Behavioral/Systems/Cognitive

Anesthetics Change the Excitation/Inhibition Balance That Governs Sensory Processing in the Cat Superior Colliculus

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The superior colliculus (SC) is a midbrain structure that plays a central role in the integration of information from different sensory modalities and the generation of orienting responses. Its normal function is thought to be governed by a strictly held balance between excitation and inhibition. This hypothesis was tested by recording from the same single units in the SC of cats before the injection of anesthetics, while anesthetics took effect, and after the injections during recovery. Sodium pentobarbital and ketamine, two agents commonly used in sensory physiology, were used. The results show a plethora of dose-dependent and nonlinear effects: the magnitude of evoked responses, receptive field properties, first spike latency, and bimodal integration were affected by both anesthetics in all units tested. Notably, prominent facilitation was observed at low levels of anesthesia, and inhibitory responses were changed into excitatory. Overall, the results challenge a fundamental tenet of sensory physiology: anesthesia, while decreasing single-unit responsiveness, leaves unaltered basic physiological properties.

Key words: **superior colliculus; multisensory; sensorimotor; ketamine; sodium pentobarbital; anesthesia**

Introduction

The superior colliculus (SC) is a sensorimotor integration structure that plays a fundamental role in the generation and control of gaze shifts (Wurtz and Albano, 1980; Sparks, 1986). It integrates sensory information from different modalities (Gordon, 1973) and sends axons to motor centers (Huerta and Harting, 1984). The SC is also the target of numerous inhibitory inputs (Appell and Behan, 1990) and has an extensive intrinsic inhibitory network (Mize et al., 1994).

Central to the integrative functions of the SC are neurons in its intermediate layers (SCi) that encode information from different sensory modalities (Bell et al., 1964; Jassik-Gerschenfeld, 1966). In anesthetized animals, a large proportion of those neurons exhibit bimodal enhancement (Newman and Hartline, 1981; Meredith and Stein, 1983; King and Palmer, 1985), a form of nonlinear summation of sensory responses thought to underlie behavioral facilitation (Stein and Meredith, 1993). The reaction times of responses to bimodal stimuli are shorter than those to unimodal stimuli (Frens and van Opstal, 1998; Schröger and Widman, 1998;Taylor et al., 1999). Therefore, if enhanced bimodal interactions were a mechanism underlying behavioral facilitation, they should be readily observed in the responses of SC units in a behaving preparation.

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Populin and Yin (2002) tested for the presence of bimodal enhancement in the SC of behaving cats that showed behavioral facilitation in orienting to bimodal stimuli but found no enhanced interactions between the auditory and visual modalities. They found, instead, prominent depressive effects in SC neurons. They hypothesized that bimodal enhancement may result from the spurious effects of anesthetics, which interfere with the balance between excitation and inhibition that governs normal SC function. It is well documented that the motor output of the SC is shaped by a strictly held balance between excitation and inhibition. Local injections of bicuculline (a GABA antagonist), muscimol (a GABA agonist), or muscimol into the substantia nigra pars reticulata, an inhibitory input to the SC (Graybiel, 1978; Harting et al., 1988), affect the animal's oculomotor behavior (Boussaoud and Joseph, 1985; Hikosaka and Wurtz, 1985a,b). Thus, questions arise as to whether the processing of sensory inputs in the SC is also under the control of the hypothesized excitation/inhibition balance and whether facilitation can result from altering such balance with anesthetics. Low levels of volatile and intravenous anesthetics facilitate synaptic transmission (Archer et al., 2001) and responses to somatic pain (Dundee, 1960; Arora et al., 1972; Briggs et al., 1982; Ewen et al., 1995; Zhang et al., 2000).

To address these questions, single units in the SC of the cat were studied individually, initially in the behaving state and after injections of either sodium pentobarbital or ketamine, two anesthetics used in studies of sensory processing in the SC of the cat (Meredith and Stein, 1983; Wise and Irvine, 1983; Middlebrooks and Knudsen, 1984; Hirsch et al., 1985). These data, mostly acquired in the context of the auditory modality, showed that sensory processing in the SC was affected nonlinearly. A preliminary account of this work has been presented previously (Populin, 2002).

Materials and Methods

General. The experimental procedures, including behavioral training and physiological recordings, have been published previously (Populin and Yin, 1998, 2002; Populin et al., 2004). Briefly, cats used in these experiments underwent two surgical procedures. In the first, a head post to immobilize the head and eye coils to measure eye position (Judge et al., 1980) were implanted. In the second procedure, which took place after the cat learned the required behavioral tasks (Populin and Yin, 1998), a recording cylinder was implanted perpendicularly to the horizontal plane at stereotaxic coordinates anteroposterior–mediolateral (0, 0). All surgical and experimental procedures were approved by the University of Wisconsin Animal Care Committee and were in accordance with the National Institutes of Health *Guide for the Care and Use of Laboratory Animals*.

Subjects, experimental setup, and stimulus presentation. Physiological recordings from single neurons were obtained from six female cats. The initial experiments were done in a single-walled acoustic chamber, and later experiments were done in a double-walled acoustic chamber. The interior walls of both chambers and the major pieces of equipment in them were covered with acoustic foam (Ilbruck, Minneapolis, MN) to attenuate reflections.

Acoustic stimuli were presented with Radio Shack supertweeters (model 40–1310A; Radio Shack, Fort Worth, TX) modified to transduce low frequencies. With the exception of two experiments in which trains of 100 μs clicks presented at 5 Hz were used, the acoustic stimuli were broadband (0.1–20 kHz) noise bursts with 7 ms linear rise/fall windows of different durations presented at ~20 dB above the threshold of each unit. Visual stimuli were presented with red light-emitting diodes (LEDs). The LEDs were positioned in front of the speakers. They subtended a visual angle of 0.2°. Bimodal stimuli consisted of acoustic and visual stimuli presented simultaneously from the same spatial location.

Eye movement recording, experimental tasks, and electrophysiology. All experiments were done with the head of the cat restrained. Eye movements were recorded with the scleral search coil technique (Robinson, 1963). The analog output of the coil system (CNC Engineering, Seattle, WA) was sampled digitally at 500 Hz. Eye position signals were calibrated with a behavioral procedure that relied on the cat's tendency to look at spots of light, which were presented at known positions in a dimly lit environment (Populin and Yin, 1998).

No effort was made to control for effects of eye position on auditory responses recorded in the SCi during the control behaving condition, because behavioral control was lost after the injection of anesthetics. Accordingly, the fixation task (Populin and Yin, 1998), in which acoustic, visual, or bimodal stimuli are presented without temporal or spatial behavioral contingencies, was used. In the control condition, various targets were used to motivate the cat to participate in the experimental session while emphasizing the presentation of stimuli within the best area of the unit; the majority of trials were focused on the selected target. This was essential for the study of units with best areas located outside the cat's oculomotor range, because they were trained to orient to the sources of stimuli for rewards and not to sit quietly. To avoid problems associated with response habituation, the same configuration of trials was used in the anesthetized conditions.

Extracellular recordings were obtained from well isolated single units in the SCi with tungsten electrodes covered with parylene (Micro Probe, Potomac, MD) driven by a Narishige microdrive (Narishige International, East Meadow, NY). The neural signal was amplified (Bak Electronics, Mount Airy, MD) and bandpass filtered (0.3–3 kHz; Krohn-Hite, Brockton, MA). Single pulses, generated by a window discriminator (Tucker Davis Technologies, Alachua, FL) when action potentials met amplitude and temporal criteria set by the investigator, were recorded with a custom-made event timer with microsecond accuracy and saved on a disk for off-line analysis. Care was exercised to ensure that in every condition of an experiment, recordings were performed from the same single unit. A cumulative record of all action potentials that met the temporal and spatial criteria set by the investigator at the start of the recording was kept on a digital storage oscilloscope.

In a typical electrode penetration, activity was recorded sequentially as follows: light-driven activity in cortex, silence in the superior cistern, and light-driven activity in the superficial layers of the SC. With the tip of the electrode in the superficial layers of the SC, which was encountered ~15 mm below the surface of the cortex, the cat was required to fixate on an LED straight ahead. Then, to determine the location of the recording electrode within the SC map, visual stimuli were presented on the curtain covering the speakers in front of the cat with a handheld ophthalmoscope or a laser pointer. No attempt was made to isolate units in the superficial layers. Auditory activity was found ~1.5 mm below the top of the light-driven activity in the SC. The end of all recordings was determined by the loss of the unit.

Anesthetizing methodology and data analysis. Sodium pentobarbital and ketamine were selected for the present study, because they have been used in physiological studies of the SC (Meredith and Stein, 1983; Wise and Irvine, 1983; Middlebrooks and Knudsen, 1984; Hirsch et al., 1985) and can be administered intravenously during recordings from single units. Both drugs were injected in the form of racemic mixtures. Sodium pentobarbital, a barbiturate, acts by potentiating $GABA_A$ receptors (Barker and Ransom, 1978; Franks and Lieb, 1994). Ketamine, a cyclohexylamine, inhibits the action of glutamate on NMDA receptors (Anis et al., 1983; Monaghan et al., 1989).

