

Tooth Pulp- and Facial Hair Mechanoreceptor-evoked Responses of Trigeminal Sensory Neurons Are Attenuated during Ketamine Anesthesia

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Background: Evidence exists that ketamine, administered systemically using a dose required for inducing a state of anesthesia, may antagonize nociceptive but not innocuous input to lumbar dorsal horn neurons. However, it is unclear whether ketamine exerts this selective action on sensory inputs to trigeminal sensory neurons. The current study was undertaken to compare the responses evoked in trigeminal sensory neurons by electrical stimuli applied to the tooth pulp *versus* air-puff stimuli applied to facial hair mechanoreceptors (FHMs) during quiet wakefulness *versus* ketamine anesthesia.

Methods: Accordingly, responses of rostral trigeminal sensory nuclear complex (TSNC) and trigeminothalamic tract neurons evoked by tooth pulp (a source of small-diameter fiber input) and FHMs (a source of larger-diameter fiber input) were recorded extracellularly from chronically instrumented cats before, during, and after recovery from the anesthetic state induced by a single (2.2 mg/kg) intravenous injection of ketamine.

Results: Overall, tooth pulp-evoked responses of TSNC neurons were maximally suppressed by 50% within 5 min after the intravenous administration of ketamine. Ketamine also suppressed the FHM-evoked responses of TSNC and trigeminothalamic neurons by 45%. The time course of ketamine's suppressive action was equivalent for tooth pulp- and FHM-evoked responses. However, the recovery of tooth pulp-evoked TSNC neuronal responses at suprathreshold intensities was markedly prolonged compared with neuronal responses driven by threshold stimuli or FHM.

Conclusions: These electrophysiologic results in the chronically instrumented cat preparation indicate that a nonselective suppression of orofacial somatosensory information occurs during ketamine anesthesia. The prolonged recovery of suprathreshold responses of TSNC neurons mediated by small-diameter afferent fiber input may partly underlie the analgesic action of ketamine that is clinically relevant at subanesthetic doses. (Key words: Brainstem; main sensory nucleus; nucleus oralis.)

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THE dissociative anesthetic ketamine has recently received interest for its use as an effective analgesic agent in patients suffering from certain chronic orofacial pain syndromes, such as postherpetic neuralgia.^{1,2} Several electrophysiologic studies have suggested that ketamine's analgesic actions *per se* may arise, in part, from its selective suppression of nociceptor-driven sensory neurons. For example, in experiments performed on barbiturate-anesthetized cats, anesthetic doses of ketamine suppress noxious stimulus-evoked responses of spinal cord dorsal horn neurons³ without altering responses evoked by low-threshold mechanoreceptors.^{3,4} Similarly, in awake cats, the systemic administration of ketamine was claimed to selectively suppress noxious but not innocuous input to the spinal cord dorsal horn.⁵ Ketamine is also known to abolish the "wind up" responses of rat dorsal horn class 2 type neurons induced by repeated electrical stimulation of their receptive field or peripheral nerve.^{6,7} Collectively, these electrophysiologic studies performed on lumbar sensory neurons suggest that ketamine, in doses known to produce its

typical state of anesthesia, may act to selectively suppress nociceptive input to the central nervous system.⁵

Ketamine's *analgesic* action in patients suffering from various orofacial pain syndromes might be partly caused by a selective action on nociceptive inputs to trigeminal sensory nuclear complex (TSNC) neurons.^{1,2} The dose range for ketamine used in the majority of these clinical studies is much lower than that used in acute electrophysiologic studies. These facts notwithstanding, it remains to be determined whether ketamine, administered at a dose producing its known dissociative anesthetic state,^{8,9} exerts selective suppressive effects on orofacial inputs to the TSNC as it seems to do in the spinal dorsal horn. The rostral TSNC is not an equivalent analogue, either anatomically or functionally, of the spinal cord dorsal horn. Rostral TSNC neurons are excited almost exclusively by low-threshold mechanoreceptors located in facial cutaneous receptive fields. Functionally, this part of the TSNC has been thought to convey innocuous sensory information from the face to the thalamus.¹⁰ However, several lines of evidence support an important role for the rostral TSNC in the transmission of nociceptive information from the oral cavity and in particular from the teeth.¹¹⁻¹⁴ Thus, the unique anatomic and physiologic attributes of the rostral TSNC make it ideal to test the hypothesis that anesthetic doses of ketamine exert a selective suppression of nociceptive orofacial input.

Using the chronically instrumented cat preparation to address this question, we examined the effect of ketamine on responses evoked in TSNC neurons *via* electrical activation of tooth pulp, a source of smaller-diameter A δ afferent fibers.^{15,16} We compared this with the effect of ketamine on responses of TSNC neurons evoked by air-puff stimuli directed at facial hair mechanoreceptors (FHMs), a source of large A α/β fiber input.^{17,18} Based on results obtained for dorsal horn neurons of the spinal cord, we hypothesized that tooth pulp- but not FHM-evoked TSNC neuronal activity would be suppressed during the anesthetic state produced by systemically administered ketamine.

Materials and Methods

Surgical Implant Procedures

Experiments were conducted in four intact, unanesthetized, chronically instrumented cats, which were implanted under deep gaseous anesthesia (45-60% N₂O in a 1.5-2.5% halothane/oxygen mixture) with a head-restraining device and electrodes for monitoring behav-

ioral states.^{11,19} Electrodes were also implanted into the frontal sinus (electroencephalogram [EEG]), lateral geniculate nucleus of the thalamus (pontogeniculoocipital [PGO] wave activity), the orbital plate (electrooculogram), and neck muscles (electromyogram [EMG]) and were used for monitoring behavioral state. Through the use of these electrodes, the behavioral state of quiet wakefulness could be clearly differentiated from sleep or anesthesia by the presence of a desynchronized, low-voltage cortical EEG waveform pattern that was also accompanied by a tonic EMG activity, and a paucity of eye movements or PGO wave activity.

