). The acute nature of this experiment makes the reduction of baroreflex sensitivity entirely accountable for by increased sympathetic activity (beta adrenergic increase in heart rate) and or reduced parasympathetic tone (Pickering *et al.,* 1972; Julius and Elser, 1975; Takeshita *et al.,* 1978; Wallace, 1975; Johnson, 1980; Goldstein, 1983; Adigun *et al.,* 1984 and 1991).

The reduction of BS by nicotine is in concurrence with it's known activation of sympathetic nervous system (Cryer *et al.,* 1976; Mancia, 1990 and Winnifford *et al.,* 1990). It is also an indication that nicotine do interact with baroreflex pathway to inhibit baroreflex response either 1. Centrally: to increase sympathetic activity, similar to stimulation of hypothalamic or rage centre in laboratory animals (Hilton, 1965) and events occurring in man stress (Brod *et al.,* 1959), exercise (Pickering *et al.,* 1972) and heart failure (Julius *et al.,* 1971) and or 2. peripherally, by interacting with the receptors to reduces afferent information to the centre, as has been observed in afferent traffic oblation experiment in animals (Doba and Reis, 1973; Nathan and Reis, 1977). Thus acute nicotine-induced in baroreflex sensitivity, indicating reduced baroreflex buffering of arterial blood pressure might lend an important contribution to the sustained blood pressure response it produces.

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