

Excitatory and inhibitory neurotransmitters in the nucleus rotundus of pigeons

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(RECEIVED September 19, 1994; ACCEPTED February 3, 1995)

Abstract

Rotundal neurons in pigeons (*Columba livia*) were examined for the effects of glutamate and its agonists NMDA and AMPA, antagonists CPP and CNQX, as well as of GABA and its antagonist bicuculline, on visual and tectal stimulation-evoked responses. Glutamate applied by iontophoresis excited all 48 rotundal cells tested, and this excitation was blocked by CNQX but not by CPP in 98% of cases, with 2% of cells being blocked by either CNQX or CPP. Out of 21 cells excited by AMPA, 20 were also excited by NMDA, indicating that AMPA and NMDA receptors may coexist in most rotundal cells. Action potentials were evoked in 36 additional cells by electrical stimulation applied to the tectum and they were also blocked by CNQX but not CPP. Visual responses recorded from a further eight luminance units and 21 motion-sensitive units were also blocked by CNQX and not CPP. On the other hand, GABA inhibited visual responses as well as responses evoked by tectal stimulation. An inhibitory period following tectal stimulation was eliminated by bicuculline. Taken together, these results indicate that glutamate may be an excitatory transmitter acting predominantly through non-NMDA receptors (AMPA receptors) in tectorotundal transmission. Meanwhile, GABA may be an inhibitory transmitter in the pigeon nucleus rotundus.

Keywords: Neurotransmitter, Receptor, Microiontophoresis, Nucleus rotundus, Pigeon

Introduction

In the avian visual system there are two main pathways sending visual information to the telencephalon. The first is designated the tectofugal pathway. The retinal fibers have a primary projection to the contralateral optic tectum (OT), whose large neurons in the deeper layers project mainly to the nucleus rotundus (nRt), the most prominent nucleus of the diencephalon. Nucleus rotundus then projects to the ectostriatum (Karten & Revzin, 1966; Benowitz & Karten, 1976; Nixdorf & Bischof, 1982). This projection system may be comparable to the mammalian extrageniculocortical (retina-superior colliculus-pulvinar-extrastriate) pathway. In the second or thalamofugal pathway retinal fibers project to the thalamic dorsolateral complex, which relays signals to the visual wulst. This pathway may be homologous to the geniculocortical system of mammals (Cowan et al., 1961; Karten et al., 1973; Nixdorf & Bischof, 1982; Güntürkün & Karten, 1991).

In the tectofugal pathway, the nRt is involved in the analysis of geometric pattern, brightness, color, and fine spatial detail (Hodos & Karten, 1966; Hodos et al., 1973; Macko & Hodos, 1984). Physiological studies have shown that the nRt may be organized into several functionally distinct subdivisions where

different types of visual information such as color, luminance, Z-axis motion, and occluding edge motion are processed (Wang & Frost, 1992; Wang et al., 1993). These physiological subdivisions are consistent with anatomical and histochemical data (Benowitz & Karten, 1976; Nixdorf & Bischof, 1982; Martinez-de-la-Torre et al., 1990). Although its subdivisions are differentially stained for AChE (Martinez-de-la-Torre et al., 1990), the nRt appears to lack both muscarinic and nicotinic cholinergic receptors (Wächtler, 1985; Dietl et al., 1988a; Watson et al., 1988; Güntürkün & Karten, 1991; Bagnoli et al., 1992) and fails to label for ChAT (Sorenson et al., 1989; Güntürkün & Karten, 1991). It is suggested that this pattern of AChE distribution may be unrelated to cholinergic neurotransmission. Moreover dopamine, 5-HT, and several peptides are not detected in the nucleus (Dubé & Parent, 1981; Sako et al., 1986; Dietl & Palacios, 1988; Güntürkün & Karten, 1991; Anderson et al., 1991; Anderson & Reiner, 1991; Bagnoli et al., 1992).