The animals were used regularly for other studies. Recordings for this study took place with at least 4 weeks of separation for each of the subjects to avoid habituation to the drugs and unnecessary stress. The method used to administer anesthetics intravenously to behaving cats was adapted from the study by Kuwada et al. (1989). A nonpermanent catheter was chosen over a permanent catheter to minimize the risk of infection resulting from the long tenure of the animals used in this study. The disadvantage of this approach concerned having to insert the catheter in the awake animal before a recording session.

Cats were placed in a veterinary restraining bag, and the fur covering the front of the front legs was shaved. Under gentle restraint, a 22–26 gauge disposable catheter was inserted into the cephalic vein of one of the front legs, and an extension line filled with saline was connected to the catheter. Both the catheter and the extension line were secured with surgical tape and veterinary wrap. The success of the procedure depended heavily on not over-restraining the animal and on a speedy completion. None of the cats showed signs of distress after the catheter was inserted into the cephalic vein and secured to the leg.

With the catheter in place, the search for single units in the SCi proceeded as described previously (Populin and Yin, 2002; Populin et al., 2004). To maximize the chances of success (i.e., record from the same unit before and after the administration of an anesthetic), it was important to isolate a single unit early in the experiment and to administer the anesthetic while the animal was in the most cooperative state. Administering the anesthetic late in an experimental session increased the chances of the animal moving excessively, causing the loss of the unit. Recordings were taken immediately after every injection of anesthetic. At the end of recording sessions in which an anesthetic was injected, the animal was placed under a heating lamp and observed until it was able to stand on its own.

The effects of anesthetics on the responses of single SCi units were evaluated for the following physiological variables: magnitude of auditory responses evoked with stimuli presented within the best area of each single unit, auditory spatial tuning, auditory first-spike latency (FSL), and bimodal (audition plus visual) integration. The magnitude of evoked responses was evaluated by counting the number of action potentials evoked by the stimuli within 200–2000 ms windows, depending on the type of responses evoked; the size of the analysis window selected for each unit was kept constant across conditions. The average magnitude of the discharge and 95% confidence intervals were computed for each of the conditions to evaluate the effect of the anesthetics. Mean FSL was computed by taking into account the first action potential occurring within a window starting 5 ms after the onset of the stimulus; trials in which the first action potential occurred >100 ms after the onset of the stimuli were excluded from the FSL analysis. Bimodal integration was evaluated by computing a bimodal index (BI) (King and Palmer, 1985; Populin and Yin, 2002) as follows: $BI = [(Bi - A - V)/(A + V)]^*100$, where Bi is the response to the bimodal stimuli, V is the response to the visual stimuli, and A is the response to the acoustic stimuli in number of spikes.

Histology. Two of the six cats used in this study continue to serve as subjects in physiological experiments; thus, there is no histology available from them. However, the pattern of activity described above was observed in every electrode penetration. In general, electrode penetrations that missed the SC rostrally did not yield auditory-driven activity, and penetrations that missed the SC caudally yielded very-low-threshold auditory activity from the inferior colliculus at a depth of ~15 mm instead of the strong light-driven activity of the superficial layers of the SC. The remaining four cats, which served as subjects in previous studies (Populin and Yin, 2002; Populin et al., 2004), were killed at the end of the recordings, and their brains were extracted and processed as described previously (Populin et al., 2004). All visible electrode penetrations aimed at the SC were located within the structure.

Results

Dataset

The responses of sixteen SC units were studied in the control, awake-behaving state and after the injection of anesthetics. All units were found in a strip that expanded ~0.7–0.8 mm dorsoventrally, ~1.2–1.3 mm below the surface of the SC, which corresponds to the stratum griseum intermediale (Huerta and Harting, 1984) and responded preferentially to stimuli presented in the field contralateral to the recording side. Fourteen of the SC units were studied with acoustic stimuli only, and two units were studied with bimodal (visual and acoustic) stimuli. Ketamine caused nystagmus within seconds of intravenous administration, rendering the animals unable to perform the experimental task. Sodium pentobarbital, in contrast, appeared to act more slowly, changing the dynamics of saccadic eye movements and causing the eyes to drift before rendering the animals unable to execute the experimental task.

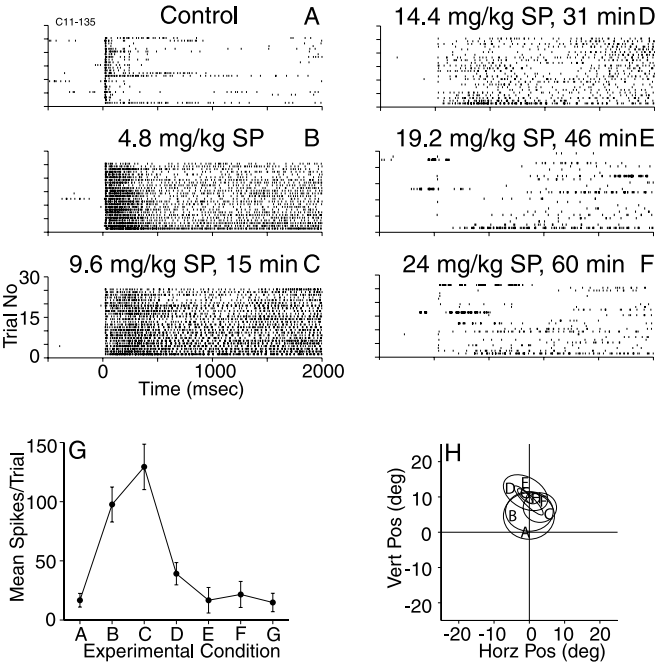

Figure 1. Effect of sodium pentobarbital on the magnitude of auditory responses of a single unit from the intermediate layers of the superior colliculus. The stimulus was a 2000 ms broadband noise presented from a speaker at (18°, 0°). ***A–F***, The doses of sodium pentobarbital (SP) and the time of administration are shown above each panel. A summary of the observations in the form of mean number of spikes per trial is plotted for each condition in ***G***. The position of the eyes during the various experimental conditions is plotted on a Cartesian plane in ***H***. Horz Pos, Horizontal position; Trial No, trial number; Vert Pos, vertical position.

Effect of anesthetics on the magnitude of auditory-evoked responses

Sodium pentobarbital

Figure 1 illustrates the responses of an SCi unit to broadband noise stimuli presented from a speaker located at (18°, 0°). Under control conditions (Fig. 1*A*), the unit responded with a transient burst followed by lower-frequency discharge for 100–150 ms. Very little activity was observed during the last 1500 ms of acoustic stimulation. Transient responses to sustained broadband acoustic stimuli, such as these, are typically observed in the SC of the behaving cat (Populin and Yin, 2002; Populin et al., 2004).

The injection of 4.8 mg/kg sodium pentobarbital significantly changed the responsiveness of the unit to acoustic stimulation (Fig. 1*B*). The duration of the initial burst was lengthened to nearly 300 ms, as was the tonic component of the response, which extended until the end of the stimulus (2000 ms). The magnitude of the responses to the same stimulus further increased after the injection of a second dose of 4.8 mg/kg sodium pentobarbital (9.6 mg/kg in total) 15 min after the first injection (Fig. 1*C*). Measured over the entire duration of the stimulus, the magnitude of the response was increased 10-fold relative to the control (Fig. 1*G*). The increasing magnitude of the response was reversed by the injection of a third dose of 4.8 mg/kg sodium pentobarbital (14.4 mg/kg in total) 31 min after the injection of the first dose (Fig. 1*D*). An additional injection of 4.8 mg/kg sodium pentobarbital (19.2 mg/kg in total) 46 min after the first injection further changed the responses of the unit to the acoustic stimuli; the initial transient burst was reduced, and the tonic component of the response showed signs of habituation (Fig. 1*E*). The first trial, plotted at the bottom of the raster in Figure 1*E*, showed the largest sustained response. In subsequent trials, the tonic component developed later during the course of the stimulus. Interestingly, the average magnitude of the response was similar to the control (Fig. 1*G*) but with a very different profile. The initial burst was reduced to a single action potential in some trials and eliminated in others. The tonic component of the response, in contrast, was preserved for the duration of the stimulus. Data acquired after an additional injection of 4.8 mg/kg sodium pentobarbital (24 mg/kg in total) 60 min after the first injection (Fig. 1*F*) and after a last injection of 4.8 mg/kg sodium pentobarbital (not shown in raster format) showed little change in the magnitude of the responses (Fig. 1*G*). The position of the cat's eyes during these physiological recordings is illustrated in Figure 1*H*. For each condition, the area of space covered by the eye movements was drawn by hand. This animal did not orient to the acoustic source at (18°, 0°) in the control condition, although it did orient to visual stimuli presented from the same location (data not shown). Note that, in general, the position of the eyes was consistent within and across the various experimental conditions. At the end of the recording session, the cat was not able to stand and required several hours to recover.

