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NITROUS OXIDE MODIFIES VISUAL RESPONSES IN THE CAT RETINA, STRIATE CORTEX AND SUPERIOR COLLICULUS

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SUMMARY

Extracellular records from 54 single cells in cat optic tract (14), visual cortex (18) and superior colliculus (22), have shown that ventilation of acute animals with a 70% : 30% mixture of N_2O/O_2 can modify unit responses to visual stimuli. Results indicate that, under nitrous oxide, (a) responses to flashed or moving stimuli may be severely reduced, and frequently abolished. This may be accompanied by either a sharp decrease; or, conversely, by a dramatic increase, in the resting discharge rate; (b) the degree of directional preference of a given unit, in response to a moving visual stimulus, may be substantially modified; (c) the temporal distribution of unit firing may be modified. While about half (57%) of the units in the optic tract were affected by N_2O, only 28% of cortical cells showed any N_2O-related response modification. The largest effect was observed in the superior colliculus, where 86% of cells were influenced by the anaesthetic. It is suggested that these results might be explained by a selective interference of N_2O with serotonergic transmitter mechanisms.

INTRODUCTION

For well over 100 years, nitrous oxide (N_2O) has been widely used as an anaesthetic during minor surgery in humans. Humphrey Davy's early (1799) observation that this inorganic gas 'may be used with advantage during surgical operations', although initially unheeded, introduced a new, powerful and relatively safe tool into clinical medicine. To this day, minor surgery in humans is frequently performed under N_2O anaesthesia, although the gas may lack full effectiveness in fit subjects, and has to be routinely supplemented with opioids and muscle relaxants[13].

During the past three decades, nitrous oxide/oxygen mixtures in concentrations of up to 80% N_2O/20% O_2 have been frequently employed as the sole anaesthetic agent during electrophysiological experiments with cats. Recently, however, its anaesthetic properties in the latter species have been questioned[16,29–31]. The ensuing debate[7,17,37] has left little doubt that nitrous oxide alone, in concentrations that do not induce hypoxia (i.e. $< 80\%$), is incapable of producing, or reliably maintaining, a satisfactory state of surgical anaesthesia or analgesia in cats.

We now report that — in addition to its previously demonstrated inadequacies as an anaesthetic — nitrous oxide severely modifies, and frequently abolishes, the responses of single units recorded from the cat's optic tract, superior colliculus, and striate cortex, to various forms of visual stimulation. A brief report of partial results has been given elsewhere[23].

METHODS

Nine cats were prepared under Ketalar (ketamine hydrochloride, 15 mg/kg i.m.). After intubation with a cuffed endotracheal tube coated with Xylocaine, the left femoral vein was cannulated for subsequent drug infusion. Two stainless steel EEG electrodes were implanted in the skull, one overlying the dura of the marginal gyrus, the other the dura of the ectosylvian gyrus. Access to the right visual cortex, the right superior colliculus, and the right optic tract was provided via small craniotomies. In 4 of the animals, the brain stem was transected at the mid-pontine pretrigeminal level[38], using a special retractable leucotome. The instrument was inserted at an angle of 30° to the coronal plane, under stereotaxic guidance, via two small holes in the interparietal bone. In these latter animals, the administration of Ketalar was discontinued, and unit records were obtained from the unanaesthetized pretrigeminal preparations. With the remaining 5 animals, i.v. infusion of Ketalar was maintained for the entire duration of the experiment. During the experiments animals were kept paralyzed with an i.v. infusion of Flaxedil (gallamine triethiodide, 20 mg/h). The state of consciousness of the paralyzed animals was closely observed by continuous monitoring of their EEG. In addition, arterial blood pressure, end-tidal CO_2 (3.8–4%; Godart Capnograph), and rectal temperature (38–39 °C) were continuously recorded. A drop of a 1% solution of atropine sulphate was instilled into the left eye, and an optically neutral contact lens was inserted. Extra-ocular lenses were used to bring patterns, displayed on a tangent screen some 30 cm from the animal's eye, into focus on the retina. The right eye was kept occluded. Monocular visual stimuli consisted of a variety of patterns including a small bright disc (0.5–1.2° diameter); a small light bar (approx. 0.3 × 1°) moving against a dark background; a dark 'tongue' moving against a light background; and drifting, or stationary flashed, square-wave gratings (0.3–0.8 cycles/deg.). The bright pattern areas did not exceed 12 cd/sq.m. Unit responses were recorded extracellularly with either glass coated platinum electrodes, or glass pipettes filled with Wood's metal. Responses were measured by determining pulse density probabilities from peristimulus time histograms. Histograms were constructed using narrow bins of fixed duration (5 msec) regardless of duration of the response; they were filtered, prior to plotting, with a 'Hanning' filter having a cosine bell of 22 msec.

The effects of 70%:30% mixtures of N_2O/O_2 on the responses of: (1) optic tract fibres; (2) simple and complex cells in areas 17 and 18 of the right (contralateral) visual cortex; and (3) units in the superficial and intermediate layers of the right (contralateral) superior colliculus, to monocular visual stimulation, were tested. Unit records were obtained either from unanaesthetized (except for N_2O tests) mid-pontine pretrigeminal preparations, *or* from intact animals maintained on a continuous i.v. infusion of Ketalar (15 mg/kg/h). The latter drug is compatible with nitrous oxide, and the dose used is adequate for maintaining a state of surgical anaesthesia over a period of several hours. (Although Ketalar is chemically incompatible with barbiturates, it is specifically recommended for clinical use as a safe and effective supplement to low potency anaesthetic agents such as N_2O)[21]. Furthermore, in the concentration used here, Ketalar was found to have no measurable effects upon visual responses. In fact, during controlled i.v. test infusions of Ketalar in midpontine preparations, three times the normal anaesthetic dose had no significant effects upon single collicular unit responses to moving visual stimuli. A given cell was tested (a) while the animal was being ventilated with room air; (b) some 5–15 min after the introduction of the nitrous oxide/oxygen mixture; (c) some 5–15 min after nitrous oxide had been discontinued, and while the animal was being ventilated with pure oxygen to prevent the onset of diffusion hypoxia subsequent to the sudden withdrawal of nitrous oxide[14]. Forced ventilation with the N_2O/O_2 gas mixture was provided via a pair of rotameters, and a T-piece 'open' breathing circuit. Total gas flow was maintained at a relatively high level (approx. 5–6 litres/min) to minimize rebreathing of alveolar gases.

