Comparison of the cardiostimulatory effects of nicotine in dogs and monkeys

Dogs are 5–10 times more sensitive than rhesus monkeys to the effects of nicotine on metabolic and physiological responses, such as hyperglycaemia, hyperlipidaemia, increases in respiratory rate, heart rate and pressor responses (Hug & Bass, 1970; Hug & Carlson, personal communication; Tsujimoto, Nishikawa & others, 1974). Nicotine also causes greater release of catecholamine from the adrenal glands *in vivo* in dogs than in monkeys (Tsujimoto & others, 1974). It is well known that nicotine releases endogenous catecholamines from stores in the heart tissue (Burn & Rand, 1958; Bhagat, 1966; Westfall & Brasted, 1972). We have determined the effects of nicotine on the ventricular tension development in isolated perfused hearts of dogs and monkeys and on catecholamine release from and content of these hearts.

Dogs and rhesus monkeys of either sex, 5–14 kg and 4–10 kg respectively, were anaesthetized with sodium pentobarbitone (30 mg kg^{-1}, i.v.) and given heparin (1500 I.U. kg^{-1}, i.v.). Perfusion of the hearts (Langendorff, 1895) was performed at a constant pressure of 60 cm of H_2O and 35° with Krebs-Hensleit solution of pH 7·3, saturated with 5% CO_2 in oxygen. Ventricular tension was recorded with a transducer (Nihonkohden model SB–IT) attached to a thread tied into the wall of the right ventricle. The hearts were secured by two retaining threads placed in the ventricular septal tissue on either side. A resting tension of 2 g was applied to each heart. The dose response curves for development of ventricular tension were established by perfusion with increasing concentrations of nicotine for 60 s at 20 min intervals. Changes of the contractile tension and ventricular rate due to nicotine were calculated as percentage increases of the maximal ino- and chronotropic response from the baseline values. Perfusate, collected from hearts for 2 min before and after nicotine administration and hearts immediately after removal from control animals had their catecholamine content measured fluorometrically (Tsujimoto & others 1974).

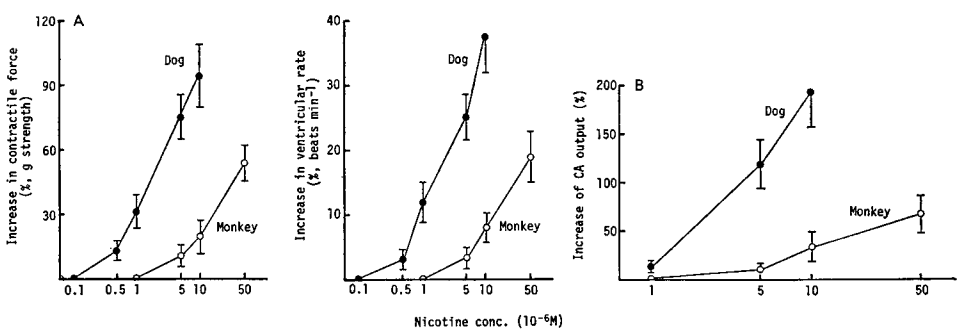

FIG. 1A. Dose-response curves to nicotine of isolated perfused hearts of dogs and monkeys. Nicotine diluted with Krebs-Hensleit solution was infused continuously for 60 s. Each point represents the mean ± s.e.m. of values in 5 dogs or monkeys. Values show maximum increases of the response as percentages of the control. The mean spontaneous vascular rates for dogs and monkeys were 98 beats min^{-1} (range 90–103 beats) and 103 beats min^{-1} (range 91–109 beats) respectively.

B. Increase of catecholamine release from isolated perfused hearts of dogs and monkeys caused by nicotine. Each point represent the mean ± s.e.m. of values in 5 dogs or monkeys. Nicotine was infused continuously for 60 s. Values show increase in catecholamine output as percentages of the control. Samples were collected for 120 s periods before, during and after perfusion of nicotine. Noradrenaline was used as a standard.

Table 1. *Catecholamine contents of the hearts of dogs and monkeys*

Animal	Tissue	Adrenaline A (μg g^{-1})	Noradrenaline NA (μg g^{-1})	$\frac{NA}{A + NA}$ (%)
Dog (5)	Heart { Atrium	0·26±0·05	1·83±0·20	88
	{ Ventricle	0·02±0·003	0·54±0·08	96
Monkey (5)	{ Atrium	0·26±0·06	1·02±0·08*	79
	{ Ventricle	0·02±0·003	0·56±0·06	97

Values are means or means ± s.e.m.
Numbers in parentheses are numbers of animals.
*Significantly different ($P<0·01$) from value for dog atrium.

When perfused through dog hearts for 60 s, 5×10^{-7} — 10^{-6}M nicotine first caused a slight negative chronotropic effect, and then stimulated the rate and amplitude of contractions. The same concentration range had no effect on monkey heart, but above 5×10^{-6}M positive ino- and chronotropic actions occurred (Fig. 1A) after short periods of initial decrease in rate and amplitude of the heart contractions. The potency of the cardiostimulatory effect of noradrenaline was approximately similar in the two species (data not shown).