In one cat, tripolar strut electrodes were chronically implanted in the (contralateral) ventrobasal thalamus (Horsley-Clarke coordinates [HC]: A 6-8, L 4-6, H -1 to 2) to permit antidromic activation of trigeminothalamic (TGT) neurons.¹² An indwelling jugular catheter was chronically implanted and used for the intravenous administration of ketamine. Silver-silver chloride dentinal pit electrodes were implanted in the mandibular and maxillary canines for electrical stimulation of tooth-pulp afferents.^{11,15} All surgical and chronic restraint procedures reported complied with international^{20,21} and institutional (University of British Columbia Animal Care Committee) guidelines.

Recording Procedures

During recording sessions, cats were loosely wrapped in a soft canvas bag and their heads painlessly maintained in a stereotaxic position. Behavioral state was constantly monitored by recording EEG, electrooculogram, PGO, and nuchal EMG activities. Behavioral state was scored using previously established criteria.^{11,12,15} Cats normally cycled between quiet drowsy wakefulness and quiet sleep; in addition, they readily entered episodes of active sleep. Using this preparation, we previously reported that the tooth pulp-evoked responses of feline TSNC neurons are suppressed during active sleep.^{11,22} Accordingly, the behavioral state of quiet wakefulness served as a control state for testing the effects of ketamine.

The extracellular spike activity of neurons located within the rostral TSNC was recorded *via* tungsten electrodes (2 M Ω) using an AC-coupled amplifier (A-M Systems, Carlsborg, WA, model 1800, bandpass, 0.3-10.0 KHz, 1,000 \times). The boundaries of the rostral TSNC were demarcated using extracellularly recorded orthodromic mass action potentials evoked by electrical stimulation of the inferior alveolar nerve and tooth pulps as well as antidromic mass action potentials evoked *via* stimula-

TRIGEMINAL NEURON ACTIVITY DURING KETAMINE ANESTHESIA

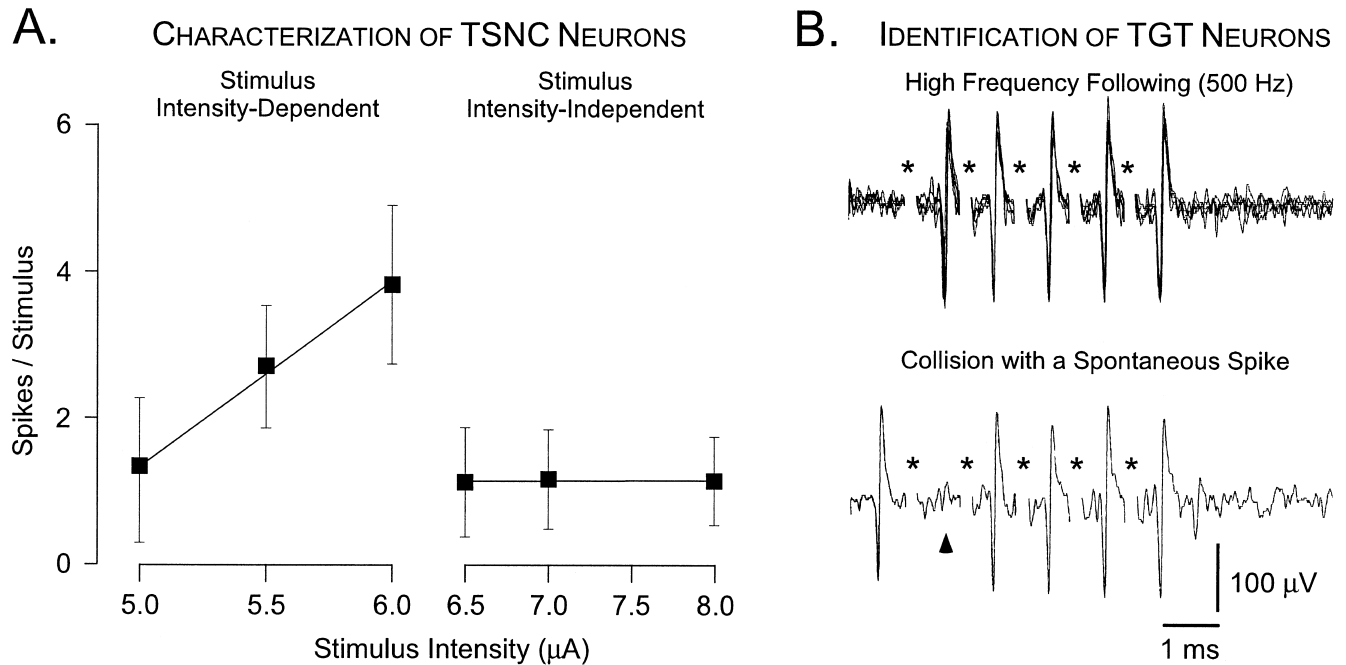


Fig. 1. Criteria used to differentiate between stimulus intensity–dependent (*A*) and –independent rostral trigeminal sensory nuclear complex (TNSC) neurons and to identify trigeminothalamic neurons (*B*). (*A*) Graphs illustrate the response profile of stimulus intensity–dependent and –independent neurons in response to tooth-pulp stimulation. The evoked activity (spikes/stimulus) of stimulus intensity–dependent neurons increases if graded electrical stimuli are applied to the canine tooth pulp. In contrast, the activity of stimulus intensity–independent neurons is not affected by similar graded stimuli. Each point on the graphs represents the mean \pm SD, $n = 50$ trials. (*B*) Five superimposed oscilloscope traces are presented of an air puff–evoked TNSC neuron responding to high-frequency stimuli (0.2 ms, 140 μ A, 500 Hz) applied to the contralateral thalamus. A single oscilloscope trace below illustrates a collision with an ongoing action potential. Asterisks denote the stimulus onset. The arrow indicates the location at which the antidromic spike should have occurred. Antidromic latency: 1.3 ms.

tion of the digastric and masseter muscles and facial nerve (fig. 1).¹¹ Poststimulus time histograms depicting cumulative responses of TNSC neurons were constructed from consecutive canine tooth-pulp stimuli at threshold (0.2 ms, 5–100 μ A) and suprathreshold (approximately 125% of threshold; fig. 1) intensities. Recorded TNSC neurons were categorized as being of the stimulus intensity–independent or stimulus intensity–dependent type by their responses to graded electrical tooth-pulp stimuli (figs. 1A and 1B; see Cairns *et al.*¹¹). The response characteristics of rostral TNSC neurons may be associated with their axonal projection; for example, trigeminothalamic tract (TGT) neurons exhibit stimulus intensity–independent responses to electrical stimulation of the tooth pulps.^{11,12,23,24}