RESULTS

General comments

Results obtained from Ketalar-treated animals were qualitatively similar to those obtained from non-anaesthetized pretrigeminal animals, except for the somewhat greater ease of finding active cells in the former preparations. A total of 54 cells in 9 cats were systematically studied. Of these, 14 were recorded from the optic tract, 18 from the visual cortex, and 22 from the superior colliculus. The observed effects of nitrous oxide upon single visual units, although by no means identical in the three areas tested, can be summarized as follows: (1) severe reduction, or total abolition, of many responses to moving or flashed stimuli. This effect may be accompanied either by a sharp *decrease* in the resting discharge rate; or, conversely, by a dramatic *increase* in the resting discharge rate that tends to obliterate any vestige of an evoked response to a visual stimulus: (2) modifications in the degree of directional preference, in response to moving visual stimuli; (3) changes in the 'shapes' of peri-stimulus histogram response peaks, i.e. in the temporal distribution of firing, with frequent histogram peak displacement by as much as 250 msec. Although no systematic attempts were made to ascertain to what extent some of these effects might have been due to modifications in the size, or spatial structure, of receptive fields, no obvious changes in the distribution of ON and OFF areas within a given field was ever observed. Furthermore, no modifications in the *orientation* (as opposed to direction) preference of cortical cells could be detected.

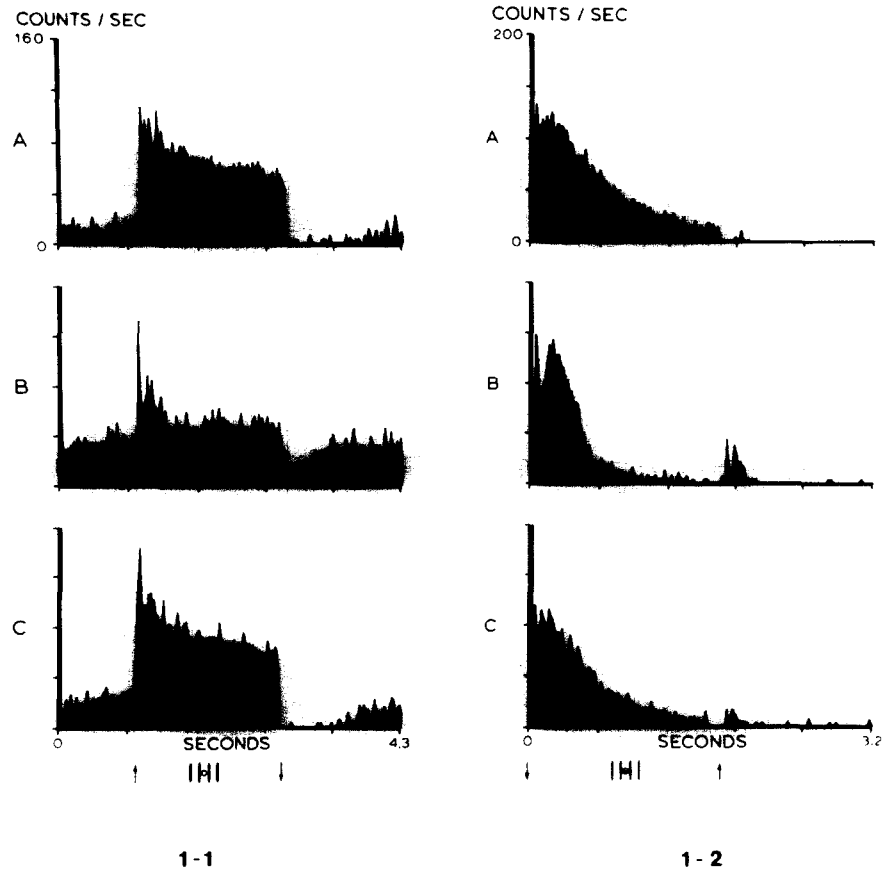

Fig. 1. Two sets of peri-stimulus time histograms illustrating the averaged responses of two optic tract fibres to a flashed (1.8 sec on, 1.8 sec off) square-wave grating with a spatial frequency of 0.3 cycles/deg. Abscissae: time during stimulus cycle. Arrows indicate the switching on (up) and the switching off (down) of the grating which in each case was positioned such that one bright half-cycle just covered the receptive field center. Ordinates: accumulated action potential counts, expressed as counts/sec. Each histogram was obtained by summating 30 responses. A: animal ventilated with room air. B: 5 min after the introduction of a 70 : 30 mixture of N_2O/O_2. C: control records, 10 min after switching ventilation from nitrous oxide to pure oxygen. 1-1: ON-center unit, responding with maintained discharged to the presentation of a grating, before (A) and after (C) nitrous oxide. Note in B the change to a phasic response, and increased 'resting' activity, during administration of the gas. 1-2: OFF-center unit, responding to the extinguishing of a grating. Note that under nitrous oxide (B) the duration of the main response was substantially shortened, while an additional small discharge appeared in response to turning the grating on.

Optic tract (retina).