Buccino, Sonnenblick & others (1966) and Bassett, Wiggins & others (1974) reported that nicotine has a direct action on cardiac contractility independent of that caused by release of catecholamine. However, much of the positive inotropic effect is indirect and probably results from nicotine-induced release of endogenous catecholamine from stores in the heart tissue (Burn & Rand, 1958; Bhagat, 1966; Westfall & Brasted, 1972).

The catecholamine contents of the hearts of dogs and monkeys, and catecholamine release from these hearts were determined. The contents (adrenaline and noradrenaline) of the atria of both species were much higher than those of the ventricles, and the noradrenaline contents of both the atria and ventricles of both species were much higher than their adrenaline contents. The noradrenaline contents of dog atria were much higher than those of monkey atria while the adrenaline contents were similar. The catecholamine contents of the ventricles of the two species were similar (Table 1). The mean spontaneous total output of catecholamine from the hearts in 5 dogs was 60 ng min^{-1} (range 35–78 ng) and that in 5 monkeys was 49 ng min^{-1} (range 23–69 ng) and more than 95% was noradrenaline in both species. Nicotine (5×10^{-6}, 5×10^{-5}M) released more noradrenaline than adrenaline from perfused hearts of both species and it (10^{-6}—10^{-5} M) liberated more catecholamines from dog than from monkey heart (Fig. 1B).

It is suggested that the difference in the cardiostimulatory response to nicotine of dogs and monkeys is due to the different amounts of noradrenaline released in the two species and it is noteworthy that there is less noradrenaline in monkey heart to be released. Trendelenburg (1965) reported that nicotine acts not only on ganglionic cells but also on a variety of sympathetic nerve terminals in the heart. The effect of nicotine on catecholamine release from isolated adrenal glands of the two species has also been shown to differ (Tsujimoto & Nishikawa, 1974). Thus, there may be similar differences between dogs and monkeys at the terminal adrenergic nerve fibres of other organs or at the sympathetic ganglia.

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REFERENCES

BASSETT, A. L., WIGGINS, J. R., DANILO, P., Jr., NILSSON, K. & GELBAND, H. (1974). *J. Pharmac. exp. Ther.*, **188**, 148–156.

BHAGAT, B. (1966). *Ibid.*, **154**, 264–270.

BUCCINO, R. A., SONNENBLICK, E. H., COOPER, T. & BRAUNWALD, E. (1966). *Circ. Res.*, **19**, 1097–1109.

BURN, J. J. & RAND, M. J. (1958). *Br. med. J.*, **1**, 137–139.

HUG, C. C., JR. & BASS, P. (1970). *Univ. Mich. Med. Ctr. J.*, **36**, 246.

LANGENDORFF, O. (1895). *Pflügers Arch. ges. Physiol.*, **61**, 291–232.

TRENDELENBURG, U. (1965). In: *Tobacco alkaloids and related compounds*, p. 167. Editor: Euler, U.S.V. New York: Pergamon Press.

TSUJIMOTO, A., NISHIKAWA, T., DOHI, T. & KOJIMA, S. (1974). *Eur. J. Pharmac.*, **26**, 236–242.

TSUJIMOTO, A. & NISHIKAWA, T. (1974). *Ibid.*, **29**, 316–319.

WESTFALL, T. C. & BRASTED, M. (1972). *J. Pharmac. exp. Ther.*, **182**, 409–418.

Evidence for a prime role of newly synthesized dopamine in mesolimbic dopamine areas*

Enhancement of dopamine synthesis in the brain following administration of haloperidol, phenothiazines or other antipsychotic drugs has been demonstrated by several investigators (Andén, Roos & Werdinius, 1964; Laverty & Sharman, 1965; O'Keefe, Sharman & Vogt, 1970). While it has been shown by Besson, Cheramy & others (1973) that newly synthesized dopamine is released during impulse flow in the nigrostriatal axon, the relative functional importance of stored versus newly synthesized dopamine in brain function has been unclear.

Recently, a report from this laboratory presented evidence that in striatal function newly synthesized dopamine is utilized preferentially to stored dopamine (Shore & Dorris, 1975). In that study it was shown that a small dose of haloperidol, which alone caused only a slight degree of catalepsy, rapidly produced profound catalepsy when given to rats soon after administration of the tyrosine hydroxylase inhibitor, α-methyl tyrosine (α-MT). At the time of marked catalepsy potentiation about 80% of striatal dopamine was shown by analysis to be still present, suggesting that after haloperidol alone, the nigrostriatal system is functionally dependent largely on newly synthesized dopamine and that the main pool of the amine contributes little to the maintenance of striatal function. Analysis of striatal homovanillic acid (HVA) after the various treatments showed that the marked haloperidol-induced elevation of this extraneuronal dopamine metabolite was greatly inhibited by the presence of α-MT, a finding which is in accord with the concept that little of the main dopamine pool could have been released into the synaptic cleft. It was thus concluded that newly synthesized dopamine has a greater role in striatal function than does the large endogenous pool, at least under conditions of compensatory activation of the striatal dopamine neuron following dopamine receptor inhibition by a neuroleptic.

The present study examines another dopamine system, that of the mesolimbic system. The results suggest that a high degree of functional dependence on newly synthesized dopamine exists in the mesolimbic dopamine system as well as in the striatal system.

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