HISTAMINE H₂-RECEPTORS IN THE BRAIN AND SLEEP PRODUCED BY CLONIDINE

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Sleep was induced in chicks aged 4–7 days by intravenous injection of clonidine hydrochloride 0.04 µmol/kg. Sleep was not prevented or altered by a preceding intramuscular injection of blockers of histamine H₂-receptors which were used in doses (as µmol/kg) of up to 800 (metiamide) and 2400 (cimetidine). Clonidine, therefore, does not cause sleep by stimulating H₂-receptors in the brain. The highest dose of cimetidine used had a hypnotic action of its own.

Introduction

In an earlier paper (Holman, Shillito & Vogt, 1971) an attempt was made to determine whether the sleep induced in chicks by intravenous injection of clonidine (Zaimis, 1970) can be considered to be an effect on central noradrenaline receptors. Although the results were compatible with that view, the antagonism between clonidine and blockers of α-adrenoceptors was only partial, a dose of phentolamine 40 µmol/kg reducing, but not abolishing, the effect of clonidine 0.04 µmol. This may well be due to the fact that central noradrenaline receptors differ in their properties from peripheral ones, but it left the possibility open that other receptors were involved. The work had further suggested that tryptaminergic receptors were not involved.

A recent paper (Karppanen, Paakkari, Paakkari, Huotari & Orma, 1976) suggested that some central effects of clonidine may be on histamine receptors of the H₂-type. The authors used rats anaesthetized with urethane, and by infusing the H₂-antagonist metiamide into the cerebral ventricles, reversed the hypotension produced by clonidine. To test whether sleep elicited by clonidine was similarly affected, two blockers of H₂-receptors, metiamide and cimetidine, were given to newly-hatched chicks before intravenous administration of clonidine.

Results

Both of the antagonists of H₂-receptors, when given in sufficiently high doses, were apt to cause eye closure in the chicks; this was seen with metiamide 800 µmol/kg and cimetidine 1600 µmol/kg. The effect lasted no more than a minute or two. When, however, cimetidine 2400 µmol/kg was injected, sleep leading to complete relaxation was produced, and lasted about 25 minutes. This dose (corresponding to 30 mg for a 50 g chick) was therefore the limit of the amount which could be injected; even these high doses did not cause any visible after-effects, indicating the very low toxicity of the compound.

Table 1 summarizes the results. In spite of the pretreatment with histamine H₂-antagonists, not a single chick failed to fall asleep, usually within the first minute, after the intravenous injection of clonidine; nor was the duration of sleep outside the normal limits. After three experiments with metiamide, known to be the less potent of the two H₂-antagonists, cimetidine was used for the remaining trials; 800 and 1600 µmol were injected intramuscularly followed by clonidine after intervals ranging between 2 and 64 minutes. In two experiments with 2400 µmol/kg, a hypnotic dose of cimetidine, one hour was allowed between the two injections to ensure that the chick was fully awake.
when receiving the clonidine. A few experiments were
carried out with low doses (10–20 μmol/kg) to
exclude the possibility that cimetidine might produce a
biphasic effect and have an antagonistic action at low
doses only.

Discussion

The preceding results rule out the possibility that the
sleep produced in chicks by clonidine is mediated
through histamine H₂-receptors. Whereas phentolamine 40 μmol/kg antagonizes the hypnotic effect
of clonidine (Holman et al., 1971), cimetidine, even in
a dose of 2400 μmol/kg, does not.

Table 1 Sleep* induced by clonidine hydrochloride
in chicks (aged 4–7 days) pretreated with metiamide
or cimetidine

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (μmol/kg)</th>
<th>Interval (min) between H₂-antagonist and clonidine</th>
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<tbody>
<tr>
<td>Metiamide</td>
<td>400</td>
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<td>800</td>
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<td>Cimetidine</td>
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<td>64</td>
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<td>2400**</td>
<td>58</td>
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<td></td>
<td>2400**</td>
<td>60</td>
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</table>

All chicks were injected intravenously with clonidine
hydrochloride 0.04 μmol/kg at various intervals (see
column 3) after intramuscular injections of either
metiamide or cimetidine. The treatment did not
modify either onset or character of sleep.
The duration of sleep until the first awakening ranged
from 2 to 6 min, which was not different from that of
cocks given clonidine only.

*Sleep is defined as complete relaxation with head or
beak touching the ground and eyes closed.

**This dose (605 mg/kg) on its own caused sleep for
approximately 25 minutes.

What is the situation concerning other central
effects of clonidine? The views originally expressed by
Karppanen et al. (1976) that H₂-receptors mediated
the hypotensive effect of clonidine have not been com-
pletely supported by a later paper from the same
group (Karppanen, Paakkari & Paakkari, 1977). The
authors argued that, if clonidine lowered the blood
pressure by stimulating H₂-receptors, the potent
agonist of H₂-receptors, 4-methylhistamine, should
do the same. In fact they found that its intra-
cerebroventricular injection did not lower, but slightly
raised the blood pressure. It is, of course, conceivable
that the action of 4-methylhistamine is complex and
that the expected hypotension is masked by other
actions of this compound. However, there have recent-
ly been other findings which throw some doubt on the
explanation of the depressor effect of clonidine as a
stimulation of H₂-receptors. In the cat (which might,
of course, respond differently from the rat), renal
hypertension was reduced by intracerebroventricular
clonidine, but this effect was antagonized by phentolamine and not by metiamide (Finch & Hicks,
1976). In the rat, on the other hand, inhibitory effects
of iontophoretically applied clonidine on the firing rate
of deep cortical cells were found to be prevented by
metiamide (Sastry & Phillis, 1977).

Furthermore, clonidine has been shown to stimulate
the accumulation of cyclic adenosine 3', 5'-
monophosphate (cyclic AMP) in guinea-pig brain, an
action inhibited by metiamide and therefore
presumably exerted on histamine H₂-receptors
(Audigier, Virion & Schwartz, 1976). However, the
importance of these findings for the in vivo actions
of clonidine is problematic: as the authors point out, the
cardiovascular effects of clonidine occur at a much
lower dose than the EC₅₀ for accumulation of cyclic
AMP. Another doubt arises from the fact that
histamine-sensitive adenylate cyclase is plentiful in
some regions of the guinea-pig brain, but rat brain
contains very little (Hegstrand, Kanof & Greengard,
1976). It is obvious that the relation between clonidine
and central histamine H₂-receptors needs further
clarification; any convincing evidence of interaction
would help in assigning a role to receptors the function
of which is still obscure.

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