Veratramine-Induced Behavior Associated with Serotonergic Hyperfunction in Mice

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ABSTRACT—The administration of veratramine produced generalized tremor, myoclonus, hindlimb abduction, backward gait and Straub tail, similar to the “5-hydroxytryptamine (5-HT) syndrome”, in mice. Pretreatment with metergoline, methysergide, mianserin or cyproheptadine ameliorated veratramine-induced myoclonus and tremor. For suppression of other symptoms, mianserin and cyproheptadine were effective. Metergoline improved hindlimb abduction and Straub tail, but did not inhibit backward gait. Methysergide was ineffective for the remaining symptoms. 5-Methoxy-N,N-dimethyltryptamine (5-MeODMT) enhanced all these symptoms except for Straub tail. 8-Hydroxy-2-[di-n-propylamino] tetralin hydrobromide (8-OH-DPAT) augmented tremor, hindlimb abduction and backward gait, but did not influence myoclonus and Straub tail. 5-Methoxy-3[1,2,3,6-tetrahydropyridin-4-yl] 1H-indole (RU 24969) did not modify the symptoms. Destruction of 5-HT neurons using 5,6-dihydroxytryptamine (5,6-DHT) resulted in suppression of the syndrome. The denervation supersensitivity caused by 5,6-DHT did not increase the response to veratramine. These findings indicate that part of the site of action of veratramine may be the presynaptic 5-HT neurons.

Veratramine, a secondary amine of veratrum alkaloids (Fig. 1), has been shown to produce generalized tremor and unique excitation expressed as “struggling” with intermittent epileptic rolling-over and vocalization in rodents (1, 2). Subsequent studies revealed that the struggling behavior is rapid, repetitive, and persistent myoclonic movements of the four extremities (3). The behavioral changes following administration of the veratrum alkaloid were not limited to tremor and myoclonus, but included hindlimb abduction, backward gait and Straub tail. Therefore, the symptoms induced by veratramine resemble the “5-hydroxytryptamine (5-HT) syndrome” (4–6). In the previous studies, veratramine-induced tremor and struggling have been demonstrated to be suppressed by methysergide (7), a non-selective 5-HT inhibitor, but not by haloperidol, phenoxybenzamine, or atropine (7, 8). Prior administration of phenytoin or

Fig. 1. Chemical structure of veratramine
morphine was also ineffective (2). The objective of the present study is to investigate the mechanisms of action of veratramine in producing central excitation in mice.

MATERIALS AND METHODS

Animals

Male ddY mice, weighing 40–50 g, were used. Animals were housed at the Institute of Laboratory Animal Sciences, Kagoshima University, at a room temperature of 22–24°C, humidity of 60–70% and lighting from 6:00–18:00.

Drug preparation and administration

Veratramine was dissolved in 0.1 N HCl, and the solution was diluted with distilled water. Mianserin, metergoline, 8-OH-DPAT and RU 24969 were dissolved in 0.9% saline solution. 8-OH-DPAT and RU 24969 were injected s.c., and the other drugs were administered i.p. Methysergide was injected 30 min prior to s.c. administration of veratramine in a dose of 3 mg/kg, equivalent to the ED₉₉ for myoclonus and tremor. Metergoline, mianserin or cyproheptadine was given 60, 120 or 120 min, respectively, prior to the veratramine injection. 5-MeODMT, 8-OH-DPAT or RU 24969 was injected 5 min before the administration of veratramine in a dose of 1.6 mg/kg, corresponding to the ED₅₀ for myoclonus.

Behavioral observation

Behavioral experiments were performed between 10:00 a.m. and 4:00 p.m. by one observer. Mice were examined for their behavior in an individual circular plastic cage (26 cm in diameter and 13 cm in height). After injection of veratramine, symptoms such as myoclonus, tremor, hindlimb abduction, backward gait and Straub tail were scored by the slightly modified method of Dickinson and Curzon (9), and they were recorded individually every 2 min for 30 min. Myoclonus, tremor, and hindlimb abduction were scored on a 0–4 rating scale: 0, absent; 1, equivocal or present a few times; 2, weak or several times; 3, moderate or frequent; and 4, marked or continuous. Backward gait and Straub tail were assessed on a 0–3 scale: 0, absent; 1, perceptible or present a few times; 2, moderate or several times; and 3, marked or frequent.