A different pattern of changes resulting from the administration of sodium pentobarbital is illustrated in Figure 2 for a different unit. The single-unit data shown in this figure are plotted in an expanded time scale relative to Figure 1 to show detail. The acoustic stimulus was broadband noise composed of 163 ms bursts (±7 ms rise/fall) consecutively repeated six times. In the control condition (Fig. 2*A*), the unit responded with the typical transient burst followed by lower-frequency activity. The injection of 14 mg/kg sodium pentobarbital increased the magnitude of the acoustically evoked responses as documented in most units (Fig. 2*B*,*F*), but it did not reduce the magnitude of the initial burst. An additional dose of 4.4 mg/kg sodium pentobarbital 18 min after the first injection reduced the sustained component of

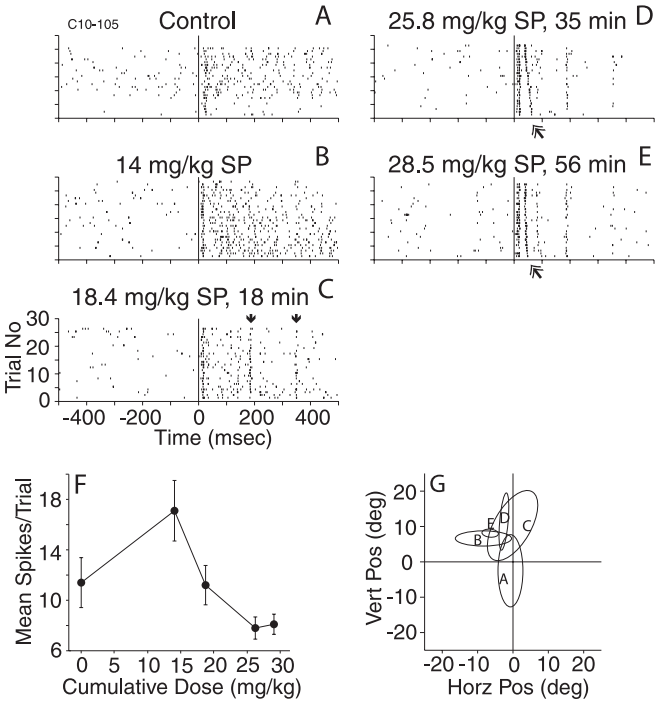

Figure 2. Effect of sodium pentobarbital on the magnitude of auditory responses of a single unit from the intermediate layers of the superior colliculus. ***A–E***, The acoustic stimulus was a 163 ms (±7 ms rise/fall) broadband noise burst repeated successively for 1000 ms, presented from a speaker at (90°, 0°). The arrows in ***C*** point to components of the responses corresponding to the offset/onset of the repeating envelope of the stimulus. The arrows in ***D*** and ***E*** point to distinct auditory inputs revealed under sodium pentobarbital anesthesia. Note the shortening of the latency of the column of spikes as the anesthesia injected just before the first trial, plotted at the bottom of the raster, progressively took effect. A summary of the observations, computed as in Figure 1, is shown in ***F***. The position of the eyes during the physiological recordings is shown in ***G***. Horz Pos, Horizontal position; SP, sodium pentobarbital; Trial No, trial number; Vert Pos, vertical position.

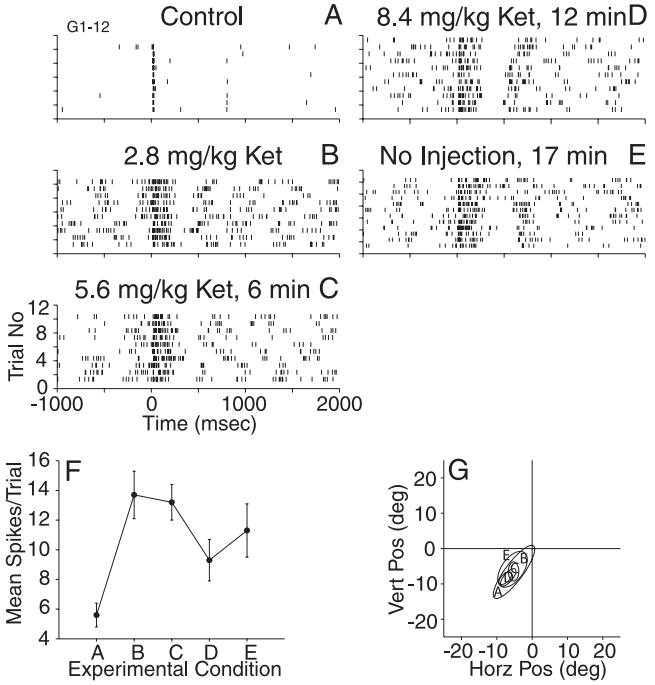

Figure 3. ***A–E***, Effect of ketamine (Ket) on the magnitude of auditory responses of a single unit from the intermediate layers of the superior colliculus. The stimulus was a 750 ms broadband noise burst presented from a speaker at (−18°, 0°). Note the changes in spontaneous activity occurring before stimulus presentation (times, −1000 to 0 ms) and duration of evoked responses. A 200 ms analysis window was used to construct the summary curve in ***F***. The position of the eyes during physiological recordings is shown in ***G***. Horz Pos, Horizontal position; Trial No, trial number; Vert Pos, vertical position.

the response and revealed the offset/onset of the envelope of the repeating bursts of the noise stimuli with well timed action potentials, as indicated by the vertical arrows in Figure 2*C*.

The recordings taken immediately after additional injections of 7.4 and 2.7 mg/kg sodium pentobarbital 35 and 56 min after the first injection (Fig. 2*D*,*E*), respectively, revealed consistent patterns of action potentials within the first 100 ms, indicating the arrival of distinct inputs to this unit. The latency of these inputs changed as the sodium pentobarbital (Fig. 2*D*,*E*, arrows) injected just before the onset of the first trial, which is plotted at the bottom of the raster, started to take effect. Unlike the initial burst of the response of the unit shown in Figure 1, the magnitude of which was reduced by sodium pentobarbital, the initial peak of the response of this unit was increased after the injection of sodium pentobarbital relative to the control (Fig. 2*A*,*D*). The dose–response curve (Fig. 2*F*) reveals a similar pattern of facilitation after the first dose of sodium pentobarbital followed by a decrease in responsiveness after subsequent doses as documented in Figure 1. The position of the cat's eyes during these recordings is shown in Figure 2*G*; these data are plotted in the format used in Figure 1*H* above. In the control condition, the cat oriented its eyes to the location of the acoustic target at (0°, −12°) but ceased to orient after the first injection, with its eyes remaining essentially above the midline. The cat was not able to stand at the end of the recording session.

Ketamine

The spontaneous discharge of all three units tested with ketamine was increased within seconds of the first injection. The magnitude of auditory evoked responses was increased in two of the three units in which the effects of this drug were studied. Figure 3*A* shows the responses of an SCi unit to 750 ms broadband noise stimuli presented from a speaker at (−18°, 0°) under control conditions. This unit had very low, practically no spontaneous activity, and it responded to the noise stimuli with a short burst of action potentials. In ~50% of the trials, the unit signaled the offset of the stimulus with a single action potential. Transient responses of this type to broadband acoustic stimuli are typical of the SCi in the behaving cat (Populin and Yin, 2002; Populin et al., 2004).

Within five seconds of the administration of 2.8 mg/kg ketamine, the unit started to discharge spontaneously and became more responsive to the same acoustic stimuli (Fig. 3*B*,*F*), as illustrated by the lengthening of the initial burst. An additional dose of 2.8 mg/kg ketamine administered 6 min after the first dose did not produce significant changes (Fig. 3*C*,*F*), but the magnitude of the responses was reduced after a third injection of 2.8 mg/kg ketamine (Fig. 3*D*,*F*) administered 12 min after the injection of the first dose. Additional data recorded from this unit are presented in Figure 10; note, in Figure 10, that 55 min after the last injection of ketamine, the responses of the unit to acoustic stimuli had not returned to the control level. Similar responses were observed in another unit studied with ketamine, whereas the responses of a third unit, which was studied with click stimuli, changed very little. In all three experiments in which ketamine was injected, the cats were not able to stand at the end of the recordings.

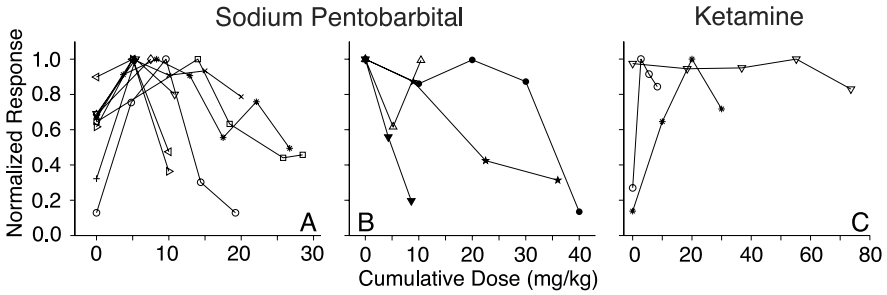

Figure 4. Summary of changes in the magnitude of auditory-evoked responses as a function of the cumulative dose of sodium pentobarbital (***A***, ***B***) and ketamine (***C***) injected. The data are normalized to the largest response of each unit. ***A***, Units with facilitated responses after the initial injection of sodium pentobarbital. ***B***, Units with depressed responses after the initial injection of sodium pentobarbital.

Figure 4, *A* and *B*, shows the summary of the changes in the magnitude of auditory-evoked responses in 13 units brought about by sodium pentobarbital. Data from the best response area of each unit were plotted normalized to the largest response as a function of the cumulative dose. Data recorded during recovery (i.e., not associated with the injection of a dose of anesthetic) are not included. Two groups were distinguished based on the responses to the initial light doses of sodium pentobarbital: 70% (9 of 13) of the units increased their discharge (Fig. 4*A*), whereas the remaining 30% decreased their discharge (Fig. 4*B*). The effects of ketamine on the same measure are summarized in Figure 4*C*. Two of the units exhibited the characteristic increase in the magnitude of auditory-evoked responses observed after the first injection of sodium pentobarbital. The similarities also included a decrease in evoked activity after subsequent injections of ketamine. The third unit, in contrast, showed remarkable resistance to ketamine over a very large dose range (Fig. 4, open triangles) despite changes in the profile of the response.

