The Effect of Neuroleptic Drugs on Drinking Induced by Central Administration of Angiotensin or Carbachol

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Abstract. The effect of a series of neuroleptic drugs on the drinking response elicited by intracerebroventricular injection of either angiotensin or carbachol into conscious rats was studied. The i.p. injection of haloperidol, cis-flupenthixol, or fluphenazine antagonized both angiotensin-induced and carbachol-induced drinking. When injected into the lateral ventricles, the neuroleptics haloperidol, fluphenazine, cis-flupenthixol and sulpiride were potent inhibitors of angiotensin-induced drinking, but had little effect on the dipsogenic action of carbachol. Clozapine, administered centrally, antagonized drinking caused by both angiotensin and carbachol. Pimozide and chlorpromazine were also potent inhibitors of angiotensin-induced drinking, while trans-flupenthixol was inactive. Our results support the concept of an involvement of dopamine in angiotensin-induced drinking.

Key words: Angiotensin – Drinking – Neuroleptics – Carbachol

The injection of angiotensin into the cerebral ventricles of rats is known to cause drinking (Booth, 1968; Epstein et al. 1970). A similar dipsogenic response to angiotensin is seen in a wide variety of other species (Fitzsimons, 1972). The drinking response to angiotensin in rats is blocked by haloperidol or spiroperidol, but is not affected by α or β adrenergic antagonists, except in toxic doses (Fitzsimons and Setler, 1975). Intracranial injection of 6-hydroxydopamine also reduces the drinking response to angiotensin (Fitzsimons and Setler, 1975). This is evidence for dopamine involvement in the dipsogenic action of angiotensin.

In this study, we investigate the actions of a range of neuroleptics and some other drugs on drinking induced by the injection of angiotensin into the lateral ventricles of conscious rats. Our experiments were to further investigate the possible involvement of dopamine in the dipsogenic action of angiotensin, and to evaluate the possible usefulness of angiotensin drinking response in the study of neuroleptic drugs.

To study the specificity of the response, we have also tested the effects of some of the same drugs on the dipsogenic action of carbachol.

Materials and Methods

Stainless steel cannulae (obtained from David Kopf) were implanted unilaterally into the lateral ventricles of male Wistar rats (about 200 g) under pentobarbitone anaesthesia. The cannulae had barrels 3.7 mm long and were implanted at coordinates A 6.2, L 1.5, and H +1.7, according to the atlas of König and Klippel (1963). After recovery the animals were housed individually with free access to food and water. The rats were not used for experiments for at least 7 days after the operation.

Angiotensin or carbachol were injected into the lateral ventricles in volumes of 1–5 μl of sterile 0.9% NaCl. Immediately after injection the rats were returned singly to their home cages, which contained food and a measured amount of water. The amount of water drunk in the 30 min (angiotensin) or 60 min (carbachol) period after injection was determined by weighing.

The effect of neuroleptics or other drugs on the responses to the two dipsogens was studied by either injecting the drugs i.p. (15 min before injection of dipsogen) or by injecting the drugs in a volume of 1–4 μl into the cannula 15 min before injection of angiotensin or carbachol.

The following drugs were used: angiotensin II, carbachol HCl, haloperidol, pimozide, cis-flupenthixol, trans-flupenthixol, clozapine, sulpiride, chlorpromazine, metoclopramide, fluphenazine, atropine sulphate, and Sar⁺Thr⁺Ang II.

All drugs were injected in 0.9% NaCl except haloperidol (lactic acid 1 mg/ml), pimozide (tartaric acid 1 mg/ml), and clozapine (10% ethanol). The pH of all solutions was suitably adjusted to pH 6–6.5. In most cases the animals were used more than once. At least 2 days were left between injections of dipsogen. After the animals had received doses of neuroleptic or other potential antagonists, they were retested with either angiotensin or carbachol alone, to ensure satisfactory response before further doses of antagonist.

