tion cimetidine was about 50 times as potent as burimamide, which corresponds rather well with previous data, whereas the reverse was true in the ileum (burimamide about 25 times as potent as cimetidine). These differences may possibly be explained by the existence of different histamine H_2-receptors in the atria and in the ileum. This theory is supported by the lack of chronotropic effect of clonidine in the atria.

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Effect of metiamide, a histamine H_2-receptor antagonist on the clonidine-induced decrease in rat brain noradrenaline turnover

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Clonidine is a potent antihypertensive agent which is thought to stimulate central α-adrenoceptors, thereby bringing about a depression of the cardiovascular system (Kobinger & Walland 1967; Schmitt et al 1973). Neurochemically, this action is reflected as a decrease in brain noradrenaline turnover presumably due to α-receptor activation which in turn, by a negative feedback mechanism, decreases the neuronal release of noradrenaline (Andén et al 1970). Recent studies have indicated that metiamide (Karppanen et al 1976; Finch et al 1977) and cimetidine (Finch et al 1977), histamine$_2$-receptor (H_2-receptor) antagonists (Black et al 1972), when administered intracerebroventricularly antagonized clonidine-induced antihypertensive activity in rats. These findings suggest a possible role for H_2-receptor stimulation in the antihypertensive effect of clonidine. Other studies have indicated that clonidine stimulates H_2-receptors in the gastric mucosa (Karppanen & Westermann 1973), heart (Csongrady & Kobinger 1974) and brain (Sastry & Phillis 1976; 1977).

In view of these observations, investigations were carried out to determine whether metiamide antagonizes the effect of clonidine on brain noradrenaline turnover. An ability to cause an alteration of this effect would be indicative of a possible relation between histamine and noradrenaline-containing neurons in the brain.

Male Sprague-Dawley rats (140–160 g, Canadian Breeding Laboratories) were used. The effects on brain noradrenaline turnover were evaluated by studying the decline of brain noradrenaline after treatment with the dopamine β-hydroxylase inhibitor Fla-63, bis-(4-methyl - 1 - homopiperazinyl-thiocarbonyl) disulphide (Regis Chemical Co.) (Andén et al 1972). Animals were injected intracerebrally into the lateral ventricle (Noble et al 1967) with saline or metiamide, and 30 min later intraperitoneally with saline or clonidine. After a further 30 min the rats were injected with saline or Fla-63 and 4 h later they were decapitated, the whole brains quickly removed, rinsed in saline and frozen. Noradrenaline was measured in homogenates of brain prepared in 0·4 M perchloric acid containing 0·1% EDTA and 0·1% ascorbic acid. Noradrenaline was isolated from the homogenate by adsorption onto alumina (Whitby et al 1961), eluted from the alumina with 0·2 M acetic acid and measured flurometrically by the method of Shellenberger & Gordon (1971).

Clonidine hydrochloride and metiamide were gifts from Boehringer Ingelheim Ltd. and Smith, Kline and French Ltd., respectively.

Neither metiamide (0·3 mg kg^{-1}, intraventricularly) nor clonidine (0·1 mg kg^{-1}, i.p.) administered alone altered brain noradrenaline concentrations (Table 1) while treatment with Fla-63 caused a depletion. Clonidine administered before Fla-63 reduced the fall in brain noradrenaline induced by Fla-63; metiamide was ineffective. Pretreatment with metiamide did not alter the clonidine-induced reduction of the fall in brain noradrenaline observed following Fla-63.

The results of this study demonstrate that administration of clonidine, but not metiamide, reduces the deple-

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Table 1. Effect of metiamide and clonidine on rat brain noradrenaline (NA) turnover. Rats were injected with metiamide or clonidine intraventricularly or intraperitoneally 5 and 4·5 h, respectively, before the animals were killed. Fla-63 was injected 4 h before the animals were killed. Each value is mean ± s.e.m. of 6 rats.

Compound	Dose (mg kg^{-1})	NA (μg g^{-1} ± s.e.m.)
Saline	—	0·22 ± 0·01
Metiamide	0·3	0·22 ± 0·01
Clonidine	0·1	0·22 ± 0·01
Fla-63	25	0·07 ± 0·01*
Clonidine + Fla-63	0·1 + 25	0·13 ± 0·01†
Metiamide + Fla-63	0·3 + 25	0·07 ± 0·01
Metiamide + Clonidine + Fla-63	0·3 + 0·01 + 25	0·12 ± 0·01††

* $P < 0·001$ *vs* saline-injected animals.
† $P < 0·001$ *vs* Fla-63-injected animals.
††*P*-not significant *vs* clonidine + Fla-63 — injected animals.

tion in brain noradrenaline resulting from inhibition of its synthesis by Fla-63. The rate of the amine's decline after inhibition of its synthesis provides an index of the rate of its turnover provided the drug treatment does not affect the steady state concentration of the amine in the time interval during which depletion is measured. In agreement with previously described findings (Andén et al 1970), clonidine had no effect on endogenous noradrenaline indicating that clonidine reduces noradrenaline turnover. This effect of clonidine is hypothesized to be related to its ability to stimulate brain α-adrenoceptors, thereby causing a decreased release of noradrenaline from adrenergic neurons by a negative feedback mechanism (Andén et al 1970). Metiamide alone did not affect brain turnover of noradrenaline, nor did it influence the clonidine-induced reduction in brain noradrenaline turnover. This latter finding suggests that the decrease in catecholamine turnover induced by the administration of clonidine is independent of any direct effect of clonidine on H_2-receptors, at least under the conditions used.

Metiamide, as shown in peripheral tissue (Black et al 1972), appears to be a specific H_2-receptor antagonist in rat brain (Haas & Bucher 1975; Phillis et al 1975; Sastry & Phillis 1976). Other evidence indicating that metiamide, administered intracerebrally, can antagonize the blood-pressure lowering effect of clonidine in the rat (Karppanen et al 1976; Finch et al 1977) and block the effects of clonidine on cortical neurons appears to indicate that clonidine can activate H_2-receptors on central neurons (Sastry & Phillis 1977). However, centrally-mediated antihypertensive effects of histamine have not been shown as yet (Finch & Hicks 1976a,b, 1977) and studies in conscious cats (Finch & Hicks 1976c) have shown that metiamide does not antagonize the antihypertensive action observed after the central administration of clonidine. Therefore, whether activation by clonidine of H_2-receptors in the brain is involved in the antihypertensive action of clonidine is not clear at this time.

Iontophorectic studies indicate that clonidine has other effects that are not related to H_2-receptor stimulation (Sastry & Phillis 1977). The present findings also suggest that reduction of brain noradrenaline turnover by clonidine is not related to H_2-receptor activation since metiamide failed to alter this reduction. It may be concluded that the blood pressure lowering activity of clonidine appears to be complex and further studies are required to determine the importance of the ability to cause H_2-receptor and α-adrenoceptor activation in this context.

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