Effects of anesthetics on auditory receptive field properties

Documenting the effects of anesthetics on the entire spatial extent of auditory receptive fields (RFs) of SCi units was not possible because of the long recording times required. Auditory RFs are large in the SCi (Gordon, 1973; Middlebrooks and Knudsen, 1984). Accordingly, the coding of information is thought to involve large neuronal populations (Sparks et al., 1975; Van Gisbergen et al., 1987; McIlwain, 1991). Proportional changes in the responses to stimuli presented from all speakers tested within the receptive field of a unit would suggest that anesthetics do not actually affect the manner in which information is encoded in the SC, but that they simply modulate the magnitude of the responses. In contrast, disproportionate changes in the responses to such stimuli would suggest that the encoding of information by the population of neurons might be affected.

In three experiments, two with sodium pentobarbital and one with ketamine, in which recording conditions were judged robust, the responses of single units to stimuli presented from several targets were characterized before and after the administration of drugs. The results of those experiments are presented below.

Sodium pentobarbital

Figure 5 illustrates the responses of a single SCi unit to stimuli presented from six speakers on the contralateral hemifield; their location on the horizontal plane is shown at the top of the figure. The stimulus was a broadband noise burst 750 ms in duration. Under control conditions (Fig. 5*A*), the unit responded to the acoustic stimuli with an initial high-frequency burst followed by low-frequency activity. The strongest responses were evoked by stimuli presented from the most eccentric targets available in the setup (−60°, 0°) and (−70°, 0°). The cat oriented to the acoustic targets that were within its oculomotor range, and, consistent with previous observations in the head restrained cat (Populin and Yin, 1998), the subject undershot such targets (Fig. 5*F*,*G*).

The injection of 5 mg/kg sodium pentobarbital changed the magnitude of the responses to stimuli presented from all speakers (Fig. 5*B*). The results are expressed as a percentage of change from the control (Fig. 5*D*,*E*); thus, linearly scaled changes should have resulted in functions parallel to the dashed lines. With the exception of the responses evoked by stimuli presented from a speaker at (−30°, 0°), which remained essentially unchanged, the high-frequency burst that characterizes most SCi responses to acoustic stimuli was reduced or abolished (Fig. 5*D*); the maximal frequency of the bursts was measured from normalized histograms constructed for this purpose (data not shown). The overall magnitude of the response, computed over a 750 ms window, was reduced for speakers closer to the midline and increased for the most eccentric (Fig. 5*E*), thus demonstrating nonlinear changes in the portion of the horizontal spatial tuning of the unit covered by the speakers relative to the control.

Behaviorally, the cat was driven into an overexcited state by the first injection of 5 mg/kg sodium pentobarbital. Eye movements directed at an acoustic target at (−18°, 0°) (Fig. 5*H*), although slower, as suggested by the shallower slope of the straight line fitted to the main sequence (Fig. 5*I*), were larger and therefore more accurate because they ended closer to the target (Fig. 5*F*). Thus, although this single unit became less responsive to the acoustic stimuli, the cat became more responsive, judging by the amplitude of its eye movements.

A second dose of 5 mg/kg sodium pentobarbital administered 17 min after the first dose, for a cumulative total of 10 mg/kg, further disrupted the responses of the unit. In this condition, the responses of the unit became erratic. At times, it discharged in bursts that were not related to the stimuli, and at other times, it remained silent for several trials (Fig. 5*C*). The cat did not attempt to orient to any of the targets in this condition, and its eyes remained near the primary position. Note that the eyes were near the straight-ahead position before (Fig. 5*G*) and after (Fig. 5*H*) the administration of the anesthetic at the time of stimulus presentation. At the end of the recording session, the cat was not able to walk or stand normally.

Figure 6 illustrates a different effect of the same dose of sodium pentobarbital on the responses of another SCi unit from a different cat to stimuli presented from various locations within its RF. Data from the horizontal and vertical aspects of the RF of the unit recorded under control conditions are plotted in Figure 6*A* and *D*, respectively. The acoustic stimulus was a 750 ms broadband noise burst. On the horizontal axis, the unit exhibited narrow tuning with the strongest responses evoked from a speaker at (−9°, 0°). On the vertical axis, the unit was less selective and responded more strongly to stimuli presented above and below the horizontal plane (Fig. 6*D*). The behavior of the cat in the control condition was consistent with previous observations

(Populin and Yin, 1998). For simplicity, only the vertical component of the eye movements to targets above (0°, 22°) and below (0°, −12°) the horizontal along the midline is plotted (Fig. 6*G*).

The injection of 5 mg/kg sodium pentobarbital increased the responsiveness of the unit to acoustic stimulation from all speaker positions tested (Fig. 6*B*,*E*). Notably, the initial burst of the response was actually larger. The cat continued to orient to the acoustic targets but less frequently (Fig. 6*I*) and with a larger undershoot. Changes in the responses of the unit to stimuli presented from the various speakers were quantified as in Figure 5 and were expressed as a percentage change from the control (Fig. 6*C*,*F*). The experiment included the administration of three additional doses of 5 mg/kg sodium pentobarbital for a total of 20 mg/kg administered 18, 30, and 42 min after the first injection, respectively.

The selectivity of the unit to stimuli presented along the horizontal axis was degraded at all four levels of sodium pentobarbital administered; note that in the summary (Fig. 6*C*), the responses are above the dashed line representing the control. Thus, they were facilitated. Surprisingly, the magnitude of the responses was not changed further across the four conditions in which additional doses of sodium pentobarbital were administered (Fig. 6*C*). The responses to stimuli presented from speakers along the vertical plane were affected in a similar manner (Fig. 6*F*). Orienting behavior to the acoustic targets practically ceased after the third injection of sodium pentobarbital. In summary, the responses to acoustic stimuli presented from various locations within the RF of each unit were clearly affected.

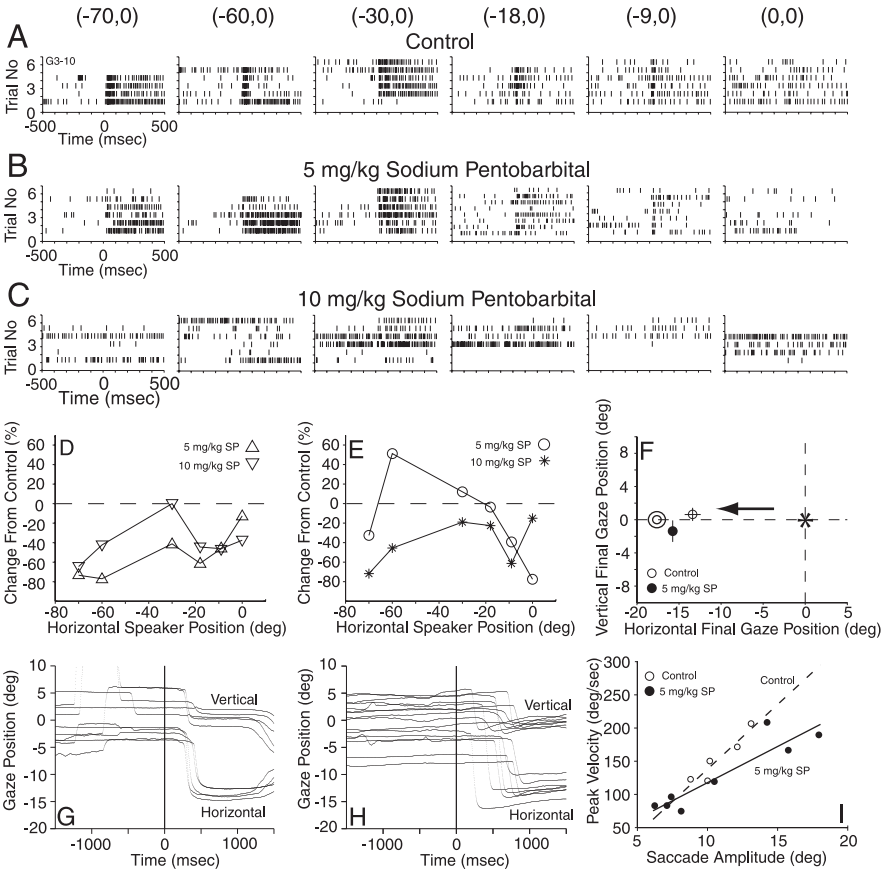

Figure 5. Effect of sodium pentobarbital on the spatial tuning of a single unit from the intermediate layers of the superior colliculus. ***A***, Control conditions. The position of the speakers used to present the acoustic stimulus is indicated at the top of each panel. The data, which were collected with the fixation task, are plotted synchronized to the onset of the stimuli. ***B***, ***C***, Horizontal aspect of the receptive field of the same unit recorded after the injection of 5 and 10 mg/kg sodium pentobarbital, respectively. ***D***, Change in the magnitude of the initial peak of the response that resulted from the injection of sodium pentobarbital, expressed as a percentage of the control for each target; the control is represented by a dashed line. ***E***, Change in the magnitude of the response caused by the injection of sodium pentobarbital, expressed as a percentage of the control for each target; the analysis was performed over a 500 ms window. ***F***, Sound localization behavior before and after the injection of the first dose. The position of the target, located at (−18°, 0°), is illustrated by the bulls-eye. The asterisk marks the center of the field, near which the cat's eyes were at the start of most trials, and the horizontal arrow illustrates the direction of the eye movements to the target. The final eye position recorded in the control and anesthetized conditions is illustrated by the open and filled symbols, respectively. The SE bars represent 95% confidence intervals. ***G***, ***H***, Horizontal and vertical components of the eye movements to the acoustic target illustrated in ***F***, recorded in the control condition and after the injection of 5 mg/kg sodium pentobarbital. ***I***, Main sequence computed from the horizontal component of the eye movements shown in ***G*** and ***H***. The straight lines fitted to the control (open symbols) and 5 mg/kg sodium pentobarbital conditions (filled symbols) were 19.5 and 11°/s, respectively. SP, Sodium pentobarbital; Trial No, trial number.

