Reduction of histamine in mouse brain by N^1-(DL-seryl)-N^2-(2,3,4-trihydroxybenzyl) hydrazine and reserpine

The monoamines, noradrenaline, dopamine and 5-hydroxytryptamine, are generally accepted to be involved in the functioning of the mammalian central nervous system. Histamine has also been suggested to be similarly involved, but the amount of evidence is less (see Green, 1970). In comparison to the monoamines, few drugs have been found to alter the concentrations of histamine in mammalian brains and wide species variations occur.

Reserpine is a classical depletor of the monoamines from mammalian brains. It blocks their granular uptake-storage mechanism and the resulting depletion approaches 100%. In contrast, only a 55–65% reduction of histamine in cat brain, and no reduction in rat brain, has been obtained after reserpine (Adam & Hye, 1966; Green & Erickson, 1964).

Inhibitors of the specific histidine decarboxylase enzyme have been widely used to deplete histamine in peripheral tissues, the two most commonly used being 4-bromo-3-hydroxybenzyloxyamine (NSD 1055) and α-hydrazinohistidine (MK 785). Using these drugs, Taylor & Snyder (1971) obtained a reduction of 35–40% in rat endogenous hypothalamic histamine.

Inhibitors of the aromatic amino-acid decarboxylase have been widely used to deplete monoamines, both in peripheral and central tissues. N^1-(DL-Seryl)-N^2-(2,3,4-trihydroxybenzyl) hydrazine (Ro 4-4602) has been frequently used, depletions of around 50% having been obtained in rat and mouse brain (see Pletscher, Gey & Burkard, 1965).

Here, the reduction of histamine in mouse brain by reserpine and Ro 4-4602 is reported.

Groups of 6 white female mice (NMRI), 18–24 g, were injected with reserpine, Ro 4-4602 or saline, alone or in combination, as indicated in Table 1. The animals were decapitated and each brain was rapidly excised and homogenized in ice-cold perchloric acid containing sodium metabisulphite and di-sodium ethylenediamine tetra-acetate. The extract of 6 pooled brains was used for the analysis of histamine. Histamine was isolated on a Dowex 50W-X4 cation exchange column and assayed spectrophotofluorimetrically using orthophthaldialdehyde as outlined by Atack & Magnusson (1970), except that, after the elution of the 5-hydroxytryptamine, histamine was eluted with 2 N aqueous HCl (4·5 ml). Spermidine has since been established to be completely separated from, and elutable after, histamine in this column procedure.

The effects of reserpine and Ro 4-4602 on the concentration of histamine in the entire mouse brain are indicated in Table 1. The significant depletion of histamine by reserpine alone is small (about 11%), but a similar depletion (about 15%) was

Table 1. *Histamine concentration in mouse brain after different drug treatments. The mice were kept at 30° for 5 h before death.*

Treatment	Histamine ng/g ± s.e. (n)
A. Controls, saline, i.p.	48·3 ± 3·344 (5)
B. Reserpine, 5 mg/kg, i.p., 7 h before death	42·8 ± 1.650 (5)
C. Ro 4-4602, 800 mg/kg, i.p., 2 h before death	32·0 ± 2·333 (5)
D. Reserpine + Ro 4-4602, doses and time intervals as above	27·3 ± 3·255 (5)

Statistical analysis of variance followed by *t*-test:
A–B, $P < 0{\cdot}025$; A–C, $P < 0{\cdot}001$; C–D, $P < 0{\cdot}025$.

obtained after the combined administration of reserpine and Ro 4-4602 compared to the depletion caused by Ro 4-4602 alone (about 34%) which was highly significant. The possibility that this latter reduction is related to the concomitant lowering of the monoamines by the Ro 4-4602 is unlikely, since many drugs known to alter the concentrations of the monoamines in mouse brain were without effect on the histamine concentrations (Atack, unpublished data).

Probably, the reduction of histamine concentration was caused by the inhibition of an enzyme converting histidine to histamine. The specificity of inhibitors of the specific histidine decarboxylase and of the aromatic amino-acid decarboxylase has not been unequivocally established (see Aures, Håkanson & Clark, 1970). Schwartz, Lampart & Rose (1970) have identified an enzyme in rat brain with physical properties resembling those of the peripheral specific histidine decarboxylase and which was inhibited by NSD 1055 but not by α-methyldopa, the latter being a specific inhibitor of the aromatic amino-acid decarboxylase. Taylor & Snyder (1971), whilst obtaining the 35–40% reduction in rat endogenous hypothalamic histamine with NSD 1055 and MK 785, found no effect with α-methyldopa, thus suggesting the involvement of only the specific histidine decarboxylase.

Therefore, whilst Burkard, Gey & Pletscher (1964) found no effect of Ro 4-4602 on a bacterial specific histidine decarboxylase *in vitro*, the effect of this drug in reducing the concentrations of histamine in mouse brain is more likely to be the result of an inhibition of the specific histidine decarboxylase. The influence of α-methyldopa on histamine concentrations in mouse brain should help to elucidate this problem.

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