FHM-evoked responses of TNSC neurons were also investigated by delivering innocuous air-puff stimuli (10–50-ms puff, 0.5 Hz) to facial receptive fields. In one cat, FHM-evoked TNSC neurons were further identified as TGT neurons based on the following criteria in response to low intensity (0.2 ms, 500 μ A) thalamic stim-

uli: (1) constant latency (variability less than 0.2 ms), (2) high frequency following (≥ 333 Hz), and (3) collision with ongoing or peripherally evoked action potentials.^{15,19,25}

Cats rested quietly in the stereotaxic setup without exhibiting any signs of distress or discomfort during stimulation of the teeth, face, or thalamus. In our experiments, we observed a gradual recovery from ketamine anesthesia (2.2 mg/kg), which was uneventful and allowed trigeminal sensory neuron activity to be monitored for periods exceeding 2 h.

Intravenous Drug Administration

Prior to the administration of ketamine, a control response to tooth pulp or FHM stimuli was obtained during the state of quiet wakefulness. Then, normal saline (0.5 ml) was slowly injected intravenously over 1 min and a second control response collected. Finally, a relatively low dose of ketamine HCl (Ketalean, MTC Pharmaceuticals, Cambridge, Ontario, Canada; 2.2 mg/kg diluted to 0.5 ml in normal saline) was slowly injected over

1 min and neuronal activity monitored at regular intervals for 1 h after drug administration. A dose of 2.2 mg/kg ketamine was chosen because it is the lowest dose employed in previous studies of lumbar dorsal horn neurons that reliably provides 5–10 min of surgical anesthesia followed by a 30–60-min recovery period.^{3,26} A maximum of two experiments was performed per week. The minimum time period between successive drug administrations during each week was 48 h.

Statistical Analysis

All data were videotaped, and analyses were performed “off-line” using computerized data acquisition software (A/DVANCE Fine Science Tools, Vancouver, Canada). Poststimulus time histograms were constructed from 50 consecutive responses and the mean activity in spikes/stimulus calculated. Evoked activity was sampled every 5 min over the first 30 min after drug infusion, and then every 10 min thereafter for a total of 60 min. The magnitude of the control response at time zero was equated to 100% and subsequent values were calculated based on this value. Ketamine-related changes in neuronal excitability were assessed for each neuron by comparing the mean activity during wakefulness with that obtained during and upon recovery from ketamine anesthesia.¹¹ A repeated-measures analysis of variance (ANOVA) and *post hoc* Dunnett’s method were applied to determine whether ketamine exerted significant changes in the magnitude of evoked responses over time. A paired Student *t* test was used to investigate differences in latency to onset and the slope of the stimulus–response relationship between control and ketamine. A Mann–Whitney test was used to compare the relative magnitude of ketamine-related suppression between air puff- and tooth pulp-evoked neuronal responses. The α value for all tests was set at 0.05. All values are reported as means \pm SD.

Results

Effect of Ketamine on Electrophysiologic Indices of Behavioral State

Indices of behavioral state were monitored throughout each experiment. Control neuronal activity was collected during the state of quiet wakefulness, which was characterized by desynchronized, low-voltage cortical EEG activity, tonic nuchal EMG activity, and a paucity of eye movement or PGO wave activity.^{11,12,19} In contrast, the anesthetic state induced by ketamine was clearly

differentiated from quiet wakefulness primarily by the presence of high-voltage EEG activity with characteristic intermittent “spike-like” slow waves, and by a tonic nuchal EMG of decreased amplitude.^{8,9} In each animal, ketamine’s action on EEG and EMG reached a peak effect 5 min after administration that recovered within 20 min. Upon recovery from ketamine, the behavioral state resembled predrug wakefulness. A representative trace of EEG, electrooculogram, PGO, and EMG activity during wakefulness, ketamine anesthesia, and recovery is shown in figure 2.

Tooth Pulp-evoked Responses of TSNC Neurons

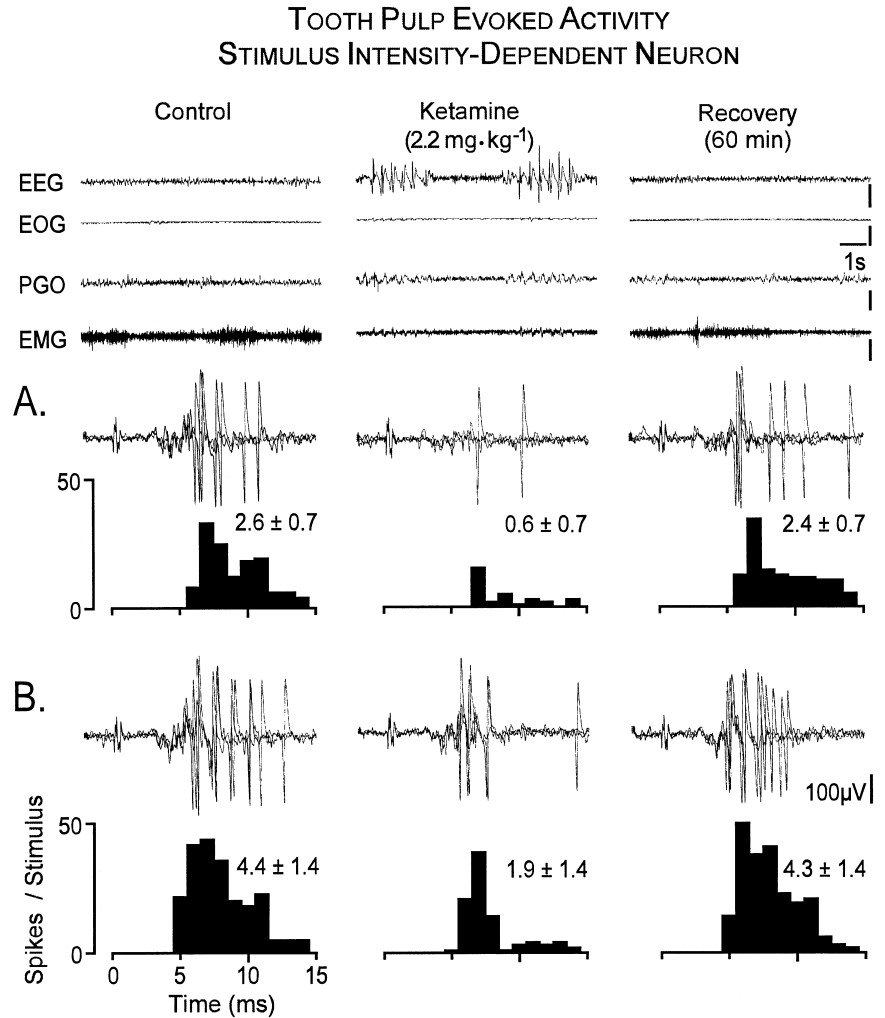
The effect of ketamine anesthesia was examined on a total of 14 tooth pulp-evoked TSNC neurons (cat 1: *n* = 2; cat 2: *n* = 6; cat 3: *n* = 4; cat 4: *n* = 2). Six of these cells were characterized as stimulus intensity-dependent neurons, and the remaining eight neurons were of the stimulus intensity-independent type. The response magnitude and latency to onset for these tooth pulp-evoked TSNC neurons during the control state of quiet wakefulness did not differ from that reported previously.¹¹