Immuno-histochemical studies have revealed that the nucleus has an apparently homogenous distribution of GABA-like terminals, which may stem from the GABAergic neurons of the subpretectal and ventral posterior thalamic nuclei (Domenici et al., 1988; Ngo et al., 1992). Furthermore, Dietl et al. (1988b) observed high binding densities of GABA-benzodiazepine receptors in the nRt. Therefore, GABA may be an inhibitory transmitter in this nucleus. Intermediate levels of L-H³ glutamate binding were also detected in the chick nRt (Mitsacos et al.,

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1990). It is suggested that L-glutamate is probably an excitatory neurotransmitter in the nRt. There is a large body of evidence indicating that glutamate acts through different types of receptors named after their selective agonists kainate, quisqualate, and N-methyl-D-aspartate (NMDA). The first two receptors, collectively termed non-NMDA receptors, have been implicated in the mediation of synaptic transmission in many excitatory pathways in the central nervous system, whereas NMDA receptors, with some exceptions (Mayer & Westbrook, 1987; Thomson, 1990), do not appear to play predominant roles in fast synaptic transmission. However, NMDA receptors have been shown to have an important function in long-term potentiation (Morris et al., 1986; Collingridge & Bliss, 1987), synaptic plasticity (Constantine-Paton et al., 1990; Robert & Nicoll, 1993), and cell death (Choi & Rothman, 1990).

In the present study, we have examined the effects of GABA and glutamate on the pigeon nRt by combining electrophysiological and microiontophoretic techniques. The aims were to obtain more direct evidence that these substances are neurotransmitters participating in tectorotundal transmission and to identify the receptor types mediating the synaptic responses.

Materials and Methods

All experiments were performed on adult homing pigeons (*Columba livia*). The animals were anesthetized with urethane (1 ml/100 g body weight, 20% solution) and placed in a stereotaxic apparatus. The body temperature was maintained at 41°C by a heating pad. Surgical exposure of the optic tectum and the overlying telencephalon were done in a conventional manner. The nucleus rotundus was approached according to its stereotaxic coordinates (Karten & Hodos, 1967). Extracellular recordings of action potentials were obtained using one barrel of a five-barrelled glass micropipette (3–5 μ m diameter, 5–15 M Ω impedance) filled with 2 M NaCl and 100 mM cobalt chloride. The other barrels contained the following chemical compounds that could be ejected microiontophoretically by appropriate ionic currents: NMDA (N-methyl-D-aspartate, Sigma Chemical Co., St. Louis, MO; 0.05 M, pH 7.5), AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, Tocris Neuramin, 0.01 M, pH 8.3), L-glutamic acid (Fluka, Switzerland; 0.5 M, pH 7.3), CPP (3-rs-2-carboxypiperazin-4-yl-propyl-1-phosphonic acid, Tocris Neuramin, 0.01 M; pH 7.5), CNQX (6-cyano-7-nitro-quinoxaline-2,3-dione, Tocris Neuramin, 0.01 M, pH 8.3), GABA (γ -aminobutyric acid, Fluka, Switzerland; 0.5 M pH 3.3), and bicuculline (Sigma Chemical Co., St. Louis, MO; 0.02 M, pH 3.5). Retaining currents ranging from 5 to 20 nA were used to prevent drug diffusion from the pipettes. In some experiments, one barrel filled with 0.165 M NaCl was used for minimizing current effects of current neutralization (Salmoiraghi & Weight, 1967) or for drug control. No apparent current effects were observed at the current intensity used in the present study.

Bipolar or concentric metal electrodes were used for stimulating the stratum griseum centrale (SGC) of the optic tectum (OT), where the tectorotundal projection neurons are located (Revzin & Karten, 1966; Benowitz & Karten, 1976). The stimulating sites were randomly distributed throughout the left optic tectum, and the electrode depth was adjusted to produce the maximal field potential in the nRt (Revzin & Karten, 1966; also see Fig. 1). Different locations did not produce obvious differences in responses. Rectangular pulses of 50–100 μ s in duration

with intensities of 0.1–0.5 mA were delivered at a frequency of 0.2–1 Hz. The visual stimuli were a 5-deg black or white disc at a distance of 40 cm from the right eye cornea, moved manually against a diffuse gray background. The illumination of the room in the vicinity of the visual display was about 35 lux. The black target was 2.0 cd/m², and the white target 30.0 cd/m², against a background of 14.2 cd/m². The black target was used in most of the experiments.