5,6-DHT treatment

5,6-DHT dissolved in 0.9% saline containing 0.02% ascorbic acid was injected into the lateral ventricle (injection needle point: 1.5 mm rostral and 1.0 mm lateral from the bregma), under light anesthesia with ether. A noradrenergic neuron protective agent was not used in this experiment (10, 11). Behavioral observation was carried out either on the 2nd day after the injection of 5,6-DHT (20 μg/2 μl, unilateral injection) or on the 14th day after the double injections of 5,6-DHT (25 μg/2 μl × 2, bilateral injection). Control mice received vehicle solution in the same volume as 5,6-DHT-treated animals. Denervation supersensitivity was checked functionally with the appearance of head twitches following the injection of 5-MeODMT (2.5 mg/kg, i.p.) (12, 13). The number of head twitches was counted every 2 min over a period of 12 min. Veratramine was administered at the ED₉₉ dose of 3.0 mg/kg when investigating the effects of 5,6-DHT on the action of veratramine on the 2nd day following the 5,6-DHT injection. To examine the effect of denervation supersensitivity produced by 5,6-DHT, veratramine was administered in an ED₅₀ of 1.6 mg/kg.

Measurement of 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) contents

This experiment was done between 9:00 and 12:00, since the amines show a circadian rhythm. 5-HT and 5-HIAA content of the whole brain was determined by the following method at each time of the experiment after 5,6-DHT injection. The brain was removed on a saline-ice plate, and the samples were immediately frozen and stored on dry ice until the monoamine assay was carried out; the assay was started within 12 hr. The tissue sample was homogenized in 0.1 M perchloric acid solution containing 0.1 M EDTA-2Na and 3,4-
dihydroxy-benzylamine (30 mg/ml), using a Polytron homogenizer (setting 6 for 10 sec; Kinematical), and centrifuged at 25,000 × g for 20 min (Kubota 20000). The supernatant was filtered through a membrane filter (FR-20, 0.2 μm, 13 mm; Fuji Photo Film Co., Tokyo), and a 10 μl aliquot of the filtered solution was analyzed by high performance liquid chromatography (HPLC; Bioanalytical System, Inc.). The HPLC system was composed of a reverse phase column (Spherisorb ODS-II, 250 mm × 4.6 mm) packed with 5 μm of Wakopak™ and an electrochemical detector (LC-4B amperometric detector) set at a potential of 0.8 V. The mobile phase consisting of a 0.15 M monochloroacetate buffer (pH 3.0) that contained 2 mM EDTA-2Na, 0.01% sodium octyl sulfate and 10% methanol was delivered with a flow rate of 1 ml/min.

Chemicals
5-MeODMT, 5,6-DHT and cyproheptadine hydrochloride were purchased from Sigma Chemical Co. (St. Louis, MO); mianserin hydrochloride and 8-OH-DPAT, from Research Biochemicals, Inc. (Wayland, MA); methysergide maleate, from Sandoz, Ltd. (Basel); and veratramine, from Aldrich Chemical Co.

Fig. 2. Effects of various drugs affecting serotonergic function on veratramine-induced myoclonus in mice. Mice were treated with methysergide (5 △ or 10 ▲ mg/kg) for 30 min and with metergoline (5 △ or 10 ▲ mg/kg), mianserin (10 △ or 20 ▲ mg/kg) or cyproheptadine (10 △ or 20 ▲ mg/kg) for 120 min, prior to administration of veratramine (3.0 mg/kg). Control animals received vehicle solution (○) for each drug pretreatment. All pretreatments had significant effects by two-way analysis of variants, with P < 0.01 for metergoline (10–20 mg/kg), methysergide (5–10 mg/kg) and mianserin (20 mg/kg) and P < 0.05 for cyproheptadine (10–20 mg/kg) and mianserin (10 mg/kg). In another series of experiments, mice were treated with 5-MeODMT (10 mg/kg, □), 8-OH-DPAT (5.0 mg/kg, ▼), RU 24969 (5.0 mg/kg, ○) or vehicle solution (○) for each drug, 5 min before the injection of a lesser amount of veratramine (1.6 mg/kg). In each case, another set of controls received the pretreatment drug and a vehicle solution (0.9% saline containing 0.1 N HCl) rather than veratramine (△). 8-OH-DPAT and RU 24969 were injected s.c., and the other drugs were administered i.p. A difference (P < 0.01) between the groups treated with veratramine with or without a pretreatment (○ vs. □) was only obtained with 5-MeODMT (10 mg/kg). Each point represents a mean score of 10 animals.
(London). Metergoline was donated by Farmitalia (Milan). RU 24969 was a gift from Dr. P. Hunt, Roussel UCLAF, Romainville, France.

