Variation in hydroxytryptamine metabolism in the rat: effects on the neurochemical response to phencyclidine

Lysergide reduces the turnover of 5-hydroxytryptamine (5-HT) in central neurons (Schubert, Nyback & Sedvall, 1970; Aghajanian, Warren & Sheard, 1968; Lin, Ngai & Costa, 1969; Sheard & Aghajanian, 1968). Lysergide was shown to produce a statistically significant increase in cerebral 5-HT concentrations in rats (Freedman & Giarman, 1962), and this increase was accompanied by decreased 5-hydroxyindoleacetic acid (5-HIAA) concentrations (Rosecrans, Lovell & Freedman, 1967). Tonge & Leonard (1969) demonstrated that four structurally dissimilar hallucinogenic drugs (phencyclidine, Ditran, lysergide and mescaline) all increased 5-HT and decreased 5-HIAA concentrations, though possibly by different mechanisms (Tonge & Leonard, 1970). But, some investigators failed to detect any increase in 5-HT concentrations after lysergide (Andén, Corrodi & others, 1968). We now report strain variation in the effects of at least one hallucinogen on 5-HT concentrations.

Drugs were administered by the intraperitoneal route to Wistar rats, 90–100 g, obtained from two sources. Animals were decapitated and 5-HT and 5-HIAA were determined in whole brain (less cerebellum). 5-HT was determined by the method of Snyder, Axelrod & Zweig (1965), 5-HIAA by that of Giacolone & Valzelli (1966) as modified by Tonge & Leonard (1969). In the presence of *p*-chlorophenylalanine, 5-HT was determined by the method of Bogdanski, Pletscher & others (1956).

The effects of phencyclidine (10 mg/kg) on brain 5-HT and 5-HIAA concentrations 30 min after injection are shown in Table 1.

Table 1. *The effects of phencyclidine* (10 mg/kg) *on brain 5-HT and 5-HIAA concentrations in Wistar rats from two sources.*

Time after injection (min)	Source A		Source B	
	5-HT	5-HIAA	5-HT	5-HIAA
	(n mol/g)		(n mol/g)	
0	2·68 ± 0·03	1·78 ± 0·01	2·38 ± 0·04	0·68 ± 0·02
30	***3·81 ± 0·06	**1·31 ± 0·02	**1·94 ± 0·05	**1·00 ± 0·01

Results are the means of 15 estimations ± s.e. Significance (Student's *t* test) is shown as: $*P = <0{\cdot}05$, $**P = <0{\cdot}01$, $***P = <0{\cdot}001$.

Table 1 shows that a dose of 10 mg/kg of phencyclidine caused an increase in 5-HT and decrease in 5-HIAA concentrations in rats from source A; directly opposite results were obtained from animals of source B.

These results suggested that there might be differences in the normal intraneuronal metabolism of 5-HT in the two sources. Both the absolute concentrations of 5-HIAA and the ratio of 5-HIAA to 5-HT are different: in source A, 5-HIAA : 5-HT = 0·66; in source B, 5-HIAA : 5-HT = 0·29.

The effects on brain 5-HT concentrations of *p*-chlorophenylalanine (PCPA) (400 mg/kg) in animals from the two sources at 0 and 16 min are (nmol/g): 2·95 ± 0·08 and ***0·89 ± 0·11 for source A and 2·93 ± 0·06 and **2·05 ± 0·07 for source B animals (significance as in Table 1; means of five estimations ± s.e.).

The difference in the rates of depletion of 5-HT after synthesis block suggests a possible explanation of the substrain variation in the response to phencyclidine.

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On the mechanism of papaverine action on the control of vascular smooth muscle contractile activity by extracellular calcium

It has been suggested recently that the relaxing effects of papaverine on smooth muscle might be exerted through cyclic phosphodiesterase (PDE) inhibition and consecutive accumulation of cyclic-3′,5′-AMP (Triner, Vulliemoz & others, 1970). Since relaxation probably follows the decrease of intracellular free Ca^{2+} ions, it still remains to be explained how cyclic AMP influences calcium movements (Stoclet, Peguet & Waeldele, 1971). Kukovetz & Pöch (1970) suggested that cyclic AMP probably increases Ca^{2+} uptake by the membranes and might enhance active Na-exclusion in vascular smooth muscle.

We now report the influence of papaverine and exogenous cyclic AMP (*N*-2′-*O*-dibutyryl adenosine-3′,5′-monophosphate) on noradrenaline-induced isometric responses of isolated aortic strips from the rat in different extracellular calcium concentration salines.

The thoracic aortae of 10 to 12 weeks old male rats (EOPS OFA) were removed from the left carotid to the diaphragm and prepared (Godfraind & Kaba, 1969). Isometric responses elicited by noradrenaline ($7{\cdot}5 \times 1^{-7}$M) were recorded under an initial tension of 1 g. Papaverine or cyclic AMP were added to the bath 10 min before noradrenaline. The reference response of each aortic strip was obtained in "normal" Krebs-bicarbonate medium (Ca content 2·5 mM). Except when $CaCl_2$ was added during the record of noradrenaline effect, any change in calcium concentration of the saline was followed by a period of equilibration to obtain a constant response to noradrenaline. With calcium concentrations lower than normal, the aortae were previously depleted by incubations for 1 h in calcium-free Krebs bicarbonate containing ethylene glycol bis amino-2-ethylether-*NN*′-tetra-acetic acid (EGTA, 1 mM).