Ketamine

Ketamine also affected the responses to stimuli presented from different speakers within the RF of a unit. Figure 7 illustrates the results of one experiment in which stimuli were presented from four speakers positioned on the vertical plane on the midline. In the control condition, the unit discharged spontaneously at a higher rate than most units found in the SCi of the behaving cat (Populin and Yin, 2002; Populin et al., 2004). The unit responded strongly to stimuli presented from below the horizontal plane (Fig. 7*A*). Stimuli presented from a speaker at (0°, 8°) exerted an inhibitory effect, as evidenced by the reduced activity during the entire duration of the 750 ms broadband noise stimuli (Figure 7*A*, arrow).

The oculomotor behavior of the cat in the control condition is illustrated in the bottom panel of Figure 7*A*. Eye movements to an acoustic target at (0°, 16°) are plotted synchronized to the onset of the acoustic stimulus at time 0 ms; the horizontal component of the eye movements was omitted for simplicity. The slope of a straight line fitted to the main sequence data (Fig. 7*G*) from the eye movements in the control condition (Fig. 7*A*) was consistent with a previous report (Populin and Yin, 1999).

The effects of an injection of 10 mg/kg ketamine are illustrated in Figure 7*B*. The responses to stimuli presented from all four speakers were changed. An initial high-frequency burst, which was conspicuously absent in the control condition, appeared in the responses evoked by the acoustic stimuli presented from all four acoustic targets. The responses to stimuli presented from all four targets were changed by ketamine. Notably, the inhibition of the spontaneous activity caused by the acoustic stimuli presented from the target at (0°, 8°) in the control condition was reversed, as indicated by the arrow with an asterisk in Figure 7*B*. Figure 7*F* shows, in the form of percentage change from the control, that the unit was more responsive to stimuli delivered from all four speaker positions, particularly to stim-

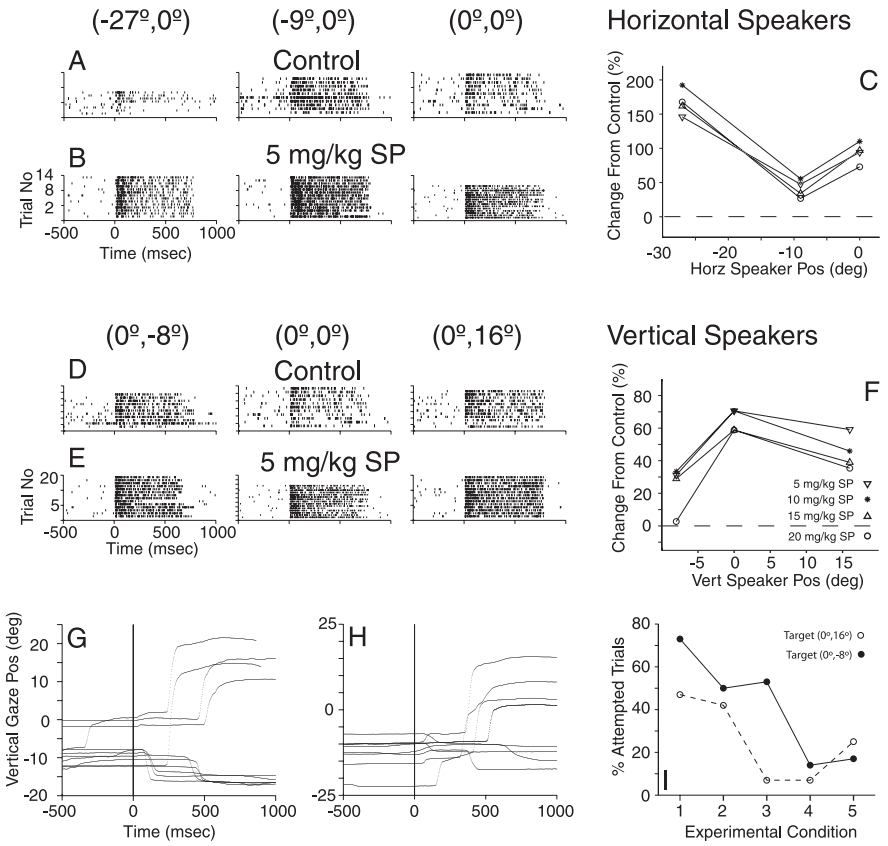

Figure 6. Effects of sodium pentobarbital on the spatial tuning of a single SCi unit. ***A***, ***D***, Responses to acoustic stimuli presented under control conditions from speakers on the horizontal and vertical axis, respectively. ***B***, ***E***, Responses of the unit to the same acoustic stimuli immediately after the injection of 5 mg/kg sodium pentobarbital. ***C***, ***F***, Summary of the responses evoked from each of the five targets used, expressed as a percentage change. The control data are plotted as a horizontal dashed line at 0%. Additional injections of 5 mg/kg sodium pentobarbital were administered 18, 30, and 42 min after the first dose. These data are plotted with the asterisks and the open circles and triangles, respectively. ***G***, ***H***, Vertical components of eye position (Pos) illustrating the amplitude of the eye movements recorded in the control condition and after the injection of 5 mg/kg sodium pentobarbital. ***I***, Percentage of attempted orienting responses recorded in each of the experimental conditions, illustrating that the participation of the animal in each recording condition decreased as the cumulative dose of anesthetic increased. Horz Speaker Pos, Horizontal speaker position; SP, sodium pentobarbital; Trial No, trial number; Vert Speaker Pos, vertical speaker position.

uli delivered from the speaker at (0°, 8°) after the injection of the first dose of ketamine.

The oculomotor behavior of the cat was also affected by the dose of 10 mg/kg ketamine. It exhibited the characteristic nystagmus, which started approximately 5 s after the first injection. The slope of the straight line fitted to the main sequence of the fast vertical component of the nystagmus had a steeper slope than the line fitted to the main sequence of the vertical component of saccadic eye movements to acoustic targets made in the control condition (Fig. 7*G*).

The magnitude and profile of the responses to acoustic stimuli presented from each of the four speakers were further affected by the injection of two additional doses of 10 mg/kg ketamine (Fig. 7*C*,*D*). The second dose of 10 mg/kg ketamine injected 10 min after the first (Fig. 7*C*) increased the amplitude of the initial burst of the response. The oculomotor behavior continued to exhibit nystagmus, but the amplitude of the fast component was slightly smaller than in the previous condition. The third dose of 10 mg/kg ketamine injected 21 min after the first, for a total of 30 mg/kg, brought little additional change in both the responses of the single unit to the broadband noise stimuli and the cat's oculomotor behavior.

A last set of recordings, obtained 42 min after the first injection shortly before losing the unit, is shown in Figure 7*E*. The responses of the unit to the same acoustic stimuli presented from all four speakers were smaller than those in the previous condition, and the eye movements continued to show nystagmus. The position of the cat's eyes during the recordings is shown in Figure 7*H*. As in previous figures, the area of space over which the eyes moved in each condition is indicated with the corresponding letter. In the control condition, the eyes of the cat were approximately at the center of the field at the time of stimulus presentation. After the first injection of ketamine, the eyes drifted ~5° to the left and 3–7° downward. At the end of the experiment, the cat was unable to stand.

Effect of anesthetics on auditory first-spike latency

FSL measures the time elapsed between the onset of a stimulus and the response of a unit. This measure is sensitive to both the spatial location and the intensity of the stimuli. Accordingly, all units were studied with stimuli presented within the most sensitive area of their RFs at ~20 dB above threshold. Under control conditions, the mean FSL of all units studied was 17.3 ms (SD, 4.6; $n = 17$). This value was indistinguishable from a previous report of 17.7 ms obtained from 80 U studied under similar conditions using the auditory fixation task (Populin and Yin, 2002). The FSLs of 14 units were included in the analysis. The remaining units were excluded because their evoked responses were too variable after the injection of the anesthetic (Fig. 5*C*).

Sodium pentobarbital

Sodium pentobarbital changed the auditory FSLs of all SCi units studied with this drug. First-spike latency was lengthened in seven units and shortened in the other four. Figure 8*A* depicts an example from the group of units with auditory mean FSL that was shortened by the injection of sodium pentobarbital. The first trial of each condition is plotted at the bottom of each panel. With some exceptions, the injection of sodium pentobarbital shortened the duration of the initial burst. In unit C10–105 (Fig. 8*A*), the injection of sodium pentobarbital revealed distinct temporal patterns of action potentials, suggesting that different inputs arrived at this unit at different times. The timing of these events, illustrated in the bottom two panels with rasters in Figure 8*A*, changed as the last doses of sodium pentobarbital took effect. A comparison of the FSL between the control (dashed lines) and the condition with the largest cumulative dose of anesthesia (solid lines) is shown below the rasters (Fig. 8*A*,*B*).

