Effects of WAY100635, a selective 5-HT\textsubscript{1A}-receptor antagonist on the micturition-reflex pathway in the rat

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Kakizaki, Hidehiro, Mitsuharu Yoshiyama, Tomohiko Koyanagi, and William C. de Groat. Effects of WAY100635, a selective 5-HT\textsubscript{1A}-receptor antagonist on the micturition-reflex pathway in the rat. Am J Physiol Regulatory Integrative Comp Physiol 280: R1407–R1413, 2001.—5-Hydroxytryptamine (5-HT) receptors in the central nervous system have been implicated in the control of micturition. The present study was undertaken to evaluate the effects of a selective 5-HT\textsubscript{1A}-receptor antagonist [N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridinyl)cyclohexanecarboxamide trihydrochloride (WAY100635)] on the micturition-reflex pathway in urethane-anesthetized female Wistar rats. Rhythmic isovolumetric bladder contractions evoked by bladder distension were abolished by 0.3- to 3-mg/kg iv or 30- to 100-\textmu g intrathecal (it) administration of WAY100635 in a dose-dependent manner for periods of 3-15 min. Intrathecal injection of WAY100635 was effective only if injected at the L6-S1 spinal cord level, but not at the thoracic or cervical cord levels. WAY100635 (30–100 \textmu g it) significantly reduced the amplitude of bladder contractions evoked by electrical stimulation of the pontine micturition center. However, the field potentials in the rostral pons evoked by bladder contractions abolished by 0.3- to 3-mg/kg iv or 30- to 100-\textmu g intrathecal (it) administration of WAY100635 in a dose-dependent manner for periods of 3–15 min. Intrathecal injection of WAY100635 was effective only if injected at the L6-S1 spinal cord level, but not at the thoracic or cervical cord levels. WAY100635 (30–100 \textmu g it) significantly reduced the amplitude of bladder contractions evoked by electrical stimulation of the pontine micturition center. However, the field potentials in the rostral pons evoked by bladder contractions abolished by 0.3- to 3-mg/kg iv or 30- to 100-\textmu g intrathecal (it) administration of WAY100635 in a dose-dependent manner for periods of 3–15 min.

A brief report of these experiments has been presented previously (12).

METHODS

Animal Preparations

Female Wistar rats, weighing 230–320 g, were used in this study. The animals were anesthetized with a subcutaneous injection of urethane (1.2 g/kg), and a cannula (PE-50) was placed in the external jugular vein for intravenous drug administration. A tracheostomy tube (PE-240) was inserted to facilitate respiration and permit artificial ventilation after neuromuscular blockade.

For insertion of an intrathecal catheter, the atlanto-occipital membrane was incised at the midline using the tip of an 18-gauge needle as a cutting edge. A catheter (PE-10) was inserted through the slit into the subarachnoid space and advanced caudally to the L6-S1 level of the spinal cord. At the
end of experiment, a laminectomy was performed to verify the position of the catheter tip. A transurethral bladder catheter (PE-90) connected to a pressure transducer was used to record the bladder pressure isovolumetrically with the urethral outlet ligated. In all animals during isovolumetric recording, both ureters were tied distally, cut, and the proximal ends were cannulated (PE-10) and drained externally. This procedure prevented the bladder from filling with urine during the experiment. In some animals, a continuous cystometry meter (CMG) was performed using a transurethral catheter of smaller caliber (PE-50) while simultaneously recording the electromyogram (EMG) of the external urethral sphincter (EUS) muscle. In continuous CMGs, the bladder was filled with a constant infusion (0.21 ml/min) of saline and allowed to empty around the catheter to elicit repetitive voidings. This method facilitates the rapid collection of data for a large number of voiding cycles (10).

To record the electrical activity of the EUS, the rostral pubic bone was removed, and two fine (50 μm) wire EMG electrodes (M. T. Giken, Tokyo, Japan) were inserted directly into the EUS. The EMG potentials were amplified and displayed on an oscilloscope. Bladder pressure and EMG data were recorded on a strip-chart recorder and a videocassette recorder for subsequent data analysis.

