Mechanism responsible for epileptogenic activity by first-generation H1-antagonists in rats

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Abstract

In the present study, we have demonstrated that multiple first-generation H1-antagonists caused behavioral and EEG seizures in rats. The epileptogenic property of pyrilamine was more potent than either chlorpheniramine or diphenhydramine. In contrast, the second-generation H1-antagonists, loratadine and ebastine did not induce detectable epileptogenic activity. Intraperitoneal injection of histidine inhibited the EEG seizures induced by pyrilamine, diphenhydramine or chlorpheniramine; however no antagonism was observed with physostigmine. These results clearly suggest that the epileptogenic activity of first-generation H1-antagonists is dependent upon a centrally acting histaminergic mechanism.

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First-generation H1-antagonists, such as diphenhydramine and chlorpheniramine, induce diminished alertness, slowed reaction time and somnolence [3]. In animal models, these drugs also cause decreased locomotor activity [12], inhibition of active avoidance responses [6], inhibition of climbing tests [9], and potentiation of thiopental-induced sleep [12]. In addition, first-generation H1-antagonists increase the EEG power spectra of the delta and theta bands, indicating that these drugs cause sedative and EEG slowing effects [7,10]. However, high doses of diphenhydramine, promethazine and pyrilamine, produced convulsions in epileptic patients and young children [15]. In animal studies, Scherkl et al. [11] reported that treatment with dimethindene and promethazine decreases electrically-induced maximal seizure thresholds. Recently, Yokoyama et al. [14] demonstrated that centrally acting H1-antagonists promote the development of amygdala kindling in rats. The present study was undertaken to clarify the epileptogenic activity of first-generation H1-antagonists delivered intravenously in rats. We examined the mechanism responsible for the generation of epileptogenic activity by the first-generation H1-antagonists using histidine and physostigmine.

Seven to eight-week-old male Wistar strain rats (Nippon SLC, Shizuoka, Japan), weighing 200–250 g, were maintained in an air-conditioned room controlled for temperature (24±2°C) and humidity (55±15%). Animals were given food and water ad libitum. Under pentobarbital anesthesia (35 mg/kg i.p., Nembutal®, Abbott Laboratories, North Chicago, IL, USA), bipolar electrodes were implanted into the right frontal cortex (A: 6.9, L: 3.0) according to the atlas of de Groot [4] after the animals were fixed to a stereotaxic apparatus. Cortical electrodes, made of stainless steel screws (1.0 mm in diameter and 1.5 mm in length), were inserted into the skull over the motor area. Electrodes were connected to a miniature receptacle, which was embedded into the skull with dental cement [13]. Post-surgical recovery time was a minimum of 2 weeks.

Behavioral seizures and EEG changes (Fig. 1) induced by the drugs were estimated by the scoring system shown in Table 1. Diphenhydramine hydrochloride (Sigma, St. Louis, MO, USA), pyrilamine maleate (Sigma), d-chlorpheniramine maleate (Sigma), loratadine (Janssen Kyowa,
Fig. 1. Example of EEG seizure induced by H1 antagonists. (a) Control; (b) spike & wave complex with short duration (within 60 s) score 1 in Table 1; (c) spike & wave complex with long duration (more than 60 s) score 3 in Table 1.

Tokyo, Japan), ebastine (Dainippon, Osaka, Japan), L-histidine hydrochloride monohydrate (Wako, Osaka, Japan) and physostigmine (Sigma) were used in these studies. H1-antagonists were injected intravenously. Histidine and physostigmine were injected intraperitoneally. All procedures involving animals were conducted in accordance with the guidelines of the Animal Care and Use Committee, Faculty of Pharmaceutical Sciences, Okayama University. The data are expressed as a mean±S.E.M. The ANOVA and Kruskal–Wallis tests were used for assessing significant effects on both behavioral and EEG seizures.