At the end of each experiment, recording sites were marked iontophoretically with cobalt chloride (anodal current pulses, 2 μ A, 0.5 s duration for 10 min). The brain was then removed and immersed in saline containing ammonium sulfide for 45 min to form a black precipitate of cobalt sulfide. The brain was fixed in 10% formalin for 48 h, and then was processed for paraffin embedding and sectioning. Serial sections were saved through the nRt and were examined with a light microscope in order to identify and localize individual recording sites (Wang et al., 1981). A constant current of 40 μ A for 60 s was applied through the stimulating electrode to verify its location by conventional histological procedures.

Results

Identification of recording positions

Electrical stimulation of the stratum griseum centrale (SGC) evoked a large characteristic field potential in the nRt, which has been shown to be a reliable indicator for determining the position of a recording electrode within this region (Revzin & Karten, 1966). Another criterion for differentiating the rotundal cells from other diencephalic neurons is their large visual receptive fields and strong excitation by a small moving object (Revzin, 1970; Wang et al., 1993). Our cobalt-sulfide markings also confirmed that extracellular responses were recorded from the nRt (Fig. 1).

Effects of amino acids and their antagonists on rotundal activity

A total of 21 cells were studied during microiontophoretic application of AMPA and NMDA. All were excited by AMPA with currents ranging from 5 to 30 nA. This excitation had a rapid onset (within 2 s), ended within 1–30 s following termination of current, and was easily controlled by varying the iontophoretic currents. No significant desensitization was observed during several applications at threshold currents, but some cells could be inactivated by an excess of AMPA. These phenomena were also seen on application of glutamate or NMDA. Applications of CNQX with iontophoretic currents ranging from 50 to 100 nA for 30–120 s blocked or remarkably reduced firing in all of the ten AMPA-excited cells tested. However, none of these cells was significantly affected by CPP, a specific NMDA-receptor antagonist (Table 1). Application of NMDA with the same current range excited 20 of the 21 identified nRt cells. The excitatory effects of NMDA on 12 nRt cells tested were specifically reduced or blocked by CPP, but not by CNQX (Table 1). The NMDA-evoked excitation was not significantly different from the excitation by AMPA, except that slow-onset (25 s) and long-lasting firing were observed in some cells. It appears that both NMDA and non-NMDA receptors are colocalized in most nRt neurons.