For stimulating the pontine micturition center (PMC) to activate the descending limb of the micturition-reflex pathway or for recording evoked potentials in PMC after pelvic nerve (PLN) stimulation, the rat was placed in a stereotaxic apparatus, and a small craniotomy was performed to insert an electrode into the dorsal pontine tegmentum. After completion of the craniotomy, the lower half of the body was rotated and abdominal skin flaps were tied to a metal frame to form a skin pool, and the cavity was filled with warm mineral oil. The PLN was placed on bipolar silver electrodes for stimulation. A fine monopolar tungsten electrode (diameter 10–20 μm), insulated with Teflon except for the tip (M. T. Giken), was used for stimulation or recording in the brain stem. Animals were paralyzed with α-bungarotoxin (0.4 mg/kg iv), a noncompetitive blocker of striated muscle nicotinic receptors to eliminate artifacts by muscle movement. This agent has a long duration of action that allowed one dose to produce complete neuromuscular blockade throughout the experiments (3–6 h) (13).

After having determined the threshold volume for inducing reflex-bladder contractions, small amounts of saline were withdrawn from the bladder until bladder contractions disappeared. The bladder volume was kept below the threshold for inducing spontaneous bladder contractions during brain stem stimulation or recording. An electrode was introduced stereotaxically into the medial part of the dorsal pontine tegmentum in 0.25- or 0.5-mm steps as described in a previous report (24). The electrode was used for stimulation in some animals and for recording in others. Electrical stimulation in the rostral pons consisted of trains of stimulation (0.2-ms pulse duration, 50 Hz, 10–15 V, 3 s). The optimal sites for evoking bladder contractions with the largest amplitude were determined in each experiment. PLN stimulation was 1–15 V, 0.05 ms in pulse duration at 100–300 Hz, 5- to 30-ms trains. These stimulus parameters were based on a previous report (13, 24). The optimal sites in the rostral pons were identified at which PLN stimulation evoked field potentials. Neural activity recorded in the pons was displayed on an oscilloscope, and 10 successive evoked potentials were averaged with a digital computer and plotted on a chart recorder. The latencies were measured from the onset of stimulation to the peak of the evoked potentials. The latency measurements were made from computer-averaged potentials. Stimulation parameters were varied to evoke a response of maximal amplitude and shortest measurable latency.

In some experiments, the PLN was cut, and the distal stump was placed on bipolar silver electrodes for stimulating the efferent innervation to the bladder. The PLN stimulation was 10–20 V, 0.05-ms pulse duration at 20 Hz for 3 s.

Experimental Protocol

Isovolumetric bladder contractions. To induce isovolumetric bladder contractions, saline was infused into the bladder (0.04 ml/min) until large-amplitude (>15 cm H2O) rhythmic bladder contractions appeared. Then the effects of WAY100635 (intrathecal or intravenous) were evaluated by measuring the duration of inhibition of the rhythmic bladder contractions.

Continuous CMG and EMG. Constant infusion of saline (0.21 ml/min) into the bladder was performed to elicit repetitive voidings. Then the effects of intrathecal administration of WAY100635 on bladder and EUS activity were examined. Descending pathway. After finding the optimal sites in the rostral pons for evoking bladder contractions, the effects of intrathecal administration of WAY100635 were evaluated as a change in the amplitude of the PMC-evoked bladder contractions.

Ascending pathway. After the optimal sites for recording the PLN-evoked field potentials were found in the rostral pons, the effects of intrathecal administration of WAY100635 were evaluated as a change in the amplitude of the evoked potentials and latency from the onset of stimulation to the peak amplitude.

Peripheral pathway to the bladder. The effects of intravenous administration of WAY100635 were evaluated as changes in the amplitude of the PLN-evoked bladder contractions.

Statistical Analysis

All values in the text are expressed as means ± SE. Repeated-measures ANOVA was used for evaluating the effects of different doses of WAY100635 on the duration of inhibition of rhythmic bladder contractions, on the amplitude of the PMC-evoked bladder contractions, and on the amplitude and latency of PLN-evoked field potentials in the pons. Tukey-Kramer multiple-comparison test was used as a post hoc analysis. The amplitude of the PLN-evoked bladder contractions before and after intravenous administration of WAY100635 was compared using a paired Student’s t-test. For all statistical tests, P < 0.05 was considered significant.