Fig. 1 shows results obtained from two optic tract fibres recorded from an animal anaesthetized with Ketalar. The three histograms in Fig. 1-1 represent the averaged responses of an ON-center unit to a flashed (1.8 sec on, 1.8 sec. off) stationary square-wave grating. The grating had a spatial frequency of 0.3 cycles/deg;

it was stationed within the receptive field such that, when flashed on, one bright bar just covered the unit's ON-center which had a diameter of approximately 1.6°. Histogram A shows the result of stimulation while the animal was being ventilated with room air. When the grating was flashed on (first arrow below abscissa of histogram C), the cell's spontaneous discharge rate increased transiently to an average value of some 100 imp./sec; subsequently, with the stimulus still present, the discharge rate gradually settled to a reasonably well 'maintained' value of about 60/sec. Extinguishing the grating (second arrow below abscissa of histogram C) resulted first in a transient decrease of the average discharge rate to some 5/sec, and a return within about 1 sec to the previous 'spontaneous' value of some 12–15/sec. Histogram B shows how the discharge characteristics of this unit were modified when ventilation was switched from room air to a 70:30 mixture of N_2O/O_2: after a latent period of some 5 min the unit's spontaneous discharge rate increased from the previous average value of 15/sec to about 40/sec (B). The initial transient response to turning the grating on increased with a sharp burst to over 130 imp./sec and then fell rapidly to an average rate of about 50/sec, which was maintained for the rest of the grating's on-cycle. Extinguishing the grating after 1.8 sec resulted in a transient total silencing of the unit, and within some 400 msec in a resumption of the previous 'spontaneous' firing rate of some 40/sec. Histogram C shows a control record, obtained from the same unit under stimulating conditions that were identical to those employed to obtain the results in A and B, but after the animal had been ventilated for 10 min with pure oxygen. Under these conditions, the unit's visual response returned essentially to the pattern it exhibited in A, with the exception of a still slightly elevated resting discharge rate, and the presence of a still somewhat exaggerated phasic component. This was most likely due to incomplete recovery from nitrous oxide anaesthesia, and not due to the effect of ventilation with pure oxygen. (Switching ventilation for brief periods from room air to pure oxygen was never observed to cause any substantial, or characteristic, changes in a unit's visual response.) Thus, the net effect of nitrous oxide upon this optic tract unit was to substantially (by a factor of more than three) increase its resting discharge rate, and to convert an essentially maintained visual response into a largely transient one.

Fig. 1-2 shows results from an OFF-center unit which responded to the extinguishing of a stationary square-wave grating, whose bright half-cycle was again placed to cover the receptive field's center. It can be seen that the cell's initial transient response to extinguishing the grating (at time zero on the abscissa, first arrow in A) was substantially shortened after the animal had been respired with a 70:30 N_2O/O_2 mixture for 5 min (B). Furthermore, a small phasic response to switching the grating on appeared in B (second arrow along abscissa), which had not been present in the absence of N_2O (A). The control record in (C), showing almost complete restoration of the unit's original behaviour under room air, was obtained after ventilation with pure oxygen for 10 min.

Of 14 optic tract units recorded, 8 (57%) showed modified visual responses under the influence of nitrous oxide; with the other 6 units no measurable changes could be detected with the methods used.