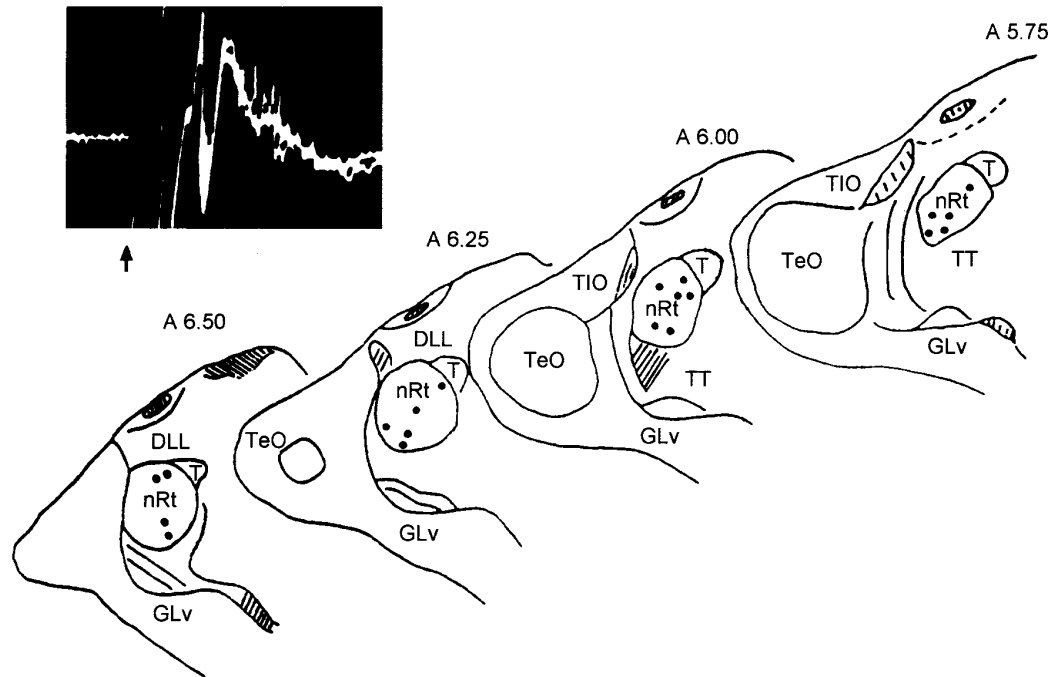


Fig. 1. Distribution of recording sites (filled circles) histologically identified with cobalt sulfide in the nucleus rotundus (nRt), where non-NMDA receptor-mediated tectorotundal transmission was found. Anterior-posterior levels are according to the atlas of Karten and Hodós. In inset is the field potential profile characteristically evoked in the nucleus rotundus by OT stimulation. Arrow points to stimulus artifact. DLL: nucleus dorsolateralis anterior thalami, pars lateralis; GLv: nucleus geniculatus lateralis, pars ventralis; T: nucleus triangularis; TeO: tectum opticum; TIO: tractus isthmo-opticus; and TT: tractus tectothalamicus.

We then tested the effect of glutamate (Glu) application on 48 additional rotundal neurons (Fig. 2, Table 1). Glu at 5–30 nA readily excited all rotundal neurons tested. Like AMPA action, excitation by Glu started rapidly (within 5 s), usually lasted for the period of application, and then stopped or sharply diminished at current offset. The effects of CNQX and CPP on glutamate-induced excitation were tested on 42 neurons (Table 1). Glutamate-induced firing was reversibly blocked by CNQX (50–100 nA, 5–120 s) in 41 of 42 neurons tested, but not by CPP (up to 200 nA, 10 min) (Fig. 2), except that CPP slowed down the response latency in more than a half of the cells tested. The remaining one cell was blocked by either CNQX or CPP.

Table 1. Effects of glutamate agonists and antagonists on rotundal neurons

Agonists ^a	Antagonists ^b	
	CNQX	CPP
Glu	48/48 (100%)	1/42 (2%)
AMPA	21/21 (100%)	0/10
NMDA	20/21 (95%)	12/12 (100%)

^aAgonist column: Ratios are fractions of tested cells activated by agonist.

^bAntagonist column: Ratios give fraction of cells tested in which the antagonist blocked responses to the agonist at the left.

Effects of glutamate antagonists on synaptic transmission

To further examine the effects of glutamate antagonists, CNQX and CPP, on tectorotundal transmission, extracellular responses to electrical stimulation of the tectum were also recorded from an additional 36 well-isolated rotundal neurons. Cells were included only if all of the appropriate antagonists were tested and recovery was observed. Spikes which satisfied the criterion for monosynaptic excitation following stimulation of OT were evoked in 32 cells encountered. These cells responded at short latencies (<7.5 ms) and were able to follow high-frequency stimulation (50–100 Hz). CPP applied with currents of up to 200 nA for up to 4 min had no effects on the monosynaptic firing in all cells (threshold current stimulation at a frequency 0.2–1.0 Hz). However, the response latency was somewhat slowed in many cases. In contrast to CPP, CNQX ejected with currents ranging from 50 to 100 nA for more than 30 s could significantly reduce or abolish responses in these neurons (Fig. 3). This depression usually appeared within 30–60 s and reached its maximum 120–180 s after onset of application, and responses completely recovered within 180 s after offset of ejection of CNQX.

To test whether CNQX was acting in a specific way or just as a local anesthetic, we examined the effects of CNQX on excitation evoked in some cells by Glu, AMPA, or NMDA, respectively. In all cells tested, CNQX readily depressed excitation induced by Glu or AMPA, but not NMDA-evoked excitation. In addition, polysynaptic excitatory responses were evoked in six cells. They were also readily depressed by CNQX. Both monosynaptic and polysynaptic responses were evoked in two

