Central antagonism of tyramine-induced systemic hypotension by mescaline

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Modification of biogenic amine concentrations within the central nervous system has been implicated in the mechanism of action of psychotomimetic agents, including mescaline and (+)-lysergic acid diethylamide (LSD). Several investigations have related the activity of these psychotogens to alterations of central adrenergic and tryptaminergic systems (Roberts & Straughan, 1968; Sugrue, 1969; Tilson & Sparber, 1972). To examine the premise that mescaline elicits central catecholaminergic antagonism as suggested by various authors (Speck, 1957; Clemente & Lynch, 1968; Gonzalez-Vegas, 1971; Ratcliffe, 1971; Dill, 1972), studies were conducted to observe the interaction of mescaline with endogenously released noradrenaline. In this investigation, centrally initiated changes in systemic blood pressure provided a means of assessing mescaline activity.

Male rabbits anaesthetized with urethane (1·2 g kg^{-1}, i.v.) were implanted with a modified Collison cannula positioned 4 mm lateral to the sagittal suture, 4 mm caudal to the coronal suture and 7–8 mm deep (Dhawan & Dua, 1971) to establish communication with the lateral cerebral ventricle. Femoral arterial blood pressure was monitored by a Narco Bio-Systems P-1000A pressure transducer and recorder. The following drugs, prepared in artificial cerebrospinal fluid (csf) (Merlis, 1940), were used: tyramine hydrochloride, mescaline sulphate, and noradrenaline bitartrate. All doses are expressed as the salt form and refer to total dose.

One group of experiments consisted of intracerebroventricular (i.c.v.) introduction, at 15 min intervals, of either 6 consecutive 50 μl volumes of artificial csf or 6 consecutive 200 μg doses of tyramine hydrochloride, each series followed 15 min later by mescaline sulphate (1 mg, i.c.v.). Another group of 6 animals received noradrenaline (i.c.v.; average dose, 135 μg).

Noradrenaline (i.c.v.) elicited a measurable fall in mean arterial blood pressure (10 $\pm$ 2 mm Hg, [n = 6]). Six successive injections of tyramine (i.c.v.) produced marked hypotension, i.e., 21 mm Hg or 26% below control levels (Table 1); this effect, more gradual and prolonged than that due to exogenous noradrenaline, correlates with its sustained noradrenaline releasing action (Neff, Tozer & others, 1965; Brodie, Cho & others, 1969). The six injections of tyramine were necessary to obtain a sustained fall in systemic blood pressure. In contrast, repeated administration of artificial csf (i.c.v.) produced no such changes (Table 1).

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Within 5 min of injection, mescaline (1 mg, i.c.v.) completely reversed the tyramine-induced hypotension. Specifically, mescaline elevated mean systemic arterial pressure 14% after artificial csf administration (control) and 43% following tyramine (Table 1). However, hypotension was present in the tyramine pretreated animals whereas control rabbits exhibited normal blood pressure; therefore, the absolute pressor response produced by mescaline did not differ significantly between these two groups.

After intravenous administration of mescaline (1 mg kg^{-1}, n = 3), blood pressure alterations were not observed, ruling out a peripheral pressor action at this dose.

Systemic hypotension elicited centrally by noradrenaline may be the result of a sympatho-inhibitory effect mediated by medullary adrenoceptors (Sinha & Schmitt, 1974). Although mescaline and noradrenaline may act on similar cortical receptors (Bevan, Bradshaw & others, 1974), iontophoretic application of mescaline to brain stem neurons antagonizes noradrenaline inhibitory receptors (Gonzalez-Vegas, 1971). This antagonism, which may occur competitively at postsynaptic sites (Ratcliffe, 1971), has been observed in the present investigation where mescaline reversed the depressor effect of noradrenaline which had been evoked by successive tyramine injections.

While central administration of mescaline resulted in a pressor response even in control animals, it can not be ascertained from these data whether mescaline acts directly on the adrenergic system, indirectly through the activation of a physiologically opposed system, or a combination of both.

Table 1. *Effect of mescaline upon mean systemic arterial blood pressure (mm Hg $\pm$ s.e.m.) in control and tyramine treated rabbits.*

	Before treatment	After treatment	After mescaline[c]
Control[a] (n = 5)	79 $\pm$ 4	77 $\pm$ 5	88 $\pm$ 3
Tyramine[b] (n = 7)	81 $\pm$ 3	60 $\pm$ 3	86 $\pm$ 5

(a) Six intracerebroventricular (i.c.v.) injections of 50 μl of artificial cerebrospinal fluid (csf) at 15 min intervals.
(b) Six i.c.v. injections of 200 μg in 50 μl csf at 15 min intervals.
(c) One mg i.c.v. 15 min after csf or tyramine.
Numbers in parentheses indicate the number of observations.

That the alterations in systemic blood pressure represent a direct interaction between drug and brain tissue is confounded by the recognition that changes in cerebral arterial tonus can modify peripheral vascular responses (Kaneko, McCubbin & Page, 1960; Mitchell, Sciven & Rosendorff, 1975). Dyer & Gant (1973) have shown that mescaline constricts umbilical vasculature and it may be inferred that systemic blood pressure changes observed in this study may reflect mescaline action at the cerebral vascular level.

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Effect of non-steroidal anti-inflammatory drugs on the tetrazolium reductase activity of leucocytes

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One property of non-steroidal anti-inflammatory drugs (NSAIDs) is their inhibitory action on the migration and phagocytic activity of monocytes. In concentrations effective in clinical treatment they also inhibit the phagocytosis of starch particles and bacteria by polymorphonuclear cells (Di Rosa, Papadimitriou & Willoughby, 1971; Di Rosa, Sorrentino & Parente, 1972; Ruutu & Kosunen, 1972; Yi-Han Chang, 1972). The inhibitory effect extends to the chemotaxis of polymorphonuclear cells induced by fragments formed during complement activation. NSAIDs also inhibit the activation of lymphocytes by mitogens (Whitehouse, 1967).

We wanted to know whether clinical treatment with some NSAIDs influenced circulating neutrophil granulocytes which play a part in the non-specific defence against microorganisms and in the development of inflammatory reactions. The reduction of nitrotetrazolium blue (NBT-test, Baehner & Nathan, 1967, 1968) has been frequently used to assess the functional state of phagocytes. Another substrate for the estimation of tetrazolium reductase activity that is particularly suited to quantitative photometric examination is iodonitrotetrazolium (INT) (Lokaj & Oburková, 1974). To our knowledge the possibility of influencing the NBT-test by NSAIDs has received only brief mention (Douwes, 1972).

For our purpose we used blood samples from patients of either sex who were being treated for post-traumatic conditions or milder forms of degenerative diseases of the locomotor system and who were otherwise clinically healthy. Their ages ranged from 35–65 years. Groups of five patients were treated with NSAIDs for two weeks. The drugs used were: acetylsalicylic acid—3 g day^{-1}

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