During the state of quiet wakefulness (W), baseline responses to threshold stimuli applied to tooth pulps were not affected by control injections of saline. However, the mean response magnitude was maximally suppressed by 50%, 5 min after the intravenous administration of ketamine (mean activity_W: 1.6 ± 0.4 spikes/stimulus; mean activity_{KETAMINE}: 0.8 ± 0.7 spikes/stimulus; $F = 7.924$, $P < 0.001$ on repeated-measures ANOVA). The ketamine-related suppression of tooth pulp-evoked activity was not associated with a change in the mean latency to onset of the first action potential (mean latency_W: 5.9 ± 0.7 ms; mean latency_{KETAMINE}: 5.9 ± 0.6 ms; $P > 0.05$, paired Student *t* test). Spike activity recovered to predrug baseline levels approximately 30 min after intravenous administration of ketamine.

Stimulus Intensity-dependent Neurons

The graded responses of stimulus intensity-dependent TSNC neurons provided the opportunity to examine the effect of ketamine on trigeminal neuronal responsiveness to both threshold and suprathreshold stimuli. The response characteristics of a stimulus intensity-dependent TSNC neuron before, during, and after recovery from ketamine anesthesia are illustrated in figure 2. Overall, tooth pulp-evoked responses of stimulus intensity-dependent neurons were maximally suppressed 5 min after the administration of ketamine at threshold

Fig. 2. Effect of ketamine on a stimulus intensity-dependent trigeminal sensory nuclear complex (TSNC) neuron. The first four traces represent 10-s epochs of electroencephalogram, electrooculogram, pontogeniculooccipital wave, and electromyogram activity characteristic of wakefulness, ketamine-induced anesthesia, and recovery. Below these traces are five overlaid oscilloscope traces illustrating the tooth pulp-evoked activity of this TSNC neuron. Poststimulus time histograms (PSTHs) were constructed from 50 consecutive responses evoked by threshold (A; 0.2 ms, 5.5 μ A, 1 Hz) and suprathreshold (B; 0.2 ms, 6.0 μ A, 1 Hz) electrical stimuli applied to the canine tooth pulp. The number above each PSTH indicates the mean (\pm SD) evoked activity, in spikes per stimulus. Note that in this cell, tooth pulp-evoked activity decreased 76% at threshold and 57% at suprathreshold intensity during ketamine anesthesia. Vertical calibration bars: 50 μ V.



(mean activity_w: 1.9 \pm 0.5 spikes/stimulus; mean activity_{KETAMINE}: 0.7 \pm 0.7 spikes/stimulus). Compared with baseline, the mean response magnitude was significantly suppressed at 5, 10, and 15 min after ketamine ($F = 2.183$, $P = 0.034$ on repeated-measures ANOVA, $P < 0.05$ by Dunnett's method).

The suprathreshold responses of stimulus intensity-dependent neurons were also maximally suppressed 5 min after ketamine (mean activity_w: 4.1 \pm 1.0 spikes/stimulus; mean activity_{KETAMINE}: 1.9 \pm 0.2 spikes/stimulus). However, ketamine's suppressive action was longer for suprathreshold *versus* threshold responses. Indeed, the mean response magnitude remained significantly suppressed, relative to baseline responses for 30 min, or twice as long as the mean response magnitude at threshold ($F = 7.276$, $P < 0.001$ on repeated-measures ANOVA, $P < 0.05$ by Dunnett's method; fig. 3).

We previously reported¹¹ that the stimulus-response curve of stimulus intensity-dependent TSNC neurons is linear (fig. 1). To further investigate the effect of ketamine on the response characteristics of this type of TSNC neuron, the slope of the stimulus-response curve for each cell was calculated as the difference between suprathreshold and threshold responses divided by the difference in stimulus intensity. Collectively, the slope of the stimulus-response relationship for all six neurons was significantly decreased (mean slope_w: 2.0 \pm 0.5 spikes/ μ A; mean slope_{KETAMINE}: 1.0 \pm 0.3 spikes/ μ A, $P < 0.05$ by paired Student *t* test). Ketamine suppressed both threshold and suprathreshold responses. However, the prolonged recovery of suprathreshold responses and the decrease in the slope of the stimulus-response curve suggests that ketamine may exert a preferential action on suprathreshold tooth pulp inputs.^{6,7}