Statistical analysis

Statistical analysis was done by one-way or two-way analysis of variance.

RESULTS

Effects of 5-HT agonists and antagonists on veratramine-induced involuntary movements

All 5-HT antagonists tested significantly suppressed myoclonus and tremor induced by the ED99 of veratramine (3.0 mg/kg), although the mode and magnitude of suppression were not equal for these compounds (Figs. 2 and 3). For example, metergoline, a non-selective 5-HT antagonist, and mianserin, a 5-HT2 antagonist, decreased markedly the score of both myoclonus and tremor in a dose-dependent fashion, whereas methysergide or cyproheptadine, both non-selective 5-HT antagonists, suppressed myoclonus markedly or moderately but only ameliorated tremor slightly.

Prior administration of 5-HT agonists, however, had varying effects on veratramine-induced myoclonus and tremor in mice (Figs. 2 and 3). 5-MeODMT, a non-selective 5-HT agonist, clearly intensified both myoclonus and tremor produced by an ED50 of veratramine (1.6 mg/kg), while 8-OH-DPAT, a 5-HT1A agonist, slightly potentiated the tremor intensity and was without effect on myoclonus; RU 24969, a 5-HT1B agonist, which shows some 5-HT1A activity, was ineffective on these movements.

In studies to investigate the effects of 5-HT agonists on veratramine-induced hindlimb abduction, Straub tail and backward gait, scores for the last two symptoms in animals given saline plus veratramine varied somewhat.

![Fig. 3. Effects of various drugs affecting serotonergic function on veratramine-induced tremor in mice. Mice were treated as described in Fig. 2. Significant differences (P < 0.01) between animals given veratramine with and without drug pretreatment were obtained with 5-MeODMT (10 mg/kg), 8-OH-DPAT (5 mg/kg), metergoline (10–20 mg/kg), methysergide (5–10 mg/kg), mianserin (5–10 mg/kg) and cyproheptadine (10–20 mg/kg) by two-way analysis of variance. Each point represents a mean score of 10 animals.](image-url)
in each experiment, although the variation was only significant (P < 0.05) between two of these control groups in backward gait (Table 1). The variation was probably due to the relatively low dose of veratramine (1.6 mg/kg) used. Prior administration of 5-MeODMT or 8-OH-DPAT enhanced veratramine-induced hindlimb abduction and backward gait significantly, but Straub tail was not influenced by these agonists. RU 24969 did not modify any of these symptoms. Among the 5-HT antagonists, cyproheptadine and mianserin inhibited all these symptoms, although the magnitude of suppression was not equal (Table 2). Metergoline attenuated hindlimb abduction and Straub tail. Backward gait was not improved. Pre-

### Table 1. Effects of 5-HT agonists on hindlimb abduction, Straub tail and backward gait induced by veratramine in mice

