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ACETYLCHOLINE AND SOMATICALLY EVOKED INHIBITION ON PERIGENICULATE NEURONES IN THE CAT

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1 Perigeniculate neurones in cats were found to be inhibited by iontophoretically applied acetylcholine (ACh) and some of them by somatic sensory stimulation under certain experimental conditions.

2 Under chloralose anaesthesia, perigeniculate neurones could be divided into two groups with regard to their spontaneous activity, sensitivity to glutamate and reaction to sensory inputs. Somatic sensory stimulation clearly inhibited the glutamate discharges of those perigeniculate neurones which were characterized by a high sensitivity to glutamate and the absence of spontaneous activity. ACh had no clear inhibitory effect.

3 Under fluothane and urethane anaesthesia, no somatic sensory influence was noticed but ACh depressed almost all perigeniculate neurones.

4 In an unanaesthetized midpontine pretrigeminal preparation, the inhibitory effect of ACh was confirmed.

5 No conditions were found under which the inhibitory influences of ACh and those of somatic sensory stimulation could be observed simultaneously on the same neurone. Therefore, it could not be established whether ACh mediates the somatic sensory influences on perigeniculate cells.

Introduction

The lateral geniculate nucleus (LGN) of mammals is the first relay station where the visual input can be influenced by an extra-retinal input (references in McIlwain, 1972; Freund, 1973). As previously shown in this laboratory by Meulders and co-workers (Meulders, Boisacq-Schepens, Godfraind & Colle, 1966; Godfraind & Meulders, 1969), somatic sensory stimulation facilitates visual responses in the LGN, and this effect is probably mediated from the midbrain reticular formation (Meulders *et al.*, 1966; Melzack, Konrad & Dubrovsky, 1968; Meulders & Godfraind, 1969; McIlwain, 1972; Tatton & Crapper, 1972; Doty, Wilson, Bartlett & Pecci-Saavedra, 1973; Freund, 1973). Indeed electrical stimulation of either the somatic sensory area or the midbrain reticular formation evokes identical phenomena in the LGN region, although the effect of the peripheral stimulation is less marked (Meulders *et al.*, 1966; Godfraind & Meulders, 1969; Meulders & Godfraind, 1969; Singer, 1973a). These observations suggest that peripheral and central stimulation activate the same interneurones. Indeed, facilitation in the LGN might be explained by the inhibition of inhibitory interneurones, i.e. disinhibition (Purpura, McMurty & Maekawa, 1966; Fukuda & Iwama, 1971; Freund, 1973; Singer, 1973a). Peripheral stimulation may have the advantage that it provides a more discrete method of stimulation, and thus may avoid some of the difficulties in interpretation experienced by others (Singer, 1973b; Krnjević, 1974; Ranck, 1975; Bagshaw & Evans, 1976; Dingledine & Kelly, 1977).

Several observations suggest that facilitations involving midbrain reticular structures are mediated by acetylcholine (ACh) (see references in Krnjević, 1974). It might be expected, therefore, that the inhibitory interneurones of the LGN would be inhibited by somatic