Drugs. Drugs used in this study included WAY100635 and α-bungarotoxin (Sigma Chemical, St. Louis, MO). Both drugs were dissolved in physiological saline. Because the pH of WAY100635 solution (10 mg in 1 ml saline) was ~4.5, it had to be adjusted to a higher pH for intrathecal injection. However, because the WAY100635 solution in this concentration is not stable at a pH >6.0, the solution was adjusted to 5.8–5.9. Before administration of WAY100635, control injections (10 μl for intrathecal or 0.3 ml for intravenous) of physiological saline with the same pH (5.8–5.9) were tested to evaluate possible injection artifacts. All drugs were freshly prepared before each experiment.
RESULTS

Isovolumetric Bladder Contractions

The effect of the intrathecal administration of WAY100635 on distention-induced rhythmic bladder contractions was tested at four dose levels ranging from 0.3 to 100 μg. In preliminary studies, a reproducible inhibition of rhythmic bladder contractions was obtained after multiple injections (4–5 times) at 30-min intervals of the same dose of WAY100635 (30 μg it). Intrathecal administration of vehicle did not produce any significant change (Fig. 1). The onset of drug effect was rapid (within 1–2 min) and persisted for 6–12 min, after which rhythmic bladder contractions resumed. Because the repeated administration of a single dose elicited brief reproducible responses, subsequent dose-response studies were conducted by administering increasing doses ranging from 0.3 to 100 μg at 30-min intervals to evaluate dose-response relationships (n = 6). WAY100635 produced an inhibition of rhythmic bladder contractions, the duration of which was dose dependent (Fig. 1); 30 and 100 μg of WAY100635 produced a significant inhibition lasting for 9.7 ± 1.0 and 15.0 ± 1.5 min, respectively, compared with vehicle, whereas the effects of 0.3 and 3 μg were not statistically significant (Fig. 2).

To evaluate the specific level of the spinal cord at which WAY100635 injected intrathecally might act, the position of the intrathecal catheter tip was changed from the original site (L6-S1) to the lower thoracic level, upper thoracic level, and then cervical level of the spinal cord by pulling back the intrathecal catheter in three steps; first by 3 cm to the lower thoracic level, by another 2 cm to the upper thoracic level, and finally by another 1.5 cm to the cervical level. Intrathecal administration of WAY100635 (30 μg) at the thoracic or cervical levels did not have any effect on rhythmic bladder contractions (n = 4).

Two doses of WAY10635 (0.3 and 3 mg/kg) were tested by intravenous injection. In preliminary studies, reproducible inhibition of rhythmic bladder contractions was obtained after multiple injections (3–4 times) of WAY10635 (3 mg/kg iv) at 30-min intervals. The effect of the drug appeared within a few minutes and persisted for ~10 min. In subsequent experiments, two doses of WAY10635 were tested in each animal (n = 6). Compared with the effect of vehicle (0.9 ± 0.1 min lengthening of interval between contractions), intravenous administration of 3 mg/kg of WAY10635, but not 0.3 mg/kg, produced a significant inhibition of rhythmic bladder contractions. The duration of inhibition was 3.5 ± 1.5 and 9.4 ± 1.7 min following administration of 0.3 and 3 mg/kg iv of WAY10635, respectively.

Continuous CMG and EMG

Continuous infusion of saline into the bladder elicited reflex-bladder contractions with a fairly regular interval. During bladder contractions, high-frequency (3.7 ± 0.6 Hz) oscillations of bladder pressure were observed, and these oscillations of bladder pressure corresponded to bursting activity in the EUS EMG, as shown previously (10, 11). Intrathecal administration of WAY100635 (30–100 μg, n = 3) abolished the large-amplitude bladder contractions as well as the EUS bursting and unmasked irregular small-amplitude bladder contractions for periods of 5–18 min (Fig. 3).
These irregular small-amplitude bladder contractions were not associated with EUS bursting (Fig. 3).