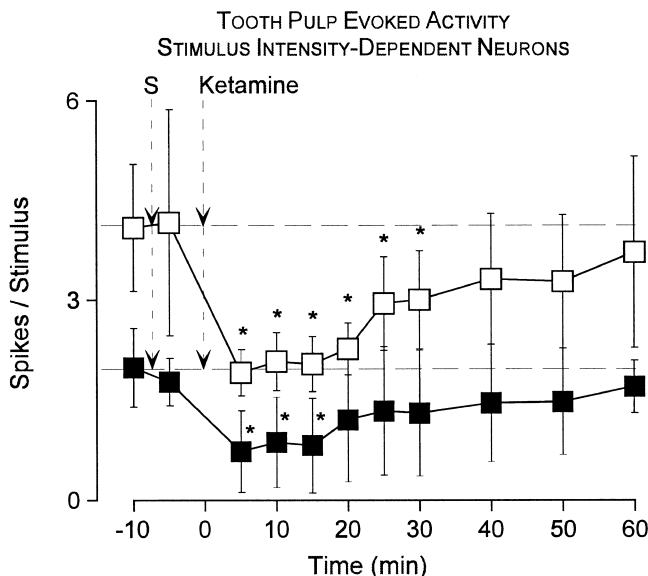


Fig. 3. Summary of ketamine's action on stimulus intensity-dependent trigeminal sensory nuclear complex neurons ($n = 6$). Time, relative to drug injection, is indicated in minutes, with time 0 representing the start of the ketamine injection. Each point on the graph represents the group mean (\pm SD). Saline (S; 0.5 ml) was injected between the first and second control measurements. Overall, tooth pulp-evoked activity at threshold (black squares) and suprathreshold (white squares) intensities were suppressed 63% and 54%, respectively, 5 min after the onset of drug administration. Mean evoked activity returned to control levels (indicated by the dashed line) approximately 30 min after ketamine infusion. Asterisks indicate statistically significant differences from control ($P < 0.05$ by repeated-measures analysis of variance, Dunnett's method).

Although ketamine anesthesia was accompanied by a marked reduction in response magnitude, it did not change the mean latency to onset of the first action potential at threshold (mean latency_w: 6.5 ± 2.4 ms; mean latency_{KETAMINE}: 6.8 ± 2.4 ms; $P > 0.05$, paired Student *t* test) or suprathreshold (mean latency_w: 5.0 ± 1.2 ms; mean latency_{KETAMINE}: 5.4 ± 1.5 ms; $P > 0.05$, paired Student *t* test) stimulus intensities.

Stimulus Intensity-independent Neurons

The action of ketamine on a stimulus intensity-independent neuron is presented in figure 4. Ketamine reversibly suppressed the tooth pulp-evoked response of this neuron. Overall, the threshold tooth pulp-evoked responses of eight stimulus intensity-independent neurons were maximally suppressed by 33% 5 min after ketamine administration (TSNC neurons; mean activity_w: 1.2 ± 0.6 spikes/stimulus; mean activity_{KETAMINE}: 0.8 ± 0.6 spikes/stimulus; fig. 5). Similar to stimulus intensity-dependent neurons, the mean response magnitude was

significantly suppressed, relative to baseline responses, at 5, 10, and 15 min after ketamine administration ($F = 4.336$, $P < 0.001$ on repeated-measures ANOVA, $P < 0.05$ by Dunnett's method). The relative magnitude of ketamine's peak suppression of stimulus intensity-independent neurons was not different from that of stimulus intensity-dependent neurons at threshold ($P > 0.05$, Mann-Whitney test; figs. 3 and 5). Administration of ketamine did not change the mean latency to onset of the first action potential of these stimulus intensity-independent neurons (mean latency_w: 5.7 ± 2.8 ms; mean latency_{KETAMINE}: 5.9 ± 3.1 ms; $P > 0.05$, paired Student *t* test).

Air Puff-evoked Responses of TSNC and TGT Neurons

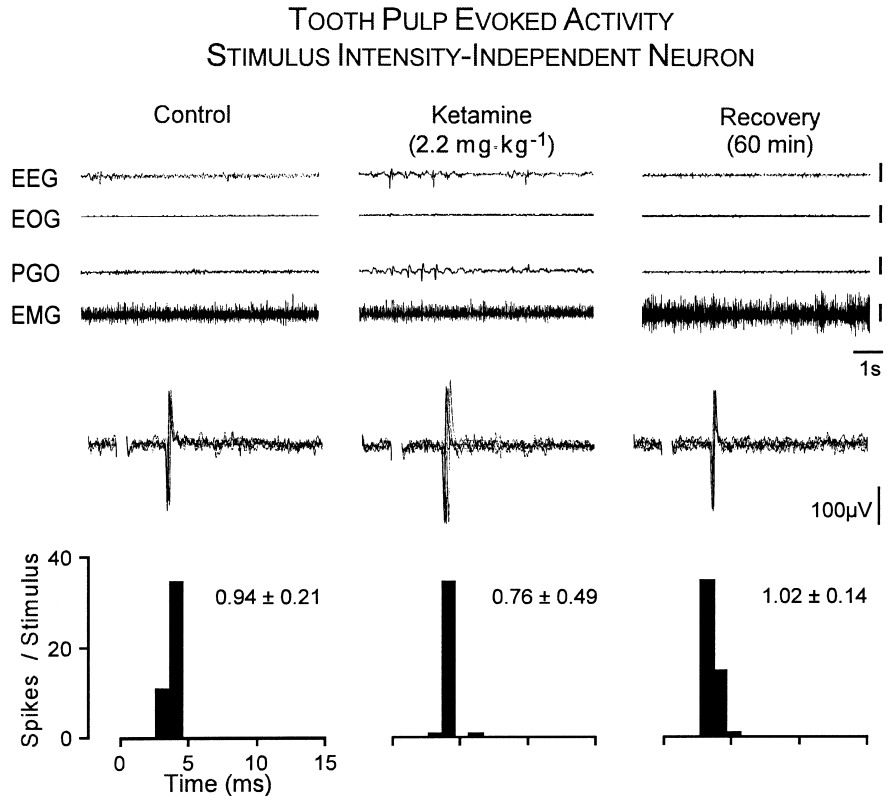
Experiments were performed on eight TSNC neurons (cat 3: $n = 3$; cat 4: $n = 5$) that responded to air-puff stimuli directed at facial receptive fields. None of these neurons responded to electrical stimulation of the tooth pulps; however, two of these neurons were identified as TGT neurons. An example of ketamine's action on an air puff-driven TSNC neuron is shown in figure 6. Note that intravenous administration of ketamine, but not saline, reversibly suppressed the air puff-evoked response of this neuron by 65%. This particular neuron was subsequently identified as a TGT neuron (fig. 1B).