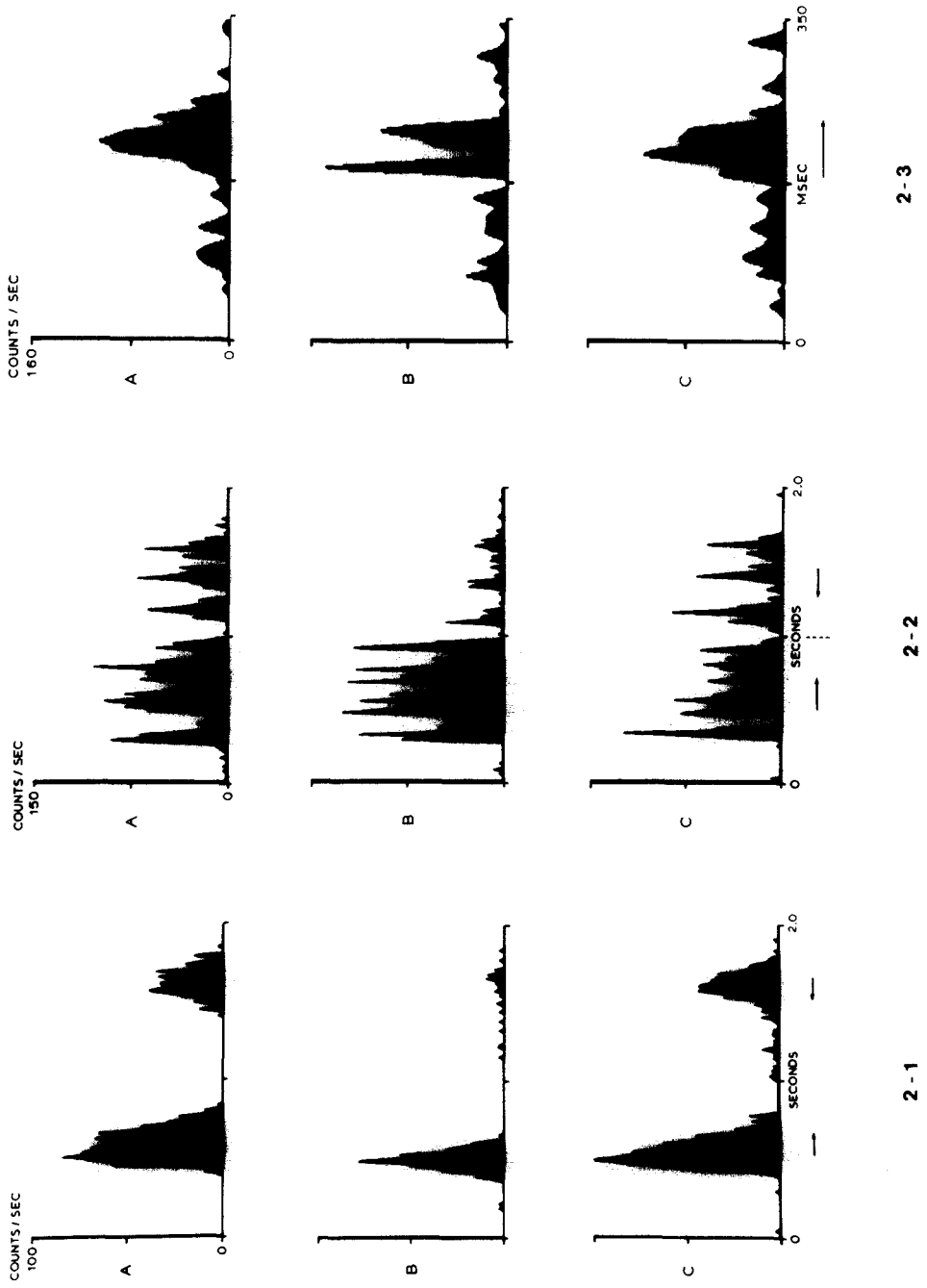

Fig. 2. Three sets of peri-stimulus time histogram, illustrating the responses to moving patterns of three units in the visual cortex (area 18). Abscissae and ordinates as in Fig. 1. Arrows under abscissae of C denote pattern movements in opposite directions. Each histogram was obtained by summating 25 responses. A: room air. B: 10 min after the start of a 70:30 N_2O/O_2 mixture. C: control records after 12 min of pure oxygen. 2-1: simple cell responding to small luminous bar (1.2 × 0.35°) moving with uniform speed (12 °/sec) back and forth across the receptive field. Note in B the disappearance of the response to one direction of movement, and the change in shape of the response to the opposite direction of movement, after 10 min of nitrous oxide. 2-2: complex cell responding to 0.6 cycles/deg square-wave grating moving with uniform speed (7.5 °/sec) back and forth. Note that after 10 min of nitrous oxide (B), the cell became highly directionally selective due to the differential effect of the anaesthetic upon the responses to opposite directions of pattern movement (i.e. increased response to one direction, decreased response to the opposite direction). 2-3: complex cell responding to a small luminous bar (1 × 0.3°) moving at 15 °/sec. Note that after 10 min of nitrous oxide (B), the originally single peaked response (A) was changed to a double peaked one.

Visual cortex

The proportion of visual cells affected by nitrous oxide was found to be much smaller in the cortex than in the optic tract: of 18 cortical cells tested, only 5 (28%) yielded measurable response modifications. Fig. 2-1 shows the response of a simple cell in area 18, to the back-and-forth movement of a small luminous bar (1.2 × 0.35°) across its receptive field. Histogram A represents the unit's response when the animal was on room air. It can be seen that the unit responded to both directions of pattern movement (see arrows below the abscissa of C), although there was a clear preference for one of the two directions.

After about 10 min ventilation with the standard 70:30 N_2O/O_2 mixture, the first response peak appeared markedly curtailed; more significantly, the second of the two peaks was virtually abolished (B), thus converting the cell from one that responded to both directions of pattern movement, to one that responded to one of the two directions only. Subsequent ventilation with pure oxygen restored the cell's original response pattern (C), except for an apparent small potentiation of the cell's overall response (i.e. to *both* directions of pattern movement). This, however, did not alter the original amplitude ratio of 2.2 for response peaks associated with opposite directions of pattern movement. Such a 'rebound' effect following recovery from nitrous oxide was observed with a number of visual cells. It should also be noted that the first of the two response peaks in histogram C of Fig. 2-1 did not regain the second smaller 'hump' which was originally present in A.

An example of a complex cell's response to a moving grating, and the modification of that response by nitrous oxide, is shown in Fig. 2-2. Histogram A shows that, while the cat was being ventilated with room air, this cell exhibited modulations in its discharge rate, in step with the passage of dark and light grating bars across the receptive field. Note that while the response to both directions of pattern movement was quite vigorous, the peak discharge rate associated with movement in one direction was only about 75% (leftward arrow, second half of histogram) of that evoked by movement in the opposite direction. After a 10 min exposure to nitrous oxide (B), the peak discharge rate in response to a leftward pattern movement (second half of histogram B) was reduced, while the response to the opposite direction of pattern movement (first half of histogram B) was simultaneously increased, increasing the disparity between peak responses to opposite directions of pattern movement from the original ratio of about 1:0.75 to 1:0.3. Thus, a cortical cell that originally appeared to possess only a modest directional preference, was converted into one having a very strong directional bias. During a subsequent 12 min period of ventilation with oxygen, the cell again reverted to its modest directional bias (C).

Fig. 2-3 shows another example of nitrous oxide influence upon a cortical visual cell. The 3 histograms illustrate the activity of a complex cell responding to a luminous bar (1 × 0.3°) moving in one direction with a uniform velocity of 15°/sec across the receptive field. It can be seen that the initial single-peaked response obtained under room air (A) was changed to a double-peaked one after a 10 min exposure to nitrous oxide (B), with the first of the two new peaks occurring some 25 msec before, and the second one some 17 msec after, the original single peak of histogram A. This particular