**Descending Pathway**

Electrical stimulation of the brain applied at 3-min intervals using a monopolar tungsten electrode positioned in the region of the PMC evoked short-latency (0.5–1.0 s) bladder contractions. The amplitude of the evoked bladder contractions recorded under isovolumetric conditions with bladder volume below the level for evoking a micturition reflex ranged from 15 to 60 cmH2O. The contractions were most prominent when electrodes were positioned in the pons between Bregma −8.4 to −9.4 mm, lateral 1.0–1.5 mm, and H −6.5 to −7.0 mm. The location of these optimal sites for evoking bladder contractions was consistent with previous reports (24). Intrathecal administration of vehicle did not change the amplitude of the evoked bladder contractions (Fig. 4). After constant evoked bladder contractions during several control stimulations in the optimal sites in the rostral pons were demonstrated, 30 μg of WAY100635 were injected intrathecally, and electrical stimulation was repeated at 3-min intervals. Then, after full recovery from the first dose, the effect of intrathecal administration of 100 μg of WAY100635 on the amplitude of the evoked bladder contractions was examined. These doses of WAY100635 were selected based on the dose-response data obtained in the isovolumetric studies. WAY100635 reduced the amplitude of evoked bladder contractions in a dose-dependent manner (Figs. 4 and 5). The effects were most prominent 3 min after the intrathecal administration (Figs. 4 and 5). The recovery was fairly rapid, and full recovery was observed 12–24 min after the injection (Figs. 4 and 5).

**Ascending Pathway**

Electrical stimulation of afferent axons in the PLN with trains of pulses (0.05-ms pulse duration at 100- to 300-Hz intraintrain frequency, 5- to 30-ms train duration) evoked short-latency (10–22 ms) negative field potentials in the dorsal part of the rostral pons (Fig. 6). Threshold-stimulus intensities ranged from 1 to 6 V, and amplitude of the evoked potentials ranged from 60 to 100 μV (79 ± 3.3 μV). The sites at which PLN stimulation elicited short-latency responses were located in a relatively limited area in the dorsal part of the rostral pons; Bregma −8.4 to −9.0 mm, lateral 0.5
to 1.2, and H −4.2 to −6.0 mm. This area was close to the periaqueductal gray. Ten successive evoked responses were averaged before and 3, 5, and 7 min after intrathecal injection of WAY100635 (30 or 100 µg). Neither 30 nor 100 µg of WAY100635 injected intrathecally changed the amplitude of the evoked responses or the latency from the onset of stimulation to the peak amplitude (Fig. 6 and Table 1). In three rats, the effects of intrathecal administration of WAY100635 on the evoked responses were also examined. WAY100635 (10 mg/kg iv) did not change the amplitude or latency of the evoked responses (Table 1).

Peripheral Pathway

The amplitude of the PLN-evoked bladder contractions was compared before and after intrathecal administration of a large dose of WAY100635 (10 mg/kg, n = 4). The amplitudes of the PLN-evoked bladder contractions before (25 ± 4 cmH2O, range 15–32) and 5 min after WAY100635 (24 ± 4 cmH2O, range 14–32) were not significantly different.

**DISCUSSION**

The present study evaluated the effects and sites of action of WAY100635, a selective silent 5-HT1A-receptor antagonist, on the micturition-reflex pathways in the urethane-anesthetized rat. The results indicate that intrathecal administration of WAY100635 at the lumbosacral spinal cord level inhibited the descending limb of the spinobulbospinal micturition-reflex pathway. However, the drug did not affect the ascending pathway to the rostral pons activated by stimulation of afferent nerves in the PLN nor did it alter the peripheral parasympathetic pathway to the bladder. Thus the blockade of spinal 5-HT1A receptors with WAY100635 resulted in the inhibition of micturition in the urethane-anesthetized rat. These results are consistent with previous reports that revealed 1) an excitatory role of spinal 5-HT1A receptors in the control of the micturition reflex (14) and 2) a depressant effect of intrathecal administration of WAY100635 on bladder activity (30).

5-HT receptors are widely distributed in the CNS, including several areas involved in control of the micturition-reflex pathway. In the spinal cord, 5-HT1A and 5-HT1B receptors have been identified at the lumbosacral level (22, 33), where preganglionic neurons innervating the urinary bladder and urethra are located. Intracerebroventricular or intrathecal administration of 5-HT facilitated micturition in urethane-anesthetized rats (14), whereas electrical or chemical stimulation of midline raphe nuclei that contain 5-HT neurons projecting to the spinal cord was reported to inhibit bladder activity in the cat (1, 19). These findings suggest both excitatory and inhibitory functions for central serotonergic systems in modulating micturition-reflex pathways.