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hindlimb abduction</th>
<th>Straub tail</th>
<th>Backward gait</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-MeODMT + Saline</td>
<td>37.2 ± 2.4</td>
<td>0.0 ± 0.0</td>
<td>2.8 ± 0.9</td>
</tr>
<tr>
<td>Saline + Veratramine</td>
<td>22.0 ± 1.6</td>
<td>11.5 ± 2.5</td>
<td>4.9 ± 0.9</td>
</tr>
<tr>
<td>5-MeODMT + Veratramine</td>
<td>44.7 ± 3.0**</td>
<td>6.5 ± 1.6</td>
<td>27.4 ± 3.0**</td>
</tr>
<tr>
<td>8-OH-DPAT + Saline</td>
<td>8.6 ± 1.3</td>
<td>5.5 ± 1.1</td>
<td>1.1 ± 0.4</td>
</tr>
<tr>
<td>Saline + Veratramine</td>
<td>22.2 ± 3.4</td>
<td>17.3 ± 2.3</td>
<td>10.3 ± 2.0</td>
</tr>
<tr>
<td>8-OH-DPAT + Veratramine</td>
<td>36.7 ± 1.3*</td>
<td>20.5 ± 1.8</td>
<td>14.4 ± 1.4*</td>
</tr>
<tr>
<td>RU 24969 + Saline</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
</tr>
<tr>
<td>Saline + Veratramine</td>
<td>20.3 ± 3.0</td>
<td>15.0 ± 1.8</td>
<td>5.5 ± 1.3</td>
</tr>
<tr>
<td>RU 24969 + Veratramine</td>
<td>23.9 ± 2.7</td>
<td>15.9 ± 1.3</td>
<td>4.0 ± 1.0</td>
</tr>
</tbody>
</table>

Mice were treated with 5-MeODMT (10 mg/kg), 8-OH-DPAT (5.0 mg/kg), RU 24969 (5.0 mg/kg) or vehicle solution for each drug, 5 min before the injection of a lesser amount of veratramine (1.6 mg/kg). Values represent the mean total score ± S.E. of 10 animals. *P < 0.05, **P < 0.01, as compared to saline + veratramine.

### Table 2. Effects of 5-HT antagonists on hindlimb abduction, Straub tail and backward gait induced by veratramine in mice

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (mg/kg)</th>
<th>Hindlimb abduction</th>
<th>Straub tail</th>
<th>Backward gait</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metergoline</td>
<td>0</td>
<td>40.3 ± 1.5</td>
<td>27.1 ± 1.4</td>
<td>7.5 ± 0.3</td>
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<tr>
<td></td>
<td>5</td>
<td>30.8 ± 1.8**</td>
<td>19.9 ± 1.9**</td>
<td>6.1 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>31.1 ± 2.3**</td>
<td>21.1 ± 2.2**</td>
<td>5.2 ± 1.1</td>
</tr>
<tr>
<td>Methysergide</td>
<td>0</td>
<td>35.0 ± 1.3</td>
<td>26.1 ± 1.0</td>
<td>8.3 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>31.6 ± 2.7</td>
<td>25.4 ± 1.6</td>
<td>6.7 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>28.4 ± 2.7</td>
<td>22.5 ± 1.4</td>
<td>5.1 ± 1.0</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>0</td>
<td>38.0 ± 2.4</td>
<td>26.3 ± 1.6</td>
<td>5.0 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>32.6 ± 2.7*</td>
<td>21.5 ± 1.5*</td>
<td>3.8 ± 0.5*</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>31.3 ± 2.3*</td>
<td>21.9 ± 1.8**</td>
<td>2.7 ± 0.4**</td>
</tr>
<tr>
<td>Mianserin</td>
<td>0</td>
<td>41.4 ± 1.5</td>
<td>28.9 ± 1.5</td>
<td>6.6 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>31.9 ± 4.1*</td>
<td>24.0 ± 2.8*</td>
<td>2.8 ± 0.7***</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>25.5 ± 4.2*</td>
<td>18.5 ± 2.9**</td>
<td>1.7 ± 0.5**</td>
</tr>
</tbody>
</table>

The scoring and method are the same as described in Table 1. Mice were treated with veratramine in a dose of 3.0 mg/kg. Values represent the mean total score ± S.E. of 10 animals. *P < 0.05, **P < 0.01, as compared to each control.
treatment with methysergide did not significantly lessen these symptoms.

**Effects of 5,6-DHT on veratramine-induced myoclonus**

To ascertain whether veratramine acts on presynaptic or postsynaptic 5-HT neurons, we examined behavioral responses to veratramine in animals with 5,6-DHT-induced lesions of the presynaptic neurons, with and without denervation supersensitivity of 5-HT receptors. On the 2nd day following intraventricular injection of 20 µg of 5,6-DHT, the 5-HT content of the whole brain was reduced to 83% of the control value (830 ± 88 vs. 1000 ± 19 ng/g wet tissue, n = 10 for each group, P < 0.01). 5-HIAA content was not reduced. Under these conditions, the score for myoclonus induced by veratramine (3.0 mg/kg) was lower than that in control animals that had been pretreated with vehicle solution (Fig. 4).