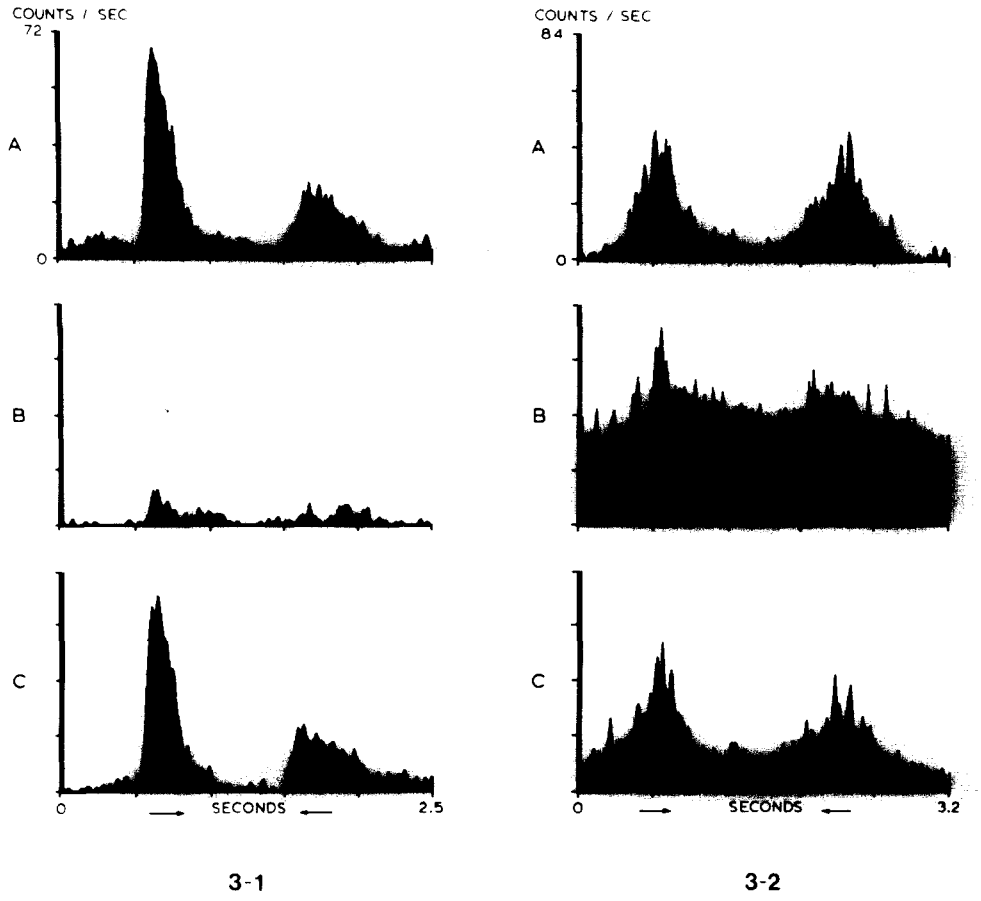

Fig. 3. Averaged responses recorded from two units, situated in the intermediate layers of the superior colliculus. The stimulus in both cases consisted of a small luminous disc (1° diameter) moving back and forth (see arrows) with uniform speed across the central activating region. Abscissae and ordinates as in Fig. 1. Each histogram was obtained by summating 30 responses. A: room air. B: 6 min after the start of a 70 : 30 mixture of N_2O/O_2. C: control records, 12 min after pure oxygen. 3-1: responses of one cell to pattern moving at uniform speed of 20 °/sec. Note in B the virtual abolition of responses, after 6 min of nitrous oxide. 3-2: responses of another cell, to pattern moving at 8 °/sec. Note in B the dramatic increase in overall activity, and decrease in response peaks above background activity.

example of a double peaked response is a good illustration of the frequent increase in the 'burstiness' of cell activity, observed in various parts of the cat visual system, under the influence of nitrous oxide. Histogram C again represents a control record obtained from the same cell after a 12 min period of ventilation with oxygen.

It should be noted that, while no detailed or systematic determinations of orientation tuning were attempted, no major shifts in the orientation preference of cortical cells under N_2O were ever observed.

Superior colliculus

Of the three visual areas investigated in the present study, the one most susceptible to the influence of nitrous oxide was found to be the superior colliculus. Of the 22 collicular cells tested only 3 were *un*affected by this anaesthetic; all other 19 units (86%) showed severe nitrous oxide induced modifications of their firing characteristics, with frequent total abolition of visual responses only minutes after the introduction of the gas. Interestingly, the abolition of collicular visual responses by nitrous oxide was accompanied in different cells by different modifications to their spontaneous resting activity: in some cells, the spontaneous activity was curtailed, whereas in others this activity showed a sharp (up to 10-fold) increase, suggesting that interference with visual responses may possibly have been caused either by hyperpolarization, or conversely, by maintained depolarization, of the cell membrane.

Fig. 3 shows examples of these two divergent effects of nitrous oxide. In Fig. 3-1 are shown results from a cell encountered in the intermediate layers of the colliculus. This unit was responding to a luminous disc (1° diameter) moving at a uniform speed of 20°/sec back and forth (see arrows below abscissa of histogram C) within the activating region. With the animal on room air, the cell responded well to the moving pattern, although considerably better to one direction than to the other (A). After some 6 min of nitrous oxide the responses to *both* directions of pattern movement were virtually abolished (B). It should be noted that abolition of responses was accompanied by a considerable decrease in the unit's 'background' firing. The control record C shows complete recovery after 12 min of ventilation with pure oxygen.

The results in Fig. 3-2 are drawn from another collicular cell whose visual response was obliterated when nitrous oxide caused a steep increase in its background activity. Histogram A illustrates the cell's bi-directional response to a bright disc (1.2° diameter) moving with a uniform speed of 8°/sec. After a 6 min period during which nitrous oxide had been administered, the cell's background activity increased from the original average rate of some 4/sec to a new high of 38/sec — an almost 10-fold increase. (In fact, after only 2 min of nitrous oxide exposure, the rate of background activity doubled.) The original visual response now appeared 'buried' in, and virtually indistinguishable from, the ongoing 'noise' (B). After nitrous oxide was withdrawn, and ventilation with pure oxygen had been applied for 12 min, the spontaneous activity returned to near-control level, and the visual responses reappeared.

In addition to eliminating visual responses altogether (or nearly so), nitrous oxide also can affect the directional preference of collicular cells. Some examples of this are shown in Fig. 4. In both Fig. 4-1 and 4-2, histograms A illustrate the initial control responses of two cells, to the movement of a bright 1° diameter disc. Histograms B show, in each of the two cases, the abolition of the response to *one* of the two directions of pattern movement, after exposure of the cat to nitrous oxide for 7 min.