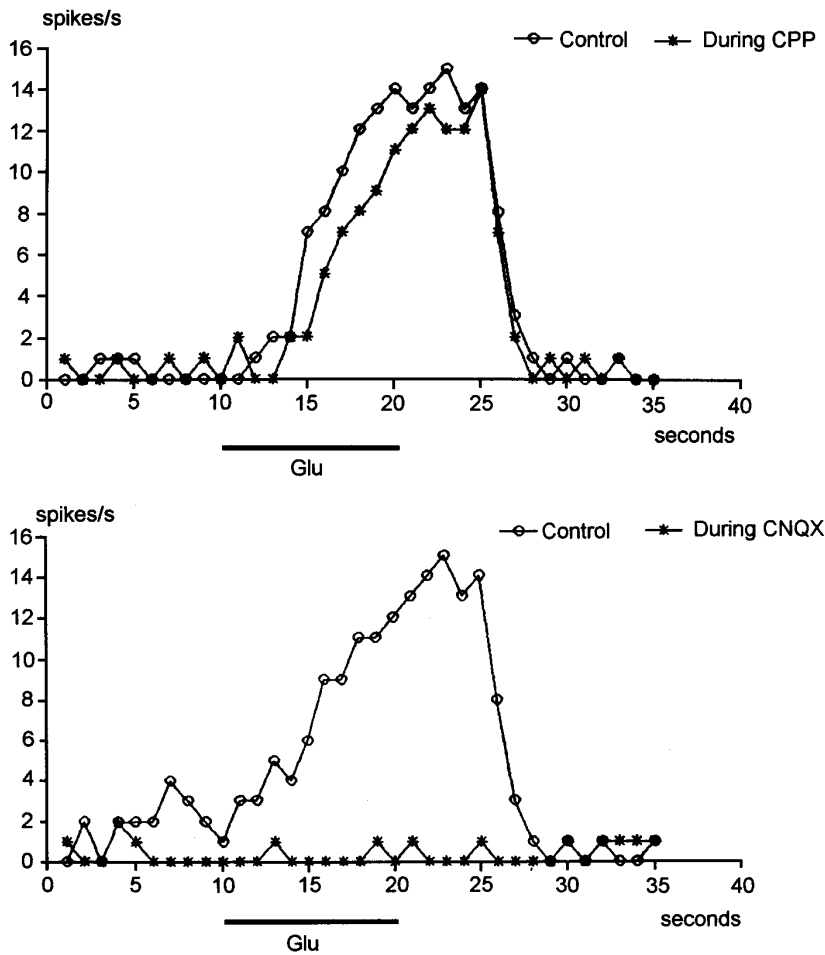


Fig. 2. Effects of CNQX and CPP on excitatory responses of a rotundal neuron induced by glutamate (Glu). CNQX blocked the Glu-evoked excitation whereas CPP had no significant effects. Bar: glutamate application.

cells, with the latter being more sensitive to CNQX. Application of CNQX (50 nA, 30 s) eliminated the long latency responses first, and then the short latency responses were completely blocked. Interestingly, the monosynaptic responses also showed a faster recovery than the polysynaptic one.

We asked whether neurons in various subdivisions of nRt or distinct physiological types might exhibit different amino-acid receptors. In our experiments, eight luminance units were isolated in the ventral nRt and 21 motion-sensitive units were distributed throughout the whole nucleus except the anterodorsal areas. In these two groups of units, CNQX reversibly reduced or blocked excitation evoked by visual stimulation. In contrast, CPP had no apparent effects on these responses, but was able to block NMDA-evoked excitation.

Effects of GABA and its antagonist on rotundal neurons

Microiontophoretically applied GABA with currents ranging from 5 to 30 nA depressed all forms of spontaneous and evoked activities in 40 rotundal cells recorded. The effects of GABA had a fast onset (less than 3 s), disappeared within 15–90 s, and could be reversibly reduced or blocked by bicuculline application at currents ranging from 50 to 100 nA for more than 60 s.

In many rotundal neurons which were spontaneously firing or activated by applied glutamate, an inhibitory period (35–70 ms) were often observed after OT stimulation. Sometimes, OT stimulation induced an inhibitory period following a short latency excitation. The excitation followed stimulation at frequencies above 50 Hz, implying a monosynaptic link, whereas the inhibition could not follow stimulus at frequencies above 10 Hz, indicating polysynaptic mediation. This inhibitory effect of OT stimulation could be eliminated by application of bicuculline (Fig. 4). The blockade usually started 60–120 s after onset of ejection and recovery occurred between 60 and 120 s after termination of application. Iontophoresis of GABA could block visual responses of rotundal units to a disc moving through their receptive fields or the OT-evoked responses (Fig. 4). Bicuculline applied at 100 nA before ejection of GABA could completely block the inhibition of GABA, which reappeared 10 min after offset of bicuculline.

