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STRYCHNINE ANTAGONIZES VAGINAL STIMULATION-PRODUCED ANALGESIA AT THE SPINAL CORD

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Summary

Vaginal-cervical mechanostimulation (VS) suppresses vocalization and withdrawal responses to noxious stimulation. To determine whether the inhibitory neurotransmitter, glycine, contributes to the action of VS, strychnine, a specific glycine receptor antagonist was administered perispinally via intrathecal catheter in dosages of 1,5,25 and 100 µg. Prior to strychnine administration, VS (400 g force) elevated thresholds to elicit vocalization in response to graded intensities of tail shock, and blocked vocalization elicited by stimulation of a skin area, previously sensitized by intradermal injection of a 20% yeast solution. After strychnine administration the analgesic effects of VS were significantly attenuated. These findings suggest that the analgesic action of VS is partially mediated by glycine at the spinal level.

Vaginal stimulation (VS) exerts an immediate, powerful and reliable inhibition against sensory and motor responses to noxious stimulation, as demonstrated by a variety of behavioral measures (1-3). VS attenuates thalamic neuronal responses to noxious stimulation, without suppressing responses to innocuous tactile stimulation (4). Moreover, the inhibitory effects of VS are expressed by the blockage of locomotion and the righting reflex (5).

A major component of the effect of VS in suppressing responses to noxious stimulation is mediated at the spinal cord, by a system of monoaminergic neurons which descend from the brainstem (6,7), and by a local spinal opiate system (8). However, despite the significant reductions in effectiveness of VS after monoaminergic or opiate blockage, a substantial component of the VS effect persists. Therefore, we investigated whether an additional inhibitory spinal system contributes to the analgesic action of VS.

Glycine is a spinal neurotransmitter which inhibits both sensory and motor neurons (9-11). We hypothesized that the release of

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glycine contributes to the analgesic effect of VS, by acting to suppress nociceptive responses at the spinal cord. To test this hypothesis perispinal strychnine was administered to determine if it antagonizes the ability of VS to suppress vocalization responses to noxious stimulation. Strychnine binds specifically to glycine receptors, and inhibits neuronal responses to glycine, but not GABA (12-16). Preliminary findings have been reported in abstract form (17).

Method

Experiments were conducted with female Sprague-Dawley rats weighing 200-300 grams, housed individually at 23°C and maintained on a reverse day-night cycle (dark from 10:00 to 20:00 hours). Food (Purina Rat Chow) and water were supplied ad libitum. A catheter (Clay Adams PE-10 tubing, 7.5 cm insertion length) was implanted chronically into the subarachnoid intrathecal space through an incision in the atlanto-occipital membrane, following the technique described by Yaksh and Rudy (18). Animals were anesthesized during surgery with Ketamine (20-25 mg i.m., Bristol Laboratories) and Xylazine (1.2 mg i.p., Haver-Lockhart) and treated with Terramycin (5 mg i.m., Pfizer Laboratories). At least seven days of recovery were allowed before testing post-surgery. VS (400 g force) was applied by pressing against the cervix with the spring-loaded plunger assembly of a calibrated glass 1 cc syringe, while holding the base of the tail to provide restraint (19).

Experiment I. To reliably elicit vocalization in response to cutaneous stimulation, rats were injected intradermally in the flank with a solution of Brewer's yeast (20% solution, 0.4 ml). One hour later, single brisk brush strokes at the injected region (against the fur grain) reliably elicited distress-type vocalizations. The number of vocalizations elicited in response to 10 successive brush strokes was counted; then VS was applied and vocalizations were counted again while the fur was brushed 10 times. Animals were held by the base of the tail to provide restraint during fur stimulation. Rats were then injected either with 5 µg strychnine sulfate (Sigma Chemical Co.) dissolved in 5 µl distilled water, or with 5 µl of Ringer's solution ("saline"), delivered "perispinally" to the intrathecal subarachnoid space of the lumbosacral spinal cord with an additional 3 µl of saline flushed from the catheter to ensure complete entry. This dose was found to reliably induce non-convulsive behavioral disturbances in previous study (17). Fifteen minutes after strychnine treatment, tests were again conducted to determine the number of vocalizations elicited by fur stroke prior to and during VS.

Experiment II: To determine vocalization thresholds, rats were placed in a tubular Plexiglas restrainer and two stainless steel electrodes were taped to the tail after applying a small amount of conductive gel (Spectra 360, Parker Laboratories). Electrical shocks (100 msec train of 60 hz sine waves) with an intershock interval of 5 sec, were delivered to the tail from a Grason Stadler Model 700 constant current shock generator, via tail electrodes. Vocalization thresholds were determined using the