It should be noted that in both cases, the remaining responses were also affected: their amplitudes were reduced, and their timing modified. For the cell of Fig. 4-1, the reduced first peak attained its maximum amplitude under nitrous oxide some 80 msec later than under control conditions. This is shown in greater detail in Fig. 4-3, where a comparison of the first response peak of Fig. 4-1A with that of 4-1B is pre-

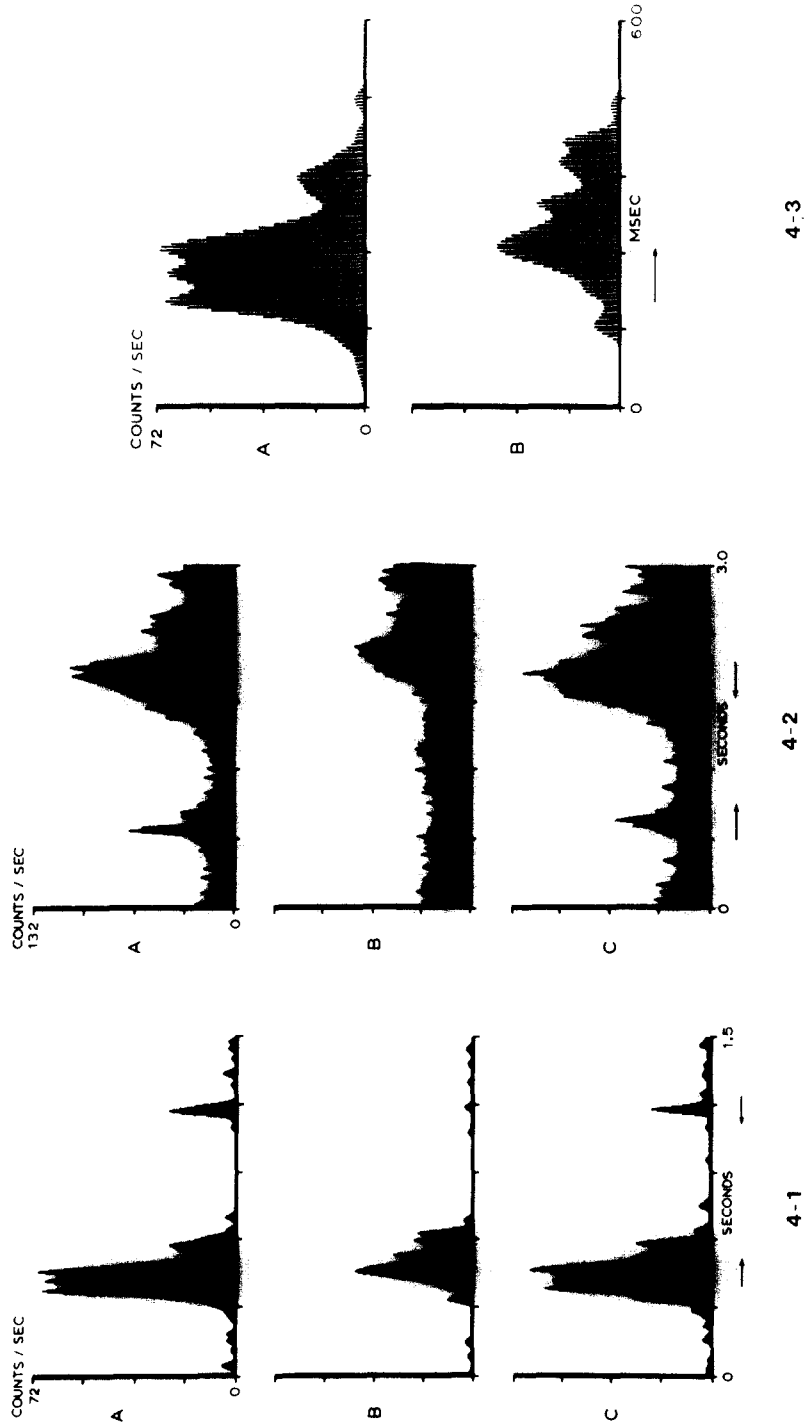

Fig. 4. Examples of changes in the degree of directional preference of two collicular cells, under the influence of nitrous oxide. Same visual stimulus as for Fig. 3. Abscissae and ordinates of histograms as in Fig. 1. Each histogram was obtained by summating 35 responses. A: room air. B: 7 min after the start of a 70 : 30 mixture of N_2O/O_2. C: control records, 15 min after switching to pure oxygen. 4-1: response of cell situated in the intermediate layers of the colliculus, and responding to stimulation at a pattern velocity of 40 °/sec. Note in B the disappearance of the response to one direction of stimulus movement, and the change in shape, and rate of rise, of the response to the opposite direction of movement. In 4-3, these latter effects upon one direction of movement are shown in more detail, with parts of 4-1A and B shown on an expanded time scale. 4-2: cell situated in superficial layers of colliculus, responding to stimulation at 10 °/sec. Note again in B the disappearance (with respect to A) of the first of the two original peaks, and the changes in shape and timing of the second peak.

sented on an expanded time scale. Similarly, the second response in histogram A of Fig. 4-2, which peaked at about 2 sec (as measured along the abscissa) attained its peak under nitrous oxide some 250 msec later (B). It is not clear whether these effects of nitrous oxide were caused by changes in the *spatial* organization (i.e. size and/or configuration) of receptive fields, or whether they represent an interference with the purely temporal aspects of unit firing (or possibly both).

DISCUSSION

The present results, although drawn from a restricted sample of cells in three selected areas of the cat visual system, clearly point to the dangers of using nitrous oxide either as the sole, or as a supplementary, anaesthetic agent in neurophysiological experimentation. Not only does nitrous oxide tend to abolish responses to various forms of visual stimulation, but — more importantly — it has a tendency to modify some basic characteristics of unit behaviour, such as the degree of directional preference to moving stimuli, the level of spontaneous background activity, and the temporal pattern of visual responses.

The question arises whether some of the observed effects might have been due, not to N_2O alone, but to the combined action of N_2O with some of the drugs that have been administered to the experimental animals. Within this context, Ketalar can be ruled out, as similar effects were observed with both Ketalar treated and unanaesthetized pretrigeminal preparations. Atropine was never administered systemically; it would, therefore, be a very unlikely co-factor responsible for the present result. A Flaxedil–N_2O interaction can, however, not be ruled out. Nevertheless, as Flaxedil has been an everpresent ingredient in many visual experiments, the demonstration of a N_2O effect upon flaxedilized animals is of major importance, regardless of the possible contributory role that Flaxedil may play in this phenomenon.