Discussion

To our knowledge, the present study is the first to use microiontophoresis to systematically investigate the neurotransmitter organization in the pigeon nRt. The results indicate that both

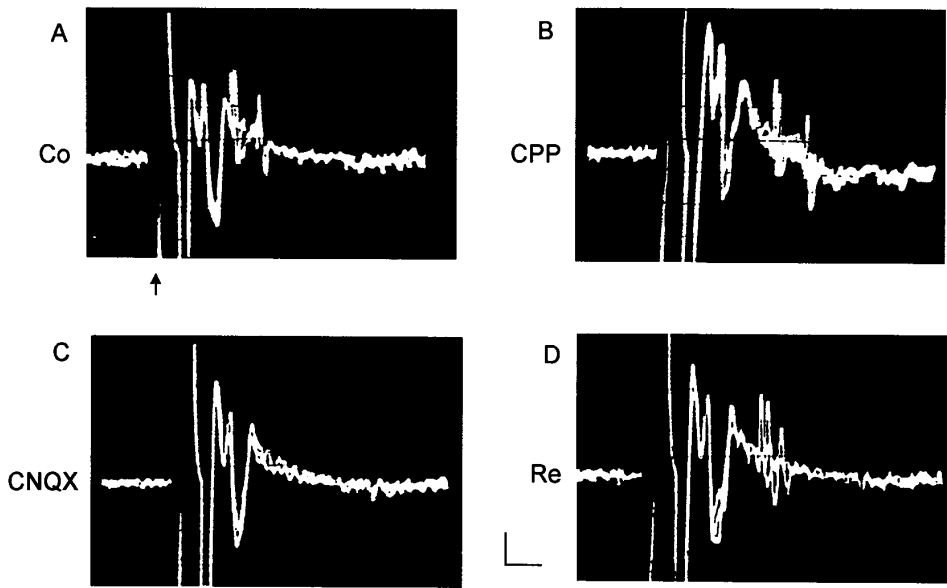


Fig. 3. Effects of CNQX and CPP on OT-evoked excitation of a rotundal neuron. A: Control (Co). B: During 100 nA CPP. C: During 50 nA CNQX. D: Recovery from CNQX (Re). Three superimposed sweeps. Scale = 0.1 mV, 2 ms. Arrow points to stimulus artifact.

NMDA and non-NMDA receptors may co-exist on most rotundal cells, and glutamate plays an excitatory transmitter role in tectorotundal transmission predominantly through a non-NMDA mechanism. In addition, GABA may be a major inhibitory neurotransmitter in this nucleus, acting *via* GABA-A receptors.

Microiontophoretically applied L-glutamate could excite all of the nRt neurons tested. This excitation could be blocked by a non-NMDA specific antagonist CNQX, which also blocked tectorotundal transmission and visual responses in the nRt. However, NMDA receptor antagonist CPP did not significantly affect these responses. The parallelism between glutamate-induced, OT-evoked, and visually driven responses with respect

to their sensitivity to CNQX and resistance to CPP suggests that L-glutamate mediates excitatory synaptic transmission in the tectorotundal pathway predominantly *via* a non-NMDA receptor mechanism. This is supported by patterns of L-H³ glutamate binding (Mitsacos et al., 1990).

Although non-NMDA receptor-mediated transmission is dominant in the nRt, we could not exclude the possibility that an NMDA receptor component may also play a role at these synapses. Many studies have shown that NMDA receptors appear to participate in high-frequency synaptic transmission (Caroline et al., 1986), long-term potentiation (Morns et al., 1986; Collingridge & Bliss, 1987), synaptic plasticity (Constantine-Paton, et al., 1990; Robert & Nicoll, 1993), and cell death