A summary of the changes in FSL brought about by sodium pentobarbital is shown in Figure 8, *C* and *D*; units with the largest changes are shown separately in Figure 8*D* for clarity. The data are plotted normalized to the mean FSL recorded in the control condition. A total of 64% of the units studied showed a lengthening of FSL caused by the depressive effect of the sodium pen-

tobarbital on neuronal responses, and the remaining 36% showed a shortening in FSL. The shortened FSLs were similar to those from acute studies of SC units that used the same anesthetic (Wise and Irvine, 1983; Hirsch et al., 1985). The magnitude of the auditory-evoked responses of those four neurons was also increased, showing facilitation in both measurements. Curiously, five units with longer FSL showed a concurrent increase in the magnitude of auditory-evoked responses, demonstrating that while one measure was depressed, the other was facilitated.

Ketamine

Auditory FSL was also affected by ketamine in all SCi units studied with this drug. The data in Figure 8*B* are a subset of those presented in Figure 7 and illustrate the shortening of auditory FSL after the injection of ketamine. The acoustic stimuli were broadband noise bursts presented from a speaker at (0°, −12°). A summary of the effects of ketamine on FSL is shown in Figure 8*E*. First-spike latency was lengthened in one unit and shortened in the other two units.

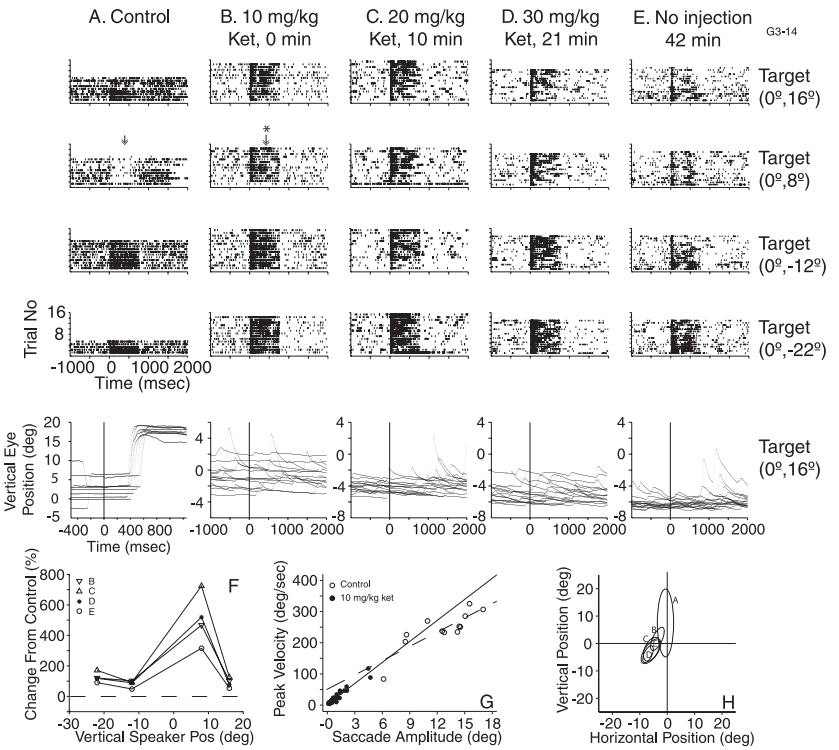

Figure 7. Effect of ketamine on auditory vertical spatial tuning of a single unit in the intermediate layers of the superior colliculus. The location of the four acoustic sources used is indicated on the right margin. This was an unusual superior colliculus unit, with a high spontaneous discharge. ***A***, Responses to the acoustic stimulus, 750 ms broadband noise burst presented at ~20 dB above threshold, in the control condition. Note that the stimulus presented from the speaker at (0°, 8°) exerted an inhibitory effect, indicated by a vertical arrow. The vertical component of eye movements to the acoustic target at (0°, 16°) is shown below the single-unit data. ***B***, Responses to the same acoustic stimulus recorded immediately after the first injection of ketamine. Clearly, the unit became more responsive to stimuli presented from all targets. Worth noticing is the change in the responses to stimuli presented from the speaker at (0°, 8°), which changed from inhibition to excitation (vertical arrow with asterisk). The vertical component of eye position recorded in this condition depicted the typical nystagmus caused by ketamine. ***C***, ***D***, Responses of the same unit after two additional injections of ketamine. ***E***, Responses recorded during the recovery period. The oculomotor behavior of the cat continued to exhibit nystagmus >21 min after the last injection of ketamine. ***F***, Summary of the responses for the various acoustic targets, expressed as percentage change from the control, as in Figures 5 and 6. ***G***, Main sequence plots of vertical saccades to acoustic targets performed in the control condition (15.3°/s) (open symbols) and the fast component of the nystagmus after the injection of 10 mg/kg ketamine (22.5°/s) (filled symbols). ***H***, Eye position measured during the physiological recordings. Ket, Ketamine; Pos, position; Trial No, trial number.

Effects of anesthetics on bimodal integration

Sodium pentobarbital

The data presented in this section were collected after the injection of a dose of 4.2 mg/kg sodium pentobarbital and the loss of the unit under study resulting from movement of the cat. Before terminating the experiment, another single unit was isolated in the anesthetized cat, the responses of which are shown in Figure 9. Thus, these data do not comprise a control condition. They were, however, in stark contrast to previous observations in the SC of behaving cats (Populin and Yin, 2002); therefore, their presentation in the current study is warranted.

The acoustic stimuli used to study this unit were 1400 ms trains of 100 μs clicks presented at 5 Hz from a speaker at (63°, 0°) at ~20 dB above the threshold of the unit. Visual stimuli were presented with a red LED located at the center of the speaker. The unit responded to each 100 μs click in a train with distinct bursts of action potentials, which were folded on the 5 Hz period of the click train for presentation and analysis (Fig. 9*A*); the method is described in the study by Tollin et al. (2004). That is, each click within a train was considered a single trial. The unit did not respond to visual stimuli presented from the same location (Fig. 9*B*), but in the bimodal condition (Fig. 9*C*), in which acoustic and visual stimuli were presented simultaneously from the same spatial location, the unit responses were significantly larger than the sum of the responses recorded in the single modality condition.

The summary of the results for the three different sound levels used is shown in Figure 9*D*. The visual condition was omitted from the plot because the unit did not discharge. These data are in complete disagreement with those obtained in previous recordings from bimodal SCi units in behaving cats, in which it was documented that the presence of visual stimuli produces a reduction, not an increase, in the magnitude of auditory responses (Populin and Yin, 2002). The BI computed for this unit was 45%, which lies outside two SDs from the mean BI observed in behaving cats using the fixation task [Populin and Yin (2002), their Fig. 3]. Thus, these data support the hypothesis that anesthetics are responsible for nonlinear increases in bimodal responses (Populin and Yin, 2002).

Ketamine

Bimodal integration in SCi units was also affected by ketamine. The data in Figure 10 show the responses of a single SCi unit under control conditions, after the injection of three doses of ketamine, and during recovery. Summaries of the mean spikes/trial, BI, and eye position are shown in Figure 10*J–L*.

In the control condition (Fig. 10*A*), the unit rarely discharged spontaneously and responded to the acoustic stimulus, a 750 ms broadband noise presented at ~20 dB above threshold, with a transient burst of action potentials at the onset of the stimulus. In some trials, it also responded with a weaker burst at the offset of the stimulus. The unit did not respond to visual stimuli presented

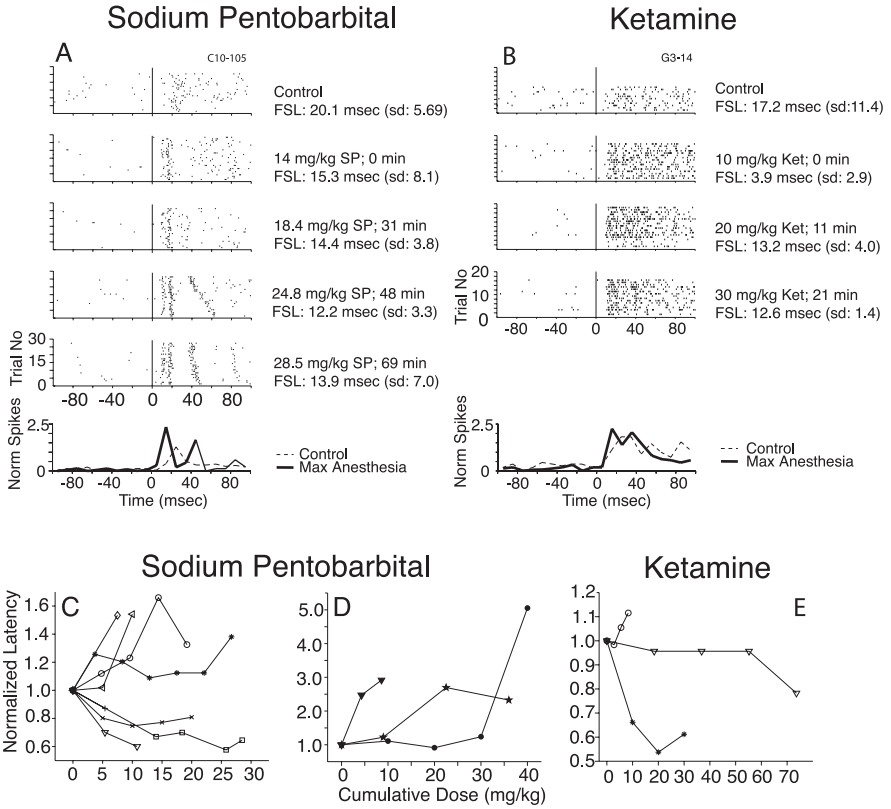

Figure 8. Effect of anesthetics on auditory first-spike latency. ***A***, Example in which an injection of sodium pentobarbital shortened auditory first-spike latency. The line plots below the rasters compare first-spike latency between the control and the condition with the largest cumulative dose of anesthetic. ***B***, Similar shortening of first-spike latency caused by the injection of ketamine. Summaries of changes in first-spike latency resulting from administration of sodium pentobarbital are shown in ***C*** and ***D***, and those of ketamine are shown in ***E***. The data from each unit are normalized to the latency recorded in the control condition. Ket, Ketamine; SP, sodium pentobarbital; Trial No, trial number.