The present study focused on the role of central 5-HT1A receptors in modulating micturition-reflex pathways, because a highly selective and potent 5-HT1A-receptor antagonist (7, 8) has been reported to suppress bladder activity after intravenous administration (30). Central 5-HT1A receptors exist as two functionally distinct populations. Somatodendritic autoreceptors are located on the cell bodies and dendrites of serotonergic neurons, whereas postsynaptic receptors are located on other neurons receiving serotonergic inputs. Owing to the differences between autoreceptor and postsynaptic 5-HT1A-receptor populations in terms of receptor reserve and receptor-effector coupling, several 5-HT1A-receptor partial agonists have been identified that act as antagonists of postsynaptic receptors and agonists at presynaptic receptors (8). However, this combination of effects can cause somewhat complex and conflicting pharmacological results. To distinguish true antagonists from partial agonists, the term “silent” 5-HT1A-receptor antagonist has been employed. WAY100635 has been shown to be a potent, selective, and silent 5-HT1A-receptor antagonist (2, 3, 7, 8, 21). The use of WAY100635 allowed us to evaluate the function of 5-HT1A receptors in the central control of micturition reflex.

In the present study, intrathecal administration of WAY100635 inhibited the descending limb of the micturition-reflex pathway from the PMC, whereas it did not have any effect on the ascending pathway. Effective intrathecal administration of WAY100635 was restricted to the L6-S1 spinal cord level. Intrathecal administration of WAY100635 to cervical or thoracic levels of the spinal cord did not affect the micturition reflex. A previous study (14) showed that intrathecal administration of a 5-HT1A-receptor agonist (8-OH-DPAT) facilitated the micturition reflex in normal rats and that intravenous administration of 8-OH-DPAT increased the amplitude of reflex-bladder contractions induced by bladder distension in chronically spinalized rats (14). Taken together, these results indicate that spinal 5-HT1A receptors at the L6-S1 level have an important role in tonically modulating the efferent limb of the micturition reflex in the rat. Because EUS bursting activity during continuous CMGs was also abolished by intrathecal administration of WAY100635, spinal 5-HT1A receptors at the L6-S1 level are likely to be involved in the control of EUS as well as bladder function.

**Table 1. Effect of WAY100635 (intrathecal and intravenous) on the amplitude and latency to the peak of the pelvic nerve-evoked potentials in the PAG**