On the 14th day following double injections of 5,6-DHT (25 µg × 2, i.v.t.), the 5-HT content of the whole brain was reduced to 68% of the control value (742 ± 25 vs. 925 ± 18 ng/g tissue, n = 10 for each group, P < 0.01). 5-HIAA content was also decreased to 80% of the control level by the treatment (411 ± 22 vs. 489 ± 24 ng/g tissue, n = 10 for each group, P < 0.01). Injection of 5-MeODMT (2.5 mg/kg, i.p.) into mice caused head twitching, a functional marker for 5-HT receptor function. The number of head twitches, counted in 2-min periods for a total of 12 min, was markedly increased in animals injected with 5,6-DHT (Fig. 4), indicating that denervation supersensitivity developed on the 14th day following the 5,6-DHT injection.

![Fig. 4. Effects of 5,6-DHT on veratramine-induced myoclonus in mice. Two groups of mice were prepared and treated intraventricularly with 5,6-DHT in a dose of 20 µg or 25 µg × 2, respectively. The 1st group was injected with 3 mg/kg of veratramine on the day following 5,6-DHT treatment, and the 2nd group was injected with 1.6 mg/kg of veratramine on the 14th day. The intensity score of myoclonus induced by the veratrum alkaloid was measured every 2 min for 30 min. The total score shows the sum total score of the mean value of each animal obtained during the observation period. The supersensitivity of 5-HT receptors was functionally checked on the 14th day following the injection of 5,6-DHT (25 µg × 2) by counting the number of head-twitches induced by 5-MeODMT (2.5 mg/kg) every 2 min for 12 min. Results are expressed as the mean ± S.E. (vertical bar) of the vehicle solution (open column) and 5,6-DHT (hatched column) treated mice, * P < 0.05, ** P < 0.01.](image-url)
amount of myoclonus induced by veratramine in a dose of 1.6 mg/kg (ED₅₀) seen in the 5,6-DHT-treated animals on the 14th day was not significantly different from that induced in unlesioned animals.

**DISCUSSION**

The present behavioral study revealed that serotonin agonists and antagonists had generally opposite effects on veratramine-induced movement disorders in mice. However, we were not able to clearly specify which subtype of 5-HT receptors was involved for each symptom. Myoclonus, for example, was markedly suppressed by metergoline (5-HT₂, 5-HT₃, 5-HT₁D antagonist), methysergide (5-HT₂, 5-HT₁C antagonist), mianserin (5-HT₂ antagonist) and moderately suppressed by cyproheptadine (5-HT₂, 5-HT₁ antagonist). Administration of 8-OH-DPAT (5-HT₁A agonist) or RU 24969 (5-HT₁B, 5-HT₁A agonist) failed to alter the symptom induced by veratramine. Among the 5-HT₂ related antagonists used in the present study, metergoline and methysergide have been shown to possess a high affinity to 5-HT₁C receptors and the former also has a high affinity to 5-HT₁D receptors. Considering evidence that the density of 5-HT₂, 5-HT₁C and 5-HT₁D is predominantly higher in the cortex, choroid plexus, and basal ganglia, respectively (14), and numerous papers have indicated that 5-HT₁D receptors appear to be present in cattle, humans, pigs and rats but do not in mice (15-18), 5-HT₁C and 5-HT₁D receptors may not be directly related. Therefore, it could be that veratramine-induced myoclonus of mice may be largely associated with 5-HT₂ receptors. On the other hand, Peroutka et al. reported that the ability to displace specific ³H-spiperone binding from 5-HT₂ receptors in rat frontal cortex and the potency of drugs to inhibit 5-HT induced head twitches were correlated (19). The antagonists study showed antimyoclonic properties of 5-HT₂ receptors (20). Yap and Taylor suggested involvement of 5-HT₂ receptors in the wet-dog shake behavior induced by 5-hydroxytryptophan in the rat (21). These behaviors are similar to the myoclonus induced by veratramine. By contrast, Luscombe et al. demonstrated that in guinea pigs, L-5-hydroxytryptophan-induced myoclonus is mediated by 5-HT₁ receptor in the brainstem (22); and Blackburn et al. reported that 5-HT agonist-induced rotational behavior in the rat was mediated via 5-HT₁ receptors (23). These differences between our results and theirs might be due to the difference in species or region of the brain.

