Effects of nicotine on the cardiovascular control of the central nervous system have been studied for many years by numerous investigators (1). Intraventricular or intracisternal administration of nicotine produced an increase or a decrease in blood pressure and heart rate in many animal species including the cat (2-6), dog (7), rat (8,9), and goat (10). Further, some investigators have studied cardiovascular responses to nicotine applied at discrete regions of the brain, including the posterior hypothalamus (11), ventral surface of the medulla oblongata (12-14), and lateral medullary reticular pressor areas (11) of the cat, and the nucleus ambiguous of the dog (15). These central actions of nicotine were abolished by hexamethonium or mecamylamine (4,7-12,15), suggesting the involvement of a central nicotinic cholinergic mechanism in the actions. Recently, nicotinic acetylcholine receptors have been detected on rodent (16-19) and human (20) brain membranes. However, exact central nicotinic mechanisms responsible for cardiovascular responses are not yet fully understood. The purpose of the present study was to localize nicotine-sensitive sites responsible for cardiovascular effects in the dorsal medulla oblongata of the rat. Central or peripheral mechanisms relating to the action of nicotine were also examined. Further, the medullary nicotine action was evaluated also in experimentally hypertensive rats.

METHODS

Male Wistar rats, weighing 250-320 g, were used. In some experiments, 5- or 15-18-week-old spontaneously hypertensive rats (SHR), age-matched Wistar-Kyoto rats (WKY), and DOC-salt hypertensive rats were used. The rats were anesthetized with urethane (1.2 g/kg, i.p.), and the femoral artery and vein were cannulated for continuous recordings of blood pressure and intravenous injections, respectively. Heart rate was computed by a cardiotachometer.

The rats were placed in a stereotaxic apparatus with the head fixed at 45°. The dorsal surface of the lower brainstem was exposed as described previously (21). Application of nicotine on the dorsal surface was made through a polyethylene tube (outer diameter, 1.3 mm) placed on the surface. Microinjections of drugs were made using a glass cannula (outer
diameter, 0.1 mm) connected to a Hamilton microsyringe and a micrometer. The location of the needle tracks was controlled microscopically.

Electrolytic lesions of the nucleus tractus solitarius were produced bilaterally by passing an anodal DC current of 5 mA for 1-2 sec through monopolar Teflon-coated stainless steel electrodes (outer diameter, 0.15 mm) with a tip exposure of 0.2 mm. In some experiments, the carotid sinus and aortic baroreceptors were denervated bilaterally according to the method described by Krieger (22).

Data are reported as mean ± S.E. and statistical significance was evaluated by Student's t-test.

RESULTS AND DISCUSSION

The Dorsal Surface Areas of the Medulla Oblongata

Following intracisternal injections of nicotine, a biphasic effect consisting of an initial rise in blood pressure followed by a delayed fall was observed in urethane-anesthetized rats (9). To examine possible areas responsible for blood pressure response to nicotine on the dorsal surface of the medulla oblongata, nicotine (3 μg) was applied using a polyethylene tube placed on the surface. When the tube was placed around the area postrema (positions 1, 2, and 4 shown in Fig. 1), nicotine produced a biphasic blood pressure response. The greatest changes in blood pressure were observed when the center of the tube was at the caudal tip of the area postrema (position 1).

To more precisely localize the nicotine-sensitive sites, nicotine (0.1 μg) was microinjected into several sites 0.2 mm below the dorsal surface. Nicotine usually produced hypertension followed by hypotension (Fig. 2) and bradycardia. Figure 3 shows the nicotine injection sites and the blood pressure responses. The highest sensitivity was observed following injections into sites just caudal to the area postrema. These findings are compatible with the study of Brezenoff and Jenden (23) who found only an insignificant fall in blood pressure following injections of nicotine into the floor of the 4th ventricle which lies more rostral to the nicotine-sensitive sites. Hexamethonium (2 μg), injected at the

![Fig. 1. Diagram of the dorsal surface of the medulla oblongata of the rat. The interrupted circles indicate the areas covered by the polyethylene tube when placed across the medulla in six positions. When applied to the striped area (position 1), the cardiovascular effect of nicotine (3 μg) was maximal. AP, area postrema; IV, fourth ventricle.](image-url)