While this work was in progress, Donaldson et al.[12] reported that, in cats anaesthetized with chloralose, visual responses in the cerebellar vermis, and in the superior colliculus, were severely depressed by the additional administration of a 50:50 mixture of N_2O/O_2. Curiously, these authors emphasized the absence of any nitrous oxide-induced changes in the spontaneous background activity of single units; they did not comment on other modifications of response properties. More recently, Mancini et al.[22] claimed a reduced firing rate as the only consistently observable effect of nitrous oxide on cortical visual cells in cat, and concluded that 'the effects of nitrous oxide on cortical units are variable'. The present results, regarding the apparent resistance of cortical cells to anaesthesia-induced changes in orientation preference, are also consistent with those reported some time ago by Lee[20].

How could the effects of nitrous oxide upon visual cells be explained? To date little is known concerning the specific action of anaesthetic agents upon the nervous system. The demonstrated selective interference of nitrous oxide with the directional specificity of unit responses, and particularly the differential effect upon the responses to opposite directions of pattern movement (Fig. 2-2), probably rule out a simple explanation solely in terms of a suppression of sensory input. While the *relative*

immunity of cortical cells to nitrous oxide might be due to nothing more than a higher cortical 'safety factor' for synaptic transmission, it might also be viewed as a reflection of the affinity of this volatile anaesthetic for one — or several — regionally specific transmitter substances.

Within this context, it is unlikely that the observed effects were caused by a selective interference with cholinergic mechanisms, because the superior colliculus, where most of the N_2O-sensitive cells were observed, has been shown to contain very few neurons responsive to iontophoretically applied ACh[33]. Glutamate (notwithstanding the difficulties inherent in attempting to gauge the degree of its action as a transmitter from its tissue content) can probably also be ruled out, its content in brain stem and collicular tissue having been variously estimated to be only a fraction (0.6 – 0.8) of that in neocortex[5,18,36]. Similarly, the regional distribution of GABA, whose content in rat, guinea pig, rabbit and monkey brain stem was reported only 0.5 – 0.8 times that in the cortex[5,15,24], could also not account for the very much larger effect of nitrous oxide on collicular cells.

Biogenic amines, on the other hand, tend to be associated with phylogenetically older parts of the nervous system. While the presence of neurons sensitive to noradrenaline and dopamine have been demonstrated not only in the retina[1,32], and the superior colliculus[33], but also in various regions of the neocortex[27,28], estimates indicate that the brain stem catecholamine content exceeds that of the visual cortex by a factor of about 1.7 in rats[35], about 2 in humans[6], and about 3 in dogs[2]. Thus, the distribution of catecholamines might account for the observed 3-times higher potency of nitrous oxide in the brain stem, as compared to the visual cortex.

One of the largest known regional differences in monoamine content, however, is that of 5-hydroxytryptamine (5-HT). 5-HT-related neural activity has been reported in the mammalian retina[1,34], the lateral geniculate nucleus[10,26], the visual cortex[27], and the superior colliculus[4,33]. Quantitative estimates of midbrain/cortex content ratios for 5-HT or related enzymes have been variously reported as 7–11:1 for the cat[8,25]; 6:1 for the rat[35]; and 40:1 for humans[9]. It is, therefore, tempting to relate the relative immunity of cortical cells to nitrous oxide, to the relative paucity (with respect to the brain stem) of cortical serotonergic mechanisms. Within this context, it is well to recall that, despite the relative scarcity of serotonergic nerve terminals in the CNS (one 5-HT terminal per 1000 synapses in cat cortex[3]), and despite the apparent lack of characteristic synaptic contacts[11], 5-HT has been implicated as a key factor in modulating consciousness during the sleep–waking cycle[19]. In view of the above speculations, a role of 5-HT in N_2O-induced modulation of sensory neural activity does, therefore, not seem implausible.

Finally, the selective (and reversible) inactivation of specific brain regions with anaesthetic agents could be used in behavioural studies, as a means of attempting to isolate the normal functional roles of different parts of the nervous system. The presently demonstrated much higher susceptibility to nitrous oxide of collicular, as compared to cortical, cells might be used as a tool toward distinguishing the functional roles of subcortical, as opposed to cortical, visual mechanisms.