either with an LED positioned approximately at the center of the area from which the best auditory responses could be evoked (−30°, 0°) or with a hand-held ophthalmoscope anywhere in the frontal hemifield. In the bimodal (auditory plus visual) condition, responses were dominated by the auditory modality (Fig. 10*J*), yielding a BI of 9% (Fig. 10*K*), which is consistent with previous observations in the behaving cat (Populin and Yin, 2002).

The intravenous administration of 2.8 mg/kg ketamine induced the unit to discharge spontaneously in short bursts within 5 s of the injection (Fig. 10*B*). The unit became more responsive to the acoustic stimuli, as shown by the lengthening of the evoked response (Fig. 10*B*) and the increase in spike count (Fig. 10*J*). In the visual condition, the spontaneous discharge resulted in an increase of the average spike count (Fig. 10*J*), but the increased activity was not linked to the stimulus. The BI dropped nearly 10% (Fig. 10*K*).

The injection of a second dose of 2.8 mg/kg ketamine 6 min after the first dose, for a total of 5.6 mg/kg (Fig. 10*C*), did not affect auditory responses but produced a large drop in the BI (Fig. 10*K*). A third dose of 2.8 mg/kg ketamine 11 min after the first injection (Fig. 10*D*) did not have an effect on the visual condition but did reduce the magnitude of the auditory response. The BI increased ~25% (Fig. 10*K*). This was the last injection of ketamine administered in this experiment.

An unusually high degree of stability was achieved in this recording session, which allowed documentation of the behavior of the unit during a prolonged recovery period. Recordings were taken at 5 min intervals (Fig. 10*J*) until the unit was lost because of movement of the animal during recovery.

Fifteen minutes after the last injection of ketamine (Fig. 10*E*), the responses to the acoustic stimuli became more sustained, and the rhythmic activity became less prominent. Most interestingly, ~20 min after the last injection of ketamine, the unit began to respond to the offset of the visual stimuli. These responses can be seen clearly in the rasters of the visual and bimodal conditions (Fig. 10*F*). Twenty-five minutes after the last injection (Fig. 10*G*) and for the remainder of the experiment (Fig. 10*I*), 1 h after the first injection of ketamine, the unit responded to both acoustic and visual stimuli. Thus, this unit, which did not respond to visual stimuli during the control condition or during the administration of ketamine, did so during recovery while the subject was under the influence of the ketamine. At the end of the experiment, >1 h after the last injection of ketamine, the cat was not able to stand.

Discussion

The data support the hypothesis that normal SC function is governed by a tightly controlled balance between excitation and inhibition, a balance that is disrupted by the action of sodium pentobarbital and ketamine. Dose-dependent, nonlinear changes were documented in the magnitude of auditory responses, auditory RF properties, FSLs, and bimodal integration.

Changes in the magnitude of auditory responses and RF properties

Auditory responses recorded under control conditions were changed by sodium pentobarbital without exception. In 30% of the units, responses were depressed at light doses of sodium pentobarbital, and in the other 70%, responses were facilitated. Although it is possible that two different populations of SCi units were encountered, the dose-dependent nature of the effect, which reversed to depression at higher doses, suggests the presence of a single population receiving inputs with a range of sensitivities to sodium pentobarbital. Units with depressed responses after the first injection may have been studied with doses of sodium pentobarbital that were too high to reveal facilitation.

Although depression can be explained by the lengthening of the mean open time of the chloride channel resulting from the action of sodium pentobarbital on the associated $GABA_A$ receptor (Study and Barker, 1982), an explanation for facilitation has remained elusive despite clinical and experimental evidence showing that low levels of volatile and intravenous anesthetics actually produce it at the cellular and systems levels (Dundee, 1960; Arora et al., 1972; Briggs et al., 1982; Ewen et al., 1995; Zhang et al., 2000; Archer et al., 2001). Facilitation could result from the action of sodium pentobarbital on the neurons under study or by indirect action on other components of the associated networks. The first mechanism would involve the (+) isomer of sodium pentobarbital, which enhances excitation in cultured neurons (Huang and Barker, 1980). The second, more plausible

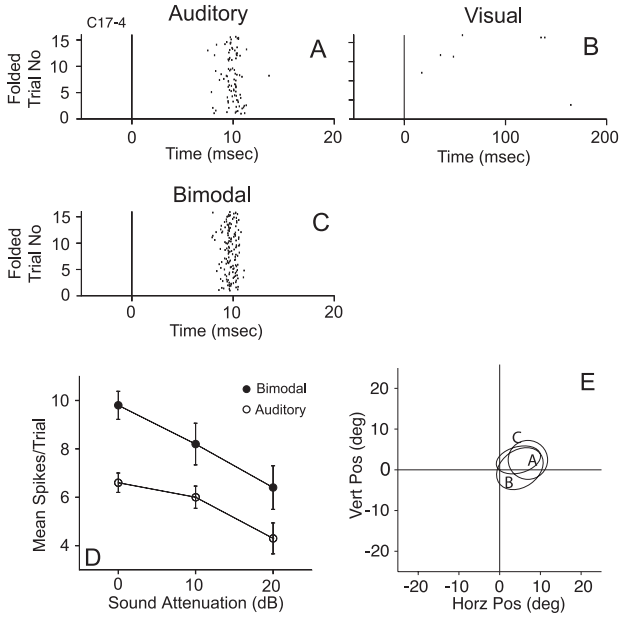

Figure 9. Effect of sodium pentobarbital on bimodal responses. ***A***, The acoustic stimuli were trains of 100 μs clicks presented at 5 Hz from a speaker at (63°, 0°). The responses to each click in the train were folded and treated as single trials. The cat was anesthetized at this point after having lost the previous unit resulting from movement after the first injection of sodium pentobarbital. ***B***, The unit did not respond to visual stimuli, a red LED located at the center of the speaker, presented from the same location in space or with a hand-held ophthalmoscope anywhere in the frontal hemifield. ***C***, Responses to bimodal (acoustic plus visual) stimuli presented from the same spatial location (63°, 0°). ***D***, Summary of the responses to acoustic and bimodal stimuli recorded at three different sound levels. The error bars represent 95% confidence intervals. ***E***, The position of the eyes during the auditory, visual, and bimodal conditions is plotted on a Cartesian plane. Horz Pos, Horizontal position; Trial No, trial number; Vert Pos, vertical position.

mechanism, would involve the (−) isomer of sodium pentobarbital, which potentiates $GABA_A$-mediated inhibition. In this scheme, facilitation results from a reduction of the effectiveness of inhibitory inputs, intrinsic or extrinsic to the SC (i.e., from disinhibition). The reversal from facilitation to depression at higher doses of sodium pentobarbital could result from the action of sodium pentobarbital on GABAergic receptors on the neuron under study, which, at higher concentrations, would tilt the balance in favor of inhibition, and from a reduction of the effectiveness of excitatory inputs. The large number of excitatory and inhibitory inputs converging on the SC (Huerta and Harting, 1984; Appell and Behan, 1990) and the intrinsic inhibitory network (Mize et al., 1994) preclude speculation about the circuits underlying these effects.

Facilitation of auditory responses by sodium pentobarbital is not unique to the SC, however. Sodium pentobarbital affects function in the early stages of the auditory system, changing inhibitory responses into excitatory in the dorsal and posteroventral cochlear nuclei (Young and Brownell, 1976; Ritz and Brownell, 1982) and shaping chopper responses in the lateral superior olive (Brownell et al., 1979). In the inferior colliculus, Walker and Teas (1974) observed initial facilitation, but Kuwada et al. (1989) found mostly depression after sodium pentobarbital injection. The higher doses, approximately one-half of the requirement for surgery, administered by Kuwada et al. (1989) as a single bolus, may explain the difference. In the visual system, sodium pentobarbital affects processing as early as the retina (Kapousta-Bruneau, 1999).

Ketamine facilitated auditory responses by increasing both the length of the initial burst and the sustained component of the responses. Unlike under sodium pentobarbital, which reduced the magnitude of responses at higher doses, auditory responses under ketamine were more resilient.

