Influence of Pyrazine Derivatives on the Day of Vaginal Opening in Juvenile Female Rats

Kenji YAMADA, Ryoichi ITOH and Akihiro OHTA
Laboratory for Pharmaceutical Education, Department of Pharmacognosy, Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan
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Abstract—Effects of pyrazine derivatives on the day of the first opening of the vagina in juvenile female rats were studied. Tetraethyl and 2,5-dimethyl pyrazine caused a significant delay in the first vaginal opening day of juvenile female rats, but no delay was noted in the case of 2,5-diethyl or triethyl pyrazine. These results suggest that tetraethyl and 2,5-dimethyl pyrazine cause delays in the onset of puberty in juvenile female rats.

The biological action of pyrazine derivatives has been reported in connection with serotonergic action (1), anti-dopaminergic action (2) and acceleration or delay in the time of sexual maturation in female mice (3-6). Furthermore, alkyl pyrazine derivatives are known to be pheromones in ants (7). Novotny and coworkers (8) have reported 2,5-dimethyl pyrazine to be present in the adrenal gland of mice. Drickamer et al. (9, 10) have recently shown that adrenalectomy but not ovariecotmy eliminates the biological activity of excreted urine toward delay in the puberty of juvenile mice. In view of these reports, we decided to examine the influence of various synthesized pyrazine derivatives on the vaginal opening day in juvenile female rats.

Wistar strain immature female rats, 18 days old were obtained from the Saitama Experimental Animal Company. The present experiment was carried out after housing the animals for 3 days. The females were housed in a controlled environment (22±2°C, 53±3% humidity, lights on 6:30 a.m.-6:30 p.m., food and water available ad libitum). The control and experimental groups contained 10 rats each. The pyrazine derivatives used were 2,5-diethyl pyrazine, triethyl pyrazine, tetraethyl pyrazine and 2,5-dimethyl pyrazine, and they were all synthesized at our laboratory. One hundred mg/kg of each derivative were suspended in 10% ethanol and administered subcutaneously once daily to each rat in the experimental group. The control group received only the vehicle (10% ethanol). The administrations were continued until the first indication of vaginal opening in the juvenile female rats.

In Table 1 are listed the effects of pyrazine derivatives on the vaginal opening day in juvenile female rats. The day of this event was not influenced by the vehicle alone. Tetraethyl pyrazine and 2,5-dimethyl pyrazine caused a significant delay, while no such effect was noted for 2,5-diethyl pyrazine or triethyl pyrazine. Rather, these two compounds (2,5-diethyl or triethyl pyrazine) caused the vaginal opening day to come sooner.

Body weight did not change during the period of the administration of any drug, nor did tetraethyl pyrazine or 2,5-dimethyl pyrazine have any influence on ovary and uterus weight. It has been established that one pyrazine derivative is a naturally occurring pheromone in the excreted urine of rodents, and it has been identified as 2,5-dimethyl pyrazine by gas-phase analysis (8). In the present study, 2,5-dimethyl pyrazine was also found to delay the vaginal opening day. The relationship of the structures of the ethyl and methyl groups with their biological activity for affecting the day of vaginal opening could not be clearly determined. From the present data, tetraethyl pyrazine and 2,5-dimethyl pyrazine may possibly effect the gonadotrophin releasing hormone or gonadotropic hormone is
Table 1. Effects of alkyl pyrazine on first opening day of vagina, body weight, ovary weight and uterus weight in juvenile female rats

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean day to reach first opening of vagina</th>
<th>Body weight (g/rat)</th>
<th>Ovary weight (mg/ovary)</th>
<th>Uterus weight (mg/uterus)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>40.2±0.46</td>
<td>148.2±2.32</td>
<td>22.5±2.64</td>
<td>266.6±6.42</td>
</tr>
<tr>
<td>Vehicle</td>
<td>40.3±0.67</td>
<td>150.9±5.68</td>
<td>20.1±2.24</td>
<td>270.0±10.15</td>
</tr>
<tr>
<td>2,5-Diethyl pyrazine</td>
<td>39.1±0.54</td>
<td>149.8±6.12</td>
<td>24.2±1.17</td>
<td>282.6±10.94</td>
</tr>
<tr>
<td>Triethyl pyrazine</td>
<td>39.7±0.86</td>
<td>149.0±5.37</td>
<td>23.4±3.15</td>
<td>267.0±9.66</td>
</tr>
<tr>
<td>Tetraethyl pyrazine</td>
<td>43.2±0.66**</td>
<td>148.4±4.86</td>
<td>20.8±2.46</td>
<td>266.4±8.75</td>
</tr>
<tr>
<td>2,5-Dimethyl pyrazine</td>
<td>42.2±0.61*</td>
<td>147.7±7.45</td>
<td>21.4±2.15</td>
<td>254.9±13.31</td>
</tr>
</tbody>
</table>

Pyrazine derivatives were administered once daily until the first indication of vaginal opening in juvenile female rats. Each value is the mean±S.E. for 10 rats. The significance of the difference from the vehicle was assessed statistically using the two-tailed Student's t-test (*P<0.05, **P<0.01).

released from the hypothalamic-pituitary in juvenile female rats.

References