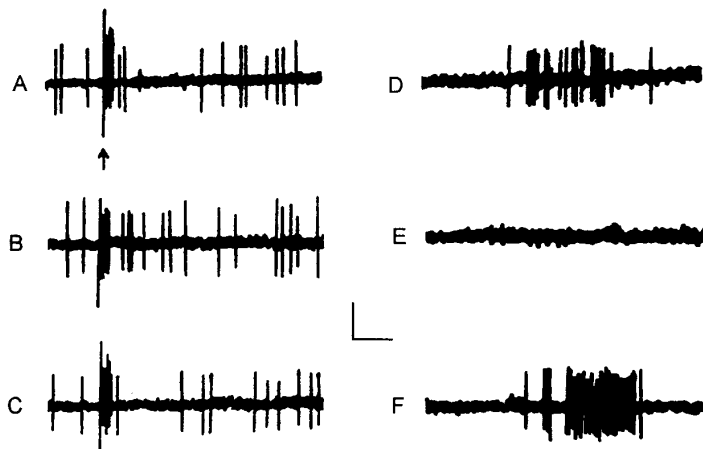


Fig. 4. Effects of GABA and bicuculline on responses induced by OT or visual stimulation. A: Control, OT stimulation evoked short latency response followed by an inhibitory period. B: During bicuculline 100 nA, the OT-evoked inhibition was blocked. C: Recovery 2 min after termination of ejection of bicuculline. D: Visual control. E: Visual responses during GABA 20 nA. F: Visual responses during bicuculline 100 nA. Note that visual responses during bicuculline were much stronger than control. Five superimposed sweeps. Scale = 0.1 mV, 10 ms in A-C, and 1 s in D-F. Arrow points to stimulus artifact.

(Choi & Rothman, 1990). Interestingly, Herrmann and Bischof (1993) have shown that the nRt undergoes dramatic changes during its development and is very susceptible to visual deprivation. On the other hand, in some other sensory pathways (Thomson, 1990; Draw & Stein, 1993), such as cortico-thalamic, cerebellorubral, retinogeniculate, and geniculocortical pathways, synaptically activated NMDA receptors clearly mediate conventional neurotransmission.

Our findings on the nRt are similar to those reported for other neural structures. It has been shown that monosynaptic transmission in the spinal cord is mediated mainly by non-NMDA receptors, and that the contribution of NMDA receptors to this transmission is very small or negligible. Extracellular studies have also shown that glutamate can evoke responses that are predominantly mediated by non-NMDA receptors, closely resembling responses to quisqualate (Peet et al., 1983). On the other hand, intracellular studies have revealed that an NMDA-receptor-mediated component of the monosynaptic EPSP exists in the spinal cord in most circumstances, particularly when the membrane potentials are depolarized (Thomson, 1990).

It has been suggested that inhibition plays some role in visual information processing in the nRt (Granda & Yazulla, 1971; Yazulla & Granda, 1973; Revzin, 1979; Wang & Frost, 1992; Wang et al., 1993). This nucleus contains homogeneously distributed GABA-like terminals, which may originate from the GABAergic neurons of the subpretectal and ventral posterior thalamic nuclei (Domenici et al., 1988). The GABA-like terminals contain flattened vesicles and make synapses with cells of the nRt (Ngo et al., 1992). High binding densities of GABA-benzodiazepine receptors were observed in the nRt. In the present study, microiontophoretically applied GABA readily depressed all forms of spontaneous and evoked activity. This inhibition could be reversibly reduced or blocked by bicuculline. Bicuculline also blocked OT-evoked polysynaptic inhibition. Taken together, these results strongly support the notion that GABA is a major inhibitory neurotransmitter in the nRt.

However, we found no evidence in this study to suggest that glutamate and GABA synaptic mechanisms are spatially correlated with the functional subdivisions of the nRt, although subdivisions of AChE staining have been reported (Martinez-de-la-Torre et al., 1990). In summary, the present study shows that both NMDA and non-NMDA receptors co-exist in most nRt neurons. L-glutamate and GABA may play important roles in mediating neurotransmission in the nRt via non-NMDA receptors and GABA-A receptors, respectively, and their synaptic mechanisms apparently have no direct relationship with the functional subdivisions of the nRt.

Acknowledgments

This work was supported by the National Natural Science Foundation of China and the Medical Research Council of Canada. We are grateful to Professor Wu, W.C. for his great help in measuring some optical parameters.

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