Table 2 shows the epileptogenic activity induced by intravenous injection of H1-antagonists. Diphenhydramine caused convulsive behavior in a dose-dependent manner at doses of 10 and 20 mg/kg. Spiking activity on the EEG was observed after treatment with diphenhydramine at a dose of 20 mg/kg. Pyrilamine induced significant convulsive behavior and EEG seizure at doses of 10 and 20 mg/kg. Chlorpheniramine also elicited significant epileptogenic activity at a dose of 20 mg/kg: both convulsive behavior and EEG seizure were observed. The second-generation H1-antagonists, loratadine and ebastine, did not induce convulsive behavior and EEG seizure even at a dose of 20 mg/kg. Table 3 shows the effects of histidine and physostigmine on epileptogenic activity induced by intravenous injection of first-generation H1-antagonists. Histidine (1,500 mg/kg, i.p.) antagonized the convulsive behavior and EEG seizure induced by diphenhydramine

Table 1
Scoring system used for estimation of seizure intensity

<table>
<thead>
<tr>
<th>Score</th>
<th>Behavior</th>
<th>EEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>no convulsion</td>
<td>no change</td>
</tr>
<tr>
<td>1</td>
<td>agitation</td>
<td>spike &amp; wave complex with short duration (within 60 s)</td>
</tr>
<tr>
<td>2</td>
<td>head nodding</td>
<td>spike &amp; wave complex with short duration (within 60 s) appearing 2–4 times</td>
</tr>
<tr>
<td>3</td>
<td>forelimbs clonus</td>
<td>spike &amp; wave complex with long duration (more than 60 s)</td>
</tr>
<tr>
<td>4</td>
<td>generalized convulsion</td>
<td>spike &amp; wave complex with long duration (more than 60 s) appearing 2–4 times</td>
</tr>
<tr>
<td>5</td>
<td>jumping and violent convulsion</td>
<td>spike &amp; wave complex with long duration (more than 60 s) appearing more than 5 times</td>
</tr>
</tbody>
</table>

Table 2
Epileptogenic activity induced by intravenous injection of certain H1-antagonists

<table>
<thead>
<tr>
<th>Drugs (mg/kg)</th>
<th>Behavior</th>
<th>EEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>0.00±0.00</td>
<td>0.00±0.00</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>0.25±0.16</td>
<td>0.25±0.16</td>
</tr>
<tr>
<td>Pyrilamine</td>
<td>0.13±0.13</td>
<td>0.13±0.58 **</td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>0.00±0.00</td>
<td>0.00±0.00</td>
</tr>
<tr>
<td>Loratadine</td>
<td>0.00±0.00</td>
<td>0.00±0.00</td>
</tr>
<tr>
<td>Ebastine</td>
<td>0.00±0.00</td>
<td>0.00±0.00</td>
</tr>
</tbody>
</table>

* Each value represents the mean S.E.M. of 7–8 rats.
* P<0.05, ** P<0.01 as compared with saline treated group.
In addition, although both compounds have potent peripheral antihistaminic activity [1,13], they only slightly inhibit the specific binding of $^3$H-pyrilamine in guinea pig cortex in vitro [1,2]. There are many reports that histamine has an anticonvulsant effect acting through H1 receptors. For example, histamine inhibits electroshock seizures in mice [15] and kindling effects in rats [5]. In addition, Haas and Woef reported that histamine acts on neurons in the rat cerebral cortex [16]. In the present study, we demonstrate that the epileptogenic activity by first-generation H1-antagonists is inhibited by histidine, but not by physostigmine. These results suggest that the induction of epileptogenic activity by first-generation H1-antagonists is dependent upon central histaminergic receptors. The epileptogenic activity of chlorpheniramine is also antagonized by histidine, but at smaller doses than those necessary for inhibiting the effects of pyrilamine or diphenhydramine. At present, however, the mechanism governing chlorpheniramine’s susceptibility to histidine antagonism remains unclear. Histidine may lower the affinity of the interaction between chlorpheniramine and its receptor. In contrast, the epileptogenic activity of the H1-antagonists used in this study was not antagonized by physostigmine even at a dose of 0.05 mg/kg. We have found that the EEG sedative patterns induced by H1-antagonists were inhibited by physostigmine at a dose of 0.002 mg/kg. These results suggest that there is no connection between the EEG sedative effects and the epileptogenic activity of H1-antagonists.

### References