Veratramine-induced tremor, on the other hand, was augmented by 5-MeODMT and 8-OH-DPAT, but not by RU 24969. This effect of 8-OH-DPAT was compatible with the proposed functional correlates of 5-HT receptor subtypes in which tremor might be 5-HT₁A-receptor-mediated (14). From the present behavioral data, we considered that veratramine-induced tremor might also be linked to the 5-HT₂ receptor, since the tremor was greatly inhibited by metergoline and mianserin. Methysergide and cyproheptadine had only a weak inhibitory action against tremor. These compounds have been shown to be a 5-HT₂ agonist with the properties of a 5-HT₁A-like partial agonist (24). Therefore, the integrated effect, which is mild against tremor, may be attributable to the possible interaction of neuronal effects at different receptors.

Hindlimb abduction and backward gait were enhanced by 5-MeODMT and 8-OH-DPAT and attenuated by mianserin and cyproheptadine. The pretreatment with metergoline was also effective in improving veratramine-induced hindlimb abduction but did not affect backward gait, although there was a tendency toward suppressing this symptom. From these data, it appears that the related receptors for hindlimb abduction may be 5-HT₂ and 5-HT₁A. The relevance of the 5-HT₂ receptor to hindlimb abduction has been previously suggested (25). The involvement of 5-HT₁A receptor in the induction of hindlimb abduction as well as Straub tail has been stressed, but these behaviors do not seem to be mediated solely by the 5-HT₁A site, as shown by the failure of isapirone, a drug having a high affin-
ity to 5-HT1A receptors, to produce these symptoms (26). It is unclear why metergoline failed to antagonize veratramine-induced backward gait, which contrasted with the results obtained with mianserin and cyproheptadine. This effect may be due to the non-selectivity of metergoline, stimulating different receptor populations. It could be that a variety of symptoms caused by veratramine should be attributable to the integrated neuronal activity in the CNS which may be triggered by the increased serotonergic function. Therefore, each symptom produced by veratramine could be highly dependent upon the localization of excited serotonergic neurons and the concurrent interaction with another neuronal system.

In a 5-HT neuron destruction experiment using 5,7-dihydroxytryptamine (5,7-DHT), it is necessary to use a noradrenergic neuron protective agent, such as desipramine. On the contrary, Baumgarten et al. confirmed that the influence of 5,6-DHT on noradrenergic neuron was negligible in rats (10). Also Berge et al. were able to observe behaviors after injection of 5,6-DHT without pretreatment with desipramine (11). Judging from these reports, 5,6-DHT seems to have less destructive effects on noradrenergic neurons than 5,7-DHT. In the present study, the selective destruction of presynaptic 5-HT neurons by 5,6-DHT resulted in the suppression of the veratramine effects in mice examined on the 2nd day, at a time when denervation supersensitivity does not yet occur, suggesting that the presence of intact presynaptic 5-HT neuron is indispensable for the full response to veratramine. The clearly developed denervation supersensitivity, as determined functionally using 5-MeODMT on the 14th day following the injection of 5,6-DHT, did not increase the score of myoclonus induced by the ED50 of veratramine (1.6 mg/kg). These findings would suggest that the site of action of the veratram alkaloid exists in the presynaptic 5-HT neuron rather than in the postsynaptic receptor sites. The apparent identical response to veratramine on the 14th day between tested and control animals may be speculated to occur as follows: since the content of 5-HT stayed at 68% of the control value on this day, the capacity of the presynaptic storage site to release 5-HT would remain subnormal. Increased synaptic levels of 5-HT resulting from veratramine induced release or reuptake inhibition (27) would stimulate postsynaptic supersensitive receptors, and thus bring the behavioral response to veratramine near control levels. Thus, veratramine may act at presynaptic serotonin neurons and produce 5-HT syndrome in mice.

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