The air puff-driven responses of all eight TSNC neurons ($n = 6$ TSNC, and $n = 2$ TGT neurons) were maximally suppressed (range, 25–92%) 5–10 min after the administration of ketamine. Overall, air puff-driven responses of all eight TSNC neurons were suppressed by 45%, 5 min after the administration of ketamine (fig. 7; mean activity_w: 2.5 ± 1.7 spikes/stimulus; mean activity_{KETAMINE}: 1.4 ± 1.4 spikes/stimulus). Ketamine exerted a suppressive action that was similar in time course to tooth pulp-evoked neurons (fig. 8). Compared with baseline responses, the mean response magnitude was significantly suppressed at 5, 10, and 15 min after ketamine administration ($F = 4.336$, $P < 0.001$ on repeated-measures ANOVA, $P < 0.05$ by Dunnett's method).

Discussion

In agreement with previous studies,^{8,9} the systemic administration of a relatively low dose of ketamine in chronically instrumented cats rapidly and reversibly induces a behavioral state of dissociative anesthesia that is characterized by distinct intermittent spike-like slow

Fig. 4. Effect of ketamine on a stimulus intensity-independent trigeminal sensory nuclear complex neuron. Oscilloscope traces represent behavioral state, and poststimulus time histograms reflecting neuronal activity were constructed as described in fig. 3. Neuronal activity was evoked by low-intensity bipolar electrical stimuli applied to the canine tooth pulps (0.2 ms, 8.0 μ A, 1.0 Hz). The number above each histogram indicates the mean (\pm SD) evoked activity, in spikes per stimulus. Note that tooth pulp-evoked activity in this neuron was reversibly suppressed by 24% during ketamine anesthesia. Vertical calibration bars (electroencephalogram, electrooculogram, pontogeniculoccipital wave, electromyogram): 50 μ V.



waves in the cortical EEG and reduced nuchal EMG activity compared with preceding episodes of quiet wakefulness. In addition, the state of ketamine anesthesia is associated with a marked reversible suppression of both tooth pulp- and FHM-evoked responses of rostral TSNC neurons.

A major limitation of the present study is that ketamine was administered systemically, and thus the site of ketamine action in exerting the suppressive action on TSNC neurons is not clear. The analgesic properties of ketamine are thought to be caused, in part, by a noncompetitive channel blockade of the postsynaptic *N*-methyl-D-aspartate (NMDA) receptor.^{4,26-28} Systemically administered ketamine (up to 5 mg/kg) has been reported to antagonize the NMDA but not non-NMDA excitatory amino acid-evoked responses in spinal cord dorsal horn neurons.^{4,26} However, other actions of ketamine are also noteworthy with respect to its putative postsynaptic actions *in vivo*. These same relatively low doses of ketamine are known to antagonize excitation of Renshaw cells by acetylcholine,⁴ and there is other *in vitro* evidence to indicate that ketamine is also a nicotinic cholinergic receptor antagonist.²⁹ In addition, it is important to note that ketamine may affect γ -aminobutyric

acid,³⁰ serotonergic,³¹ noradrenergic,³² and muscarinic cholinergic³³ systems.

Ketamine-related Suppression of Tooth Pulp-evoked Activity

The identity of the excitatory neurotransmitters responsible for mediating synaptic transmission between orofacial afferents and trigeminal sensory neurons is not known. However, tooth pulp primary afferent terminals display glutamate-like immunoreactivity, suggesting that an excitatory amino acid neurotransmitter such as glutamate or aspartate may be released in response to tooth-pulp stimulation.³⁴ Neurons comprising the TSNC and, in particular, the TGT are reactive with antibodies raised against both NMDA and non-NMDA receptor subtypes.³⁵ Microiontophoretic recording experiments performed *in vivo* have shown that local application of both NMDA and non-NMDA receptor agonists excites TSNC and TGT neurons.^{36,37} Thus, the ketamine-related suppression of orofacial-evoked activity observed herein might be explained by a blockade of postsynaptic NMDA receptor channels located on the soma of TSNC neurons.

We have suggested that stimulus intensity-dependent

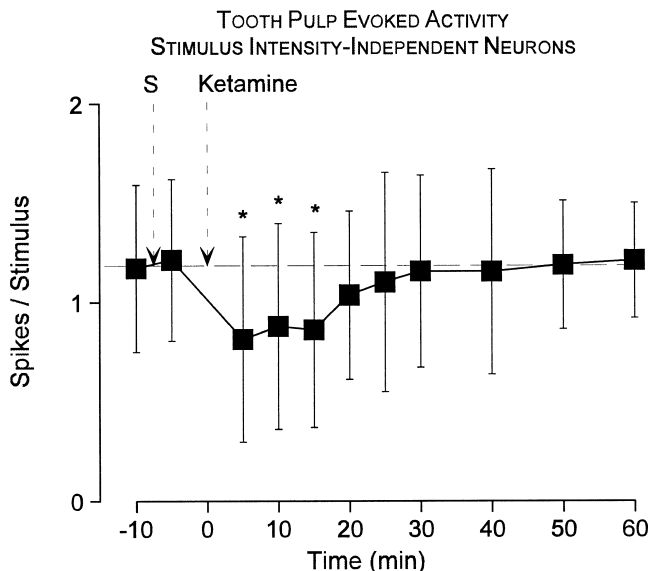


Fig. 5. Summary of ketamine's action on stimulus intensity-independent trigeminal sensory nuclear complex neurons ($n = 8$). The graph was constructed as described in fig. 4. Overall, tooth pulp-evoked activity at threshold was suppressed 33%, 5 min after the onset of drug administration. Mean evoked activity returned to control levels (indicated by the dashed line) approximately 30 min after ketamine infusion. Asterisks indicate statistically significant differences from control ($P < 0.05$ on repeated-measures analysis of variance, Dunnett's method). Error bars = \pm SD.