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REFERENCES

1 Ames III, A. and Pollen, D. A., Neurotransmission in central nervous tissue: A study of isolated rabbit retina, *J. Neurophysiol.*, 32 (1969) 424–442.
2 Amin, A. H., Crawford, T. B. B. and Gaddum, J. H., The distribution of substance P and 5-hydroxytryptamine in the central nervous system of the dog, *J. Physiol. (Lond.)*, 126 (1954) 596–618.
3 Beaudet, A. and Descarries, L., Quantitative data on serotonin nerve terminals in adult rat neocortex, *Brain Research*, 111 (1976) 301–309.
4 Beleslin, D. B. and Myers, R. D., The release of acetylcholine and 5-hydroxytryptamine from the mesencephalon of the unanesthetized rhesus monkey, *Brain Research*, 23 (1970) 437–442.
5 Berl, S. and Waelsh, H., Determination of glutamic acid, glutamine, glutathione and γ-aminobutyric acid and their distribution in brain tissue, *J. Neurochem.*, 3 (1958) 161–169.
6 Bertler, Å., Occurrence and localization of catechol amines in the human brain, *Acta physiol. scand.*, 51 (1961) 97–107.
7 Blakemore, C., Donaghy, M. J., Maffei, L., Movshon, J. A., Rose, D. and Van Sluyters, R. C., Evidence that nitrous oxide can maintain anaesthesia after induction with barbiturates, *J. Physiol. (Lond.)*, 237 (1974) 39–41P.
8 Bogdanski, F. D., Weissbach, H. and Udenfriend, S., The distribution of serotonin, 5-hydroxytryptophan decarboxylase, and monoamine oxidase in brain, *J. Neurochem.*, 1 (1957) 272–278.
9 Costa, E. and Aprison, M. H., Studies on the 5-hydroxytryptamine (serotonin) content in human brain, *J. nerv. ment. Dis.*, 126 (1958) 289–293.
10 Curtis, D. R. and Davis, R., The excitation of lateral geniculate neurones by quaternary ammonium derivatives, *J. Physiol. (Lond.)*, 165 (1963) 62–82.
11 Descarries, L., Beaudet, A. and Watkins, K. C., Serotonin nerve terminals in adult rat neocortex, *Brain Research*, 100 (1975) 563–588.
12 Donaldson, I. M. L., Long, A. C. and Tasker, T. C. G., Suppression by nitrous oxide of visual responses in the cerebellar vermis and superior colliculus of cats anesthetized with chloralose, *Brain Research*, 148 (1978) 526–529.
13 Dripps, D. R., Eckenhoff, J. E. and Vandam, L. D., *Introduction to Anaesthesia*, W. B. Saunders, Toronto, 1972.
14 Evans, F. T. and Gray, T. C., *General Anaesthesia*, Butterworth, London, 1965.
15 Fahn, S. and Côté, J. J., Regional distribution of γ-aminobutyric acid (GABA) in brain of the rhesus monkey, *J. Neurochem.*, 15 (1968) 209–213.
16 Hammond, P., On the use of nitrous oxide/oxygen mixtures for anaesthesia in cats, *J. Physiol. (Lond.)*, 275 (1978) 82P.
17 Hammond, P., Inadequacy of nitrous oxide/oxygen mixtures for maintaining anaesthesia in cats: satisfactory alternatives, *Pain*, 5 (1978) 143–151.
18 Johnson, J. L. and Aprison, M. H., The distribution of glutamate and total free amino acids in thirteen specific regions of the cat central nervous system, *Brain Research*, 26 (1971) 141-148.
19 Jouvet, M., The role of monoamines and acetycholine-containing neurons in the regulation of the sleep–waking cycle, *Ergebn. Physiol.*, 64 (1972) 166–307.
20 Lee, B. B., Effect of anaesthetics upon visual responses of neurones in the cat's striate cortex, *J. Physiol. (Lond.)*, 207 (1970) 74–75P.
21 Lewis, A. J. (Ed.), *Modern Drug Encyclopedia and Therapeutic Index*, Yorke Medical Books, New York, 1979.
22 Mancini, M. and Emerson, R. C., Effects of nitrous oxide on receptive fields in cat's visual cortex. In *ARVO Annual Spring Meet.*, 1979, p. 183, no. 30.
23 Mandl, G., Capaday, C. and Desai, N., Nitrous oxide modifies visual responses in cat superior colliculus. In *Canad. Physiol. Soc., 11th Winter Meet.*, 1979.

24 Okada, Y., Nitsch-Hassler, C., Kim, J. S., Bak, I. J. and Hassler, R., Role of γ-aminobutyric acid (GABA) in the extrapyramidal motor system. I. Regional distribution of GABA in rabbit, rat, guinea pig and baboon CNS, *Exp. Brain Res.*, 13 (1971) 514–518.
25 Peters, D. A. V., McGeer, P. L. and McGeer, E. G., The distribution of tryptophan hydroxylase in cat brain, *J. Neurochem.*, 15 (1968) 1431–1435.
26 Phillis, J. W., Tebecis, A. K. and York, D. H., The inhibitory action of monoamines on lateral geniculate neurons, *J. Physiol. (Lond.)*, 190 (1967) 563–583.
27 Reader, T. A., The effects of dopamine, noradrenaline and serotonin in the visual cortex of the cat, *Experientia (Basel)*, 34 (1978) 1586–1588.
28 Reader, T. A., Ferron, A., Descarries, L. and Jasper, H. H., Modulatory role for biogenenic amines in the cerebral cortex. Microiontophoretic studies, *Brain Research*, 160 (1979) 217–229.
29 Richards, C. D. and Webb, A. C., The effect of nitrous oxide on cats anaesthetized with Brietal, *J. Physiol. (Lond.)*, 245 (1975) 72–73P.
30 Russell, W. J., Nitrous oxide — is it an adequate anaesthetic? *J. Physiol. (Lond.)*, 231 (1973) 20–21P.
31 Steffey, E. P., Gillespie, J. R. Bery, J. D., Eger, E. I. and Munson, E. S., Anaesthetic potency (MAC) of nitrous oxide in the dog, cat and stump-tailed monkey, *J. appl. Physiol.*, 36 (1974) 530–532.
32 Straschill, M., Actions of drugs on single neurons in the cat's retina, *Vision Res.*, 8 (1968) 35–47.
33 Straschill, M. and Perwein, J., Effect of iontophoretically applied biogenic amines and of cholinomimetic substances upon the activity of neurons in the superior colliculus and the mesencephalic reticular formation of the cat, *Pflüger's Arch. ges. Physiol.*, 324 (1971) 43–55.
34 Thomas, T. N. and Redburn, D. A., Localization of serotonergic neurons in bovine retina, In *ARVO Annual Spring Meet.*, 1979, p. 280, no. 17.
35 Valzelli, L. and Garattini, S., Biogenic amines in discrete brain areas after treatment with monoamine-oxydase inhibitors, *J. Neurochem.*, 15 (1968) 259–261.
36 Van den Berg, C. J., Glutamate and glutamine. In A. Lajtha (Ed.), *Handbook of Neurochemistry, Vol. 3*, Plenum Press, 1970, pp. 355–379.
37 Venes, J. L., Collins, W. F. and Taub, A., Nitrous oxide, an anaesthetic for experiments in cats, *Amer. J. Physiol.*, 220 (1971) 2028–2031.
38 Zernicki, B., Isolated cerebrum of mid-pontine pretrigeminal preparation: a review, *Acta biol. exp. (Warsawa)*, 24 (1964) 247–284.