Data from multiple speakers are limited. Nonetheless, they demonstrate the nonlinear nature of the effects of both drugs. The fact that similar doses of sodium pentobarbital produced different effects in different units is disturbing, because it suggests that standardizing anesthetic regimes in acute experiments may not necessarily produce consistent results. Also disturbing is the fact that ketamine changed inhibitory responses into excitatory.

Changes in auditory first-spike latency

Under control conditions, the mean auditory FSL was indistinguishable from previous measurements (Populin and Yin, 2002). Sodium pentobarbital changed auditory FSLs in all SCi units tested: in 64% of units, FSL was lengthened, and in the other 36%, it was shortened. The shortening in FSL observed in four units studied with sodium pentobarbital was consistent with the concurrent increase in the magnitude of auditory responses documented in the same units; both measures showed facilitation. However, unlike the magnitude of evoked responses, which changed from facilitation at low doses of sodium pentobarbital to depression at higher doses, shortened FSLs remained shorter at higher doses, suggesting that different inputs with different sensitivities to sodium pentobarbital contributed to determine excitability and threshold. The lengthening of auditory FSL and the concurrent increase in auditory-evoked responses observed in five other units studied with sodium pentobarbital was unexpected, because in these units, one measure was depressed and the other was facilitated. This effect can also be explained by the differential effect of sodium pentobarbital on different inputs to the SC. The lengthening in FSL and the concurrent decrease in the magnitude of evoked responses can be attributed to a reduction of the responsiveness of the unit and a reduction of excitatory drive caused by sodium pentobarbital in the system.

Ketamine produced shortening of auditory FSL in two units and lengthening in another; the shortening in one unit took place at a higher dose. The similarity of the effects to those of sodium pentobarbital suggests a similar explanation (i.e., that different inputs with different sensitivities to the drug were affected differentially).

Effect of anesthetics on auditory–visual bimodal integration

The effects of sodium pentobarbital on auditory–visual interactions were studied in one SCi unit (Fig. 9). This unit, despite not responding to visual stimuli (Fig. 9*B*), exhibited bimodal integrating properties never observed in the behaving cat (Populin and Yin, 2002). Responses to bimodal stimuli were larger than responses to acoustic stimuli presented alone (Fig. 9*D*). These results, showing facilitation under light anesthesia, are consistent with those of anesthetized preparations (King and Palmer, 1985; Stein and Meredith, 1993).

The most striking effect of ketamine on bimodal integration concerned the emergence of visual responses during recovery while the cat was still under the influence of the drug. The visual responses could have resulted from a change in the integrative properties of the unit or from changes in the position of the eyes during the course of the recordings. The evidence supports the former. First, the frontal hemifield was explored with stimuli presented with an ophthalmoscope while the cat fixated on an LED at (0°, 0°) before acquiring the control data; no light-driven responses were found. Second, similar results were found with-

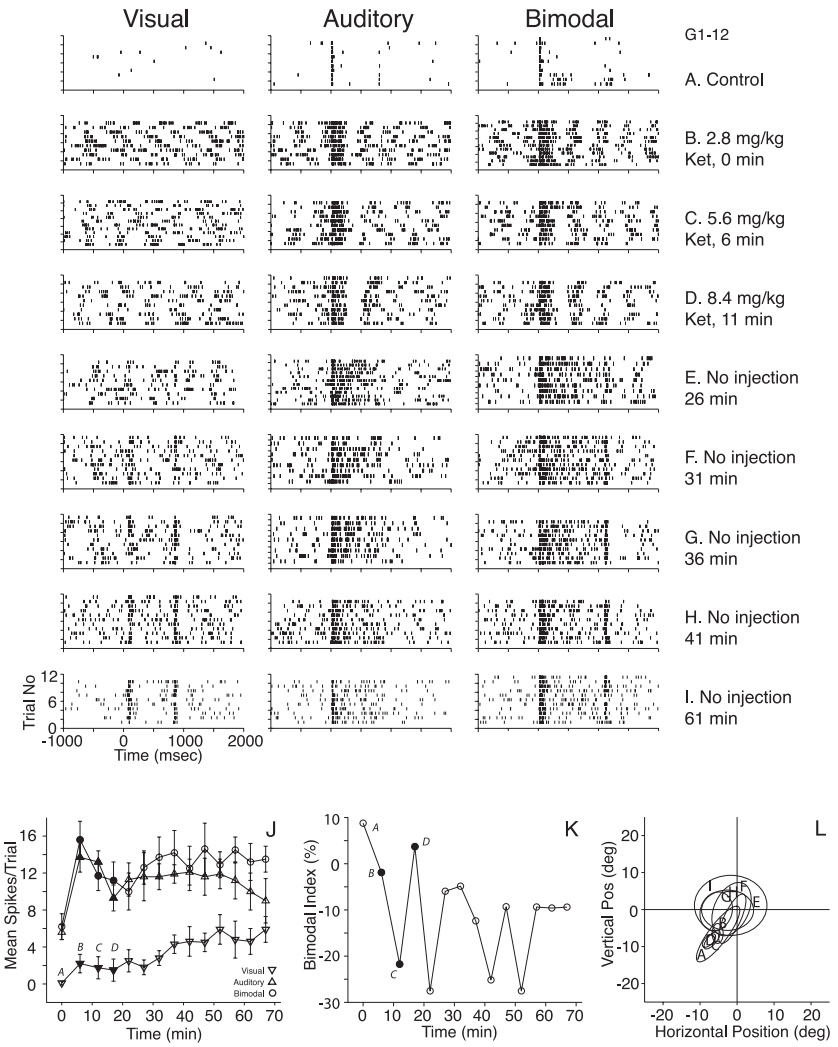

Figure 10. Effect of ketamine on bimodal responses of a superior colliculus neuron. Responses to visual, acoustic, and bimodal stimuli are plotted in raster format. The time of recordings and the doses of ketamine injected are indicated to the right of the plots. All data are plotted synchronized to the onset of the stimuli at time 0 ms. The visual stimulus consisted of a red LED at the center of the speaker for 750 ms. The acoustic stimulus was a 750 ms broadband noise burst presented from a speaker at (−30°, 0°), and the bimodal stimuli consisted of the acoustic plus visual stimuli presented for 1000 ms. ***A***, Control condition. The unit exhibited very little spontaneous activity and did not respond to visual stimuli. Auditory responses consisted primarily of an initial transient burst. Bimodal responses were slightly larger than the auditory alone. ***B–D***, Responses recorded after the injections of ketamine. ***E–I***, Responses recorded during recovery. ***J***, Summary of the magnitude of evoked responses. Filled symbols denote conditions in which ketamine was injected; ***B–D*** correspond to those of the rasters. The SE bars represent 95% confidence intervals. ***K***, Bimodal index as described by Populin and Yin (2002), computed for each of the conditions studied; filled symbols indicate conditions in which ketamine was injected. ***L***, The position of the eyes in space recorded during the auditory, visual, and bimodal conditions is plotted on a Cartesian plane. Ket, Ketamine; Trial No, trial number.

out a fixation light; a second visual stimulus outside the RF can change the responses of SC units to stimuli presented within the RF (Rizzolatti et al., 1974). Third, visual RFs in the SCi are large (Stein and Meredith, 1993). Thus, eye position should have changed considerably between the recordings taken before the first minute (Fig. 10*A–F*), in which no visual responses were observed, and the recordings taken after (Fig. 10*G–I*), in which strong visual responses were recorded, for the RF of the unit to have moved on to the stimulus. Although eye position varied within and between each set of recordings, it was consistent over time (Fig. 10*L*). Thus, it is concluded that the emergence of visual responses was attributable to changes in the bimodal integration properties of the unit brought about by ketamine.

The evidence presented clearly relates changes in single-unit response properties to the doses of the anesthetics administered and not to drifts in eye position. However, eye position modulates auditory responses in the SC of behaving animals (Jay and Sparks, 1987; Populin et al., 2004); thus, the issue requires additional consideration. Feedback from extraocular muscles could not have changed auditory responses because it does not reach the SC in the anesthetized cat (Nelson et al., 1989). The use of corollary discharge (Guthrie et al., 1983) resulting from the execution of saccadic eye movements, such as the fast phase of the nystagmus produced by ketamine, can be ruled out because it is unlikely that such information could be properly interpreted in the anesthetized state. Furthermore, under sodium pentobarbital, most eye movements were slow drifts that resembled smooth pursuit but without a smoothly moving target. Last, feedback from periorbital tissue can also be ruled out because no artificial stimulation, particularly of the magnitude and strength required to modulate auditory responses of SC units (Zella et al., 2001), was administered in the present study.

These data challenge a fundamental tenet of sensory physiology: that anesthesia, while decreasing single-unit responsiveness, leaves unaltered basic physiological properties. There is evidence in the literature demonstrating no effects of anesthetics on basic physiological properties and evidence indicating otherwise. Some studies in behaving animals that compared their results to those from anesthetized preparations using population data found no major differences (Wurtz, 1969; Yin and Greenwood, 1992). However, studies that compared single-unit activity before and after the administration of anesthetics (Goldstein, 1968; Walker and Teas, 1974; Young and Brownell, 1976; Brownell et al., 1979; Kuwada et al., 1989) invariably found significant effects of anesthetics in most, if not all, single units studied.

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