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>3 min</th>
<th>5 min</th>
<th>7 min</th>
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<tbody>
<tr>
<td>30 µg/it</td>
<td>78 ± 4 µV</td>
<td>76 ± 7</td>
<td>70 ± 7</td>
<td>74 ± 4</td>
</tr>
<tr>
<td>(n = 5)</td>
<td>29 ± 5 ms</td>
<td>29 ± 5</td>
<td>31 ± 5</td>
<td>29 ± 4</td>
</tr>
<tr>
<td>100 µg/it</td>
<td>83 ± 5 µV</td>
<td>82 ± 9</td>
<td>75 ± 8</td>
<td>81 ± 10</td>
</tr>
<tr>
<td>(n = 5)</td>
<td>27 ± 5 ms</td>
<td>27 ± 5</td>
<td>28 ± 5</td>
<td>28 ± 5</td>
</tr>
<tr>
<td>10 mg/kg iv</td>
<td>72 ± 10 µV</td>
<td>77 ± 12</td>
<td>73 ± 12</td>
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<tr>
<td>(n = 3)</td>
<td>30 ± 9 ms</td>
<td>31 ± 8</td>
<td>30 ± 8</td>
<td>31 ± 8</td>
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Values are means ± SE; n, no. of rats. PAG, periaqueductal gray; it, intrathecal.
The present study did not detect a role of 5-HT1A receptors in the control of the spinal processing of afferent inputs from pelvic viscera. However, a previous study showed that WAY100635 administered intravenously increased bladder capacity in conscious rats during CMGs (30), suggesting that the afferent limb of the micturition reflex is modulated by 5-HT1A mechanisms. It is possible that the difference in the two studies is due to the effect of anesthesia. In the present experiments, urethane anesthesia might have eliminated the serotonergic modulation of the afferent pathway because it is known that anesthetics can alter raphe neuron firing. Alternatively, it is possible that block of 5-HT1A receptors in the brain stem is involved in the effect of WAY100635 on the afferent pathway and bladder capacity. It is known that the activity of raphe serotonergic neurons is under negative-feedback control, mediated by somatodendritic 5-HT1A autoreceptors. In vitro and in vivo experiments in cats, rats, or guinea pigs revealed that 5-HT1A-receptor agonists have an inhibitory action on serotonergic neurons in the dorsal raphe nucleus due to the stimulation of somatodendritic 5-HT1A autoreceptors and that WAY100635 completely prevented this inhibition by 5-HT1A-receptor agonists (3, 7, 8, 21). In addition to this antagonistic action, WAY100635 also increased the spontaneous basal firing rate of serotonergic neurons, presumably by blocking the feedback action of endogenous 5-HT at 5-HT1A autoreceptors (7, 8). Because serotonergic midline raphe nuclei contain neurons that are sensitive to visceral afferent input and stimulation of the raphe nuclei can inhibit bladder reflexes (19, 29) as well as the firing of spinal dorsal horn neurons activated by afferents in the PLN (17), it seems likely that block of 5-HT1A autoreceptors in the brain stem would enhance firing in descending raphe-spinal pathways that inhibit spinal processing of afferent inputs from the bladder. Thus the increase in bladder capacity in conscious rats during CMGs after systemic administration of WAY100635 (30) may be mediated by the action of the drug on pontomedullary raphe nuclei. A possible role of other 5-HT-receptor subtypes in the spinal processing of afferent inputs from the bladder is worth pursuing in future research, because in the cat, serotonergic modulation of spinal ascending activity and sacral reflex activity is mediated through 5-HT3 receptors (5).

Regarding the peripheral function of 5-HT1A receptors, a previous in vitro study showed that activation of 5-HT1A receptors can elicit an inhibition of cholinergic transmission in the rabbit vesical pelvic ganglia (23). Intra-arterial administration of 5-HT produced both excitatory and inhibitory effects on the neuronal activity of cat vesical pelvic ganglia via different serotonergic receptors (26). In the present study, intravenous administration of WAY100635 in a large dose of 10 mg/kg did not affect the amplitude of bladder contractions evoked by electrical stimulation of PLN in the rat. Thus 5-HT1A receptor-mediated actions on vesical pelvic ganglia are different depending on the species.

In summary, blockade of spinal 5-HT1A receptors with a selective, silent 5-HT1A-receptor antagonist WAY100635 in urethane-anesthetized rats inhibited the micturition reflex induced by bladder distension as well as bladder contractions elicited by electrical stimulation of the pontine micturition center. These results suggest that 5-HT1A receptors at the L6-S1 level of the spinal cord have an important role in the tonic control of the descending limb of the micturition-reflex pathway in the rat.

**Perspectives**

It is clear from the results of many studies that bulbar serotonergic pathways have the potential for exerting an important modulatory action on the lumbosacral autonomic and somatic outflow to the urogenital organs (1, 4, 5, 14, 27–32). In contrast to the serotonergic inhibition of the parasympathetic outflow to the bladder, activation of central serotonergic receptors facilitates 1) the parasympathetic excitatory input to the penis, 2) the somatic input to the external urethral sphincter, and 3) sympathetic pathways in the hypogastric nerve (27–32). These observations raise the possibility that drugs that alter serotonergic mechanisms might be useful for the treatment of urinary incontinence as well as erectile dysfunction. Various types of drugs might be used to influence serotonergic control of urogenital function including those that selectively activate specific 5-HT receptors as well as those that block the metabolism or uptake of 5-HT (e.g., selective serotonin-reuptake inhibitors) (27–33) or increase the firing of serotonergic neurons (e.g., 5-HT1A antagonists) (30). The development of these therapies would no doubt be facilitated by a more detailed understanding of the location and receptor subtypes mediating central serotonergic control of urogenital function and how deficiencies in this control might contribute to neurogenic urogenital disorders.

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