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Fig. 1. Dose-response relationships for the dipsogenic actions of angiotensin (○—○) and carbachol (O—O). Each point is the mean of 7–35 observations. SEMs are indicated. Ordinate, amount of water drunk (ml)

Results

As previously reported, angiotensin produces a rapid drinking response. The animals commenced drinking within 2 min of injection and drinking was usually completed within 20 min. The threshold dose for angiotensin was about 2 pmol. The maximum response was produced by 1 nmol angiotensin. At the highest dose of angiotensin the mean amount of water drunk was 21.3 ± 0.9 (SEM) ml (mean of 10 injections in 10 rats). Rats injected with an equal volume of 0.9 % NaCl drank 0.7 ± 0.1 ml (n = 41) during the same period. The dose-response relationships for angiotensin-induced drinking are shown in Fig. 1.

Drinking was also induced by the intracerebroventricular injection of carbachol, although the time course of the response was quite different from that for angiotensin. Following carbachol injections there was a delay of 6–31 min before drinking commenced, and the response lasted for up to 60 min after injection. The dose-response relationships for carbachol-induced drinking (Fig. 1) show that angiotensin is considerably more active than carbachol.

Effect on the Drinking Response of Drugs Injected i. p.
The neuroleptics haloperidol, fluphenazine or cis-flupenthixol, injected i.p. 15 min before injection of dipsogen, reduced the drinking response produced by intracerebroventricular injection of 200 pmol angiotensin. However, these drugs also reduced drinking induced by carbachol (1080 pmol). Trans-flupenthixol had no effect on drinking produced by either angiotensin or carbachol. The results are summarized in Table 1.

Effect on the Drinking Response of Drugs Injected Intracerebroventricularly. In these experiments, drugs were injected into the cannulae 5 or 15 min before the rats received injections of angiotensin (200 pmol) or carbachol (1080 pmol). The angiotensin antagonist Sar\textsuperscript{1}Thr\textsuperscript{9}Ang II (200 pmol) was a potent antagonist of angiotensin-induced drinking, causing 98.7 ± 1.2 % (n = 6) inhibition of the response when injected 5 min before angiotensin. The same dose of Sar\textsuperscript{1}Thr\textsuperscript{9}Ang II had little effect on carbachol-induced drinking (six experiments). The dipsogenic action of carbachol was, however, almost completely abolished (96 % inhibition) by intracerebroventricular injection of 3.5 nmol atropine, a dose which caused only 15.4 ± 2.3 % (n = 6) inhibition of angiotensin-induced drinking.

Confirming the results of Fitzsimons and Setler (1975), haloperidol was found to be potent inhibitor of angiotensin-induced drinking. The dose-response characteristics for haloperidol inhibition of the angiotensin response (Fig. 2) show that haloperidol has the properties of a surmountable inhibitor of this response. The dose of haloperidol (calculated from the dose response curve) causing 50 % inhibition of response to angiotensin was 32.3 nmol. The typical neuroleptics pimozide, fluphenazine, cis-flupenthixol and chlorpromazine were also potent antagonists of angiotensin-induced drinking. Sulpiride, regarded as an atypical neuroleptic, was similarly a potent antagonist of angiotensin-induced drinking. Clozapine and metoclopramide inhibited the angiotensin response, but relatively high concentrations were required. The intracerebroventricular injection of 2 μl of tartaric acid solution (the

### Table 1. Inhibition of the drinking response to angiotensin and carbachol by the i. p. injection of neuroleptics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (μmol/kg)</th>
<th>% Inhibition of the dipsogenic response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Angiotensin</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>0.19</td>
<td>4.0 ± 2.3</td>
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<tr>
<td></td>
<td>0.95</td>
<td>62.9 ± 12.4</td>
</tr>
<tr>
<td></td>
<td>1.9</td>
<td>55.1 ± 4.3</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>1.9</td>
<td>64.6 ± 8.1</td>
</tr>
<tr>
<td>Cis-flupenthixol</td>
<td>1.9</td>
<td>44.9 ± 7.6</td>
</tr>
<tr>
<td>Trans-flupenthixol</td>
<td>1.9</td>
<td>Active</td>
</tr>
</tbody>
</table>

Results are expressed as a % inhibition (± SEM) of the responses produced by angiotensin II (200 pmol) and carbachol (1080 pmol). = not tested