neurons may act as local interneurons in the rostral TSNC.¹¹ The work of Katakura and Chandler indicates that digastric motoneuronal responses driven by tooth pulp stimuli are blocked by NMDA antagonists and antidromically identified premotor interneurons are excited by microiontophoretically applied NMDA.³⁸ The findings of Boucher *et al.*³⁹ that microinjection of ketamine (0.02 mg/kg) as well as the competitive NMDA receptor antagonist 2-amino-5-phosphonovalerate into the TSNC of awake rats suppresses the tooth pulp-evoked jaw-opening reflex corroborate the aforementioned findings. Collectively, these studies support the suggestion that antagonism of NMDA receptors by ketamine could contribute to a suppression of the synaptic transmission between tooth pulp afferents and TSNC neurons. Consistent with previous findings,^{6,7} ketamine also reduced the slope of the stimulus-response curve of all stimulus intensity-dependent neurons tested. Moreover, the recovery of suprathreshold responses of these cells from ketamine anesthesia was also prolonged, lasting up to 30 min after intravenous bolus administration. These data indicate that the drug attenuates to a greater extent high threshold rather than low threshold inputs to these cells. These data may be relevant to partially explaining the

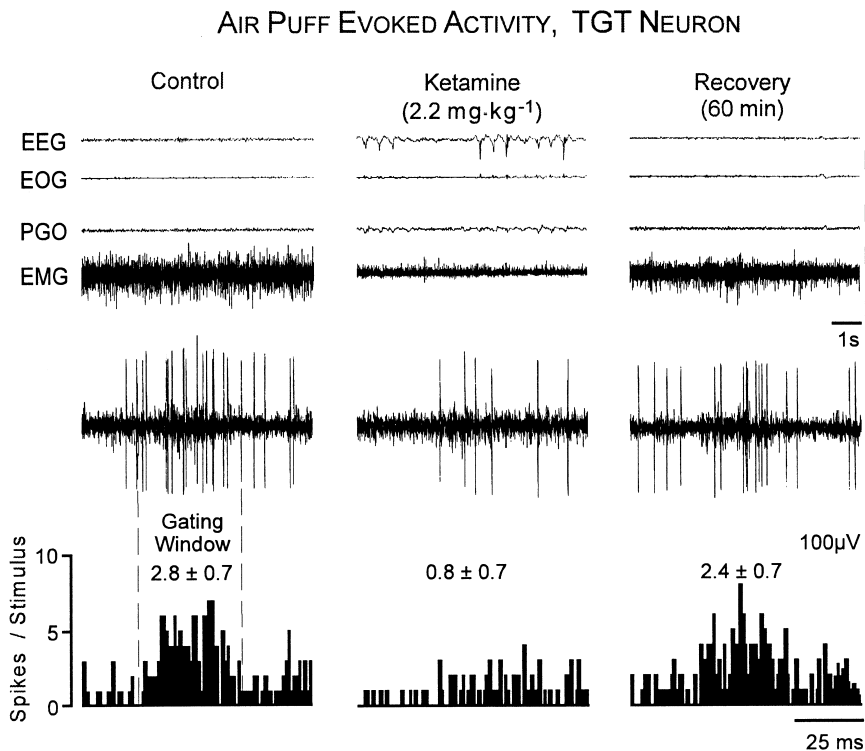


Fig. 6. Effect of ketamine on air puff-evoked activity of a trigeminothalamic (TGT) neuron. Oscilloscope traces represent behavioral state, and poststimulus time histograms reflecting neuronal activity were constructed as described in fig. 3. Neuronal activity was evoked by air-puff stimuli applied to the chin (40 ms, 0.5 psi, 0.5 Hz). Dashed vertical lines indicate the gating window used to measure the magnitude of the neuronal response. The number above each histogram indicates the mean (\pm SD) evoked activity, in spikes per stimulus. Note that air puff-evoked activity in this neuron was maximally suppressed by 65% during ketamine anesthesia. This neuron projected to the contralateral ventrobasal thalamus (antidromic latency: 1.3 ms). Vertical calibration bars (electroencephalogram, electrooculogram, pontogeniculoccipital wave, electromyogram): 50 μ V.

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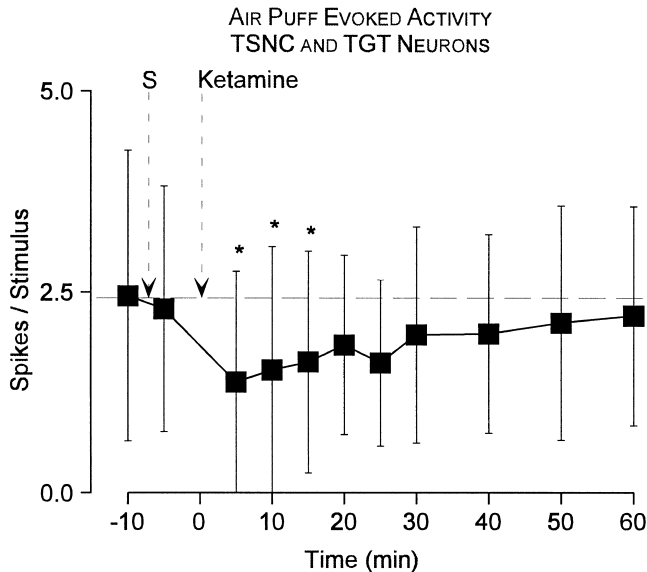


Fig. 7. Summary of ketamine's action on air puff-evoked activity recorded from trigeminal sensory nuclear complex ($n = 6$) and trigeminothalamic ($n = 2$) neurons. This graph was constructed as described in fig. 4. Overall, air puff-evoked activity was suppressed by 45% 5 min after the onset of drug administration. The time course and magnitude of ketamine's effects on air puff-evoked responses was equivalent that observed for tooth pulp-evoked responses (see fig. 8). Asterisks indicate statistically significant differences from control ($P < 0.05$ on repeated-measures analysis of variance, Dunnett's method).

analgesic properties of low doses of ketamine in conscious patients suffering from various pain syndromes.^{1,2}

Ketamine also decreased the tooth pulp-evoked activity of stimulus intensity-independent TSNC neurons. Perhaps as many as one half of all rostral TSNC neurons recorded *in vivo* that exhibit stimulus intensity-independent response characteristics similar to ours¹¹ may project to the ventrobasal thalamus.^{12,23,24} Thus, ketamine's action on stimulus-independent TSNC neurons indicates that transmission of tooth-pulp information to the thalamus and, ultimately, to the cerebral cortex is attenuated during the state of ketamine anesthesia at the level of the TSNC. This suggestion is supported by the finding that the amplitude of tooth pulp-evoked somatosensory potentials recorded in the brainstem, thalamus, and cerebral cortex of awake-behaving monkeys are suppressed after ketamine (5–15 mg/kg) administration.⁴⁰

Ketamine-related Suppression of Hair Mechanoreceptor-evoked Activity

Under our experimental conditions, the state of ketamine anesthesia was also found to be associated with decreased FHM-evoked activity in both rostral TSNC and TGT neu-

rons. This contrasts with results reported for experiments performed in acute decerebrate cat preparations, in which local or systemic administration (2–10 mg/kg) of ketamine did not affect LTM-evoked responses of unidentified spinal cord dorsal horn neurons.^{3,4} Furthermore, in the single study performed on intact, behaving cats, Collins⁴¹ concluded that ketamine (10–20 mg/kg intravenously) had no effect on non-noxious mechanoreceptor-evoked responses of unidentified lumbar dorsal horn neurons. However, Collins reported that ketamine exerted either suppressive or facilitatory actions on the non-noxious responses in 25% of the cells examined. Therefore, it is conceivable that the effect of ketamine and other NMDA antagonists on low-threshold mechanoreceptor-evoked responses of spinal cord dorsal horn neurons might depend on the type of neuron tested (*i.e.*, tract cells *vs.* segmental interneurons) or on the level of the neuraxis (*i.e.*, trigeminal *vs.* lumbar sensory neurons).

With regard to the possibility that ketamine may exert

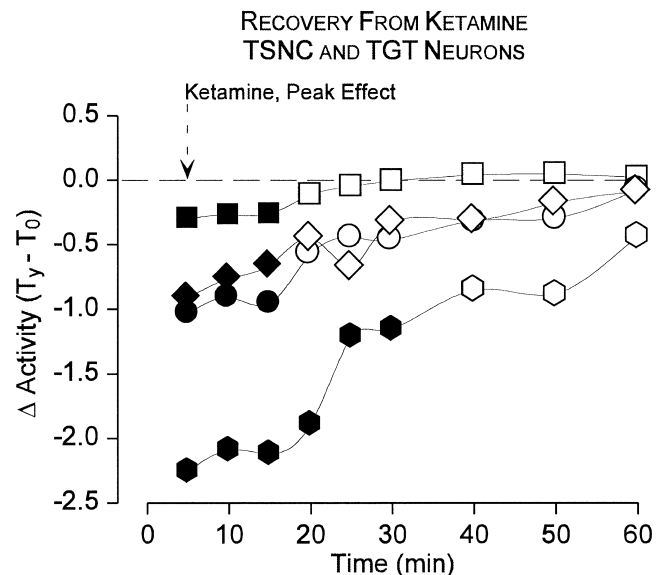


Fig. 8. Comparison of recovery from ketamine-related suppression of tooth pulp- and air puff-evoked responses recorded from trigeminal sensory nuclear complex (TSNC) neurons. The difference in evoked activity (Δ Activity) was calculated by subtracting the control response obtained after normal saline administration from responses at the indicated time points after the administration of ketamine. Closed symbols indicate statistically significant differences from control ($P < 0.05$ on repeated-measures analysis of variance, Dunnett's method). There was no difference in the time course of ketamine-related suppression if threshold responses of stimulus intensity-dependent (circles) or stimulus intensity-independent (squares) TSNC neurons were compared with air puff-evoked responses (diamonds) of TSNC neurons. However, suprathreshold responses in stimulus intensity-dependent (hexagons) remained significantly suppressed for 30 min.

different effects on local interneurons *versus* tract neurons, TGT neurons are known to display a higher density of postsynaptic NMDA receptors than other rostral TSNC neurons.³⁵ This suggests that TGT neurons could exhibit a greater sensitivity to ketamine than local TSNC interneurons. In the current study we did find that FHM-evoked responses of two TGT neurons were markedly suppressed by ketamine, but it is not clear whether this suppression was greater than for FHM-evoked responses in non-TGT TSNC neurons.

It is also conceivable that ketamine-related suppression of FHM-evoked rostral TSNC neurons may result from a distinct trigeminal site of drug action, such as on acetylcholine receptors, or an effect of ketamine on the *caudal* TSNC. Certain caudal TSNC neurons that respond to low-threshold mechanoreceptor stimuli are excited by local application of acetylcholine.^{42,43} In this mechanistic scenario, ketamine could act to decrease FHM-evoked responses in TSNC and TGT neurons *via* the suppression of a "tonic" excitatory cholinergic influence impinging on these neurons. In addition, it is thought that the caudal TSNC may exert a facilitatory influence on rostral TSNC neurons, and thus part of the suppressive effect of ketamine on FHM-evoked rostral TSNC neurons may be secondary to a ketamine-mediated decrease in the excitability of caudal TSNC neurons.⁴⁴ Nevertheless, it is also important to recognize that ketamine-related suppression of FHM-evoked responses in rostral TSNC neurons may arise by ketamine's actions on areas of the central nervous system remote from the TSNC.

Finally, in view of the fact that ketamine was administered systemically, it is important to consider recent evidence pointing to the existence of peripheral NMDA and non-NMDA receptors located in nonglabrous skin, the knee, and the temporomandibular joint, as well as the tooth pulp.⁴⁵⁻⁴⁷ Activation of peripheral NMDA receptors appears to play a role in modulating the sensitivity of cutaneous primary afferents to mechanical stimuli.⁴⁵ It remains to be determined whether or not such receptors play a functional role in resetting the excitability of FHMs by natural stimuli.

Irrespective of the site and mechanism of action, the results of the present study indicate that responses of trigeminal sensory neurons to innocuous stimuli are suppressed during the dissociative state of surgical anesthesia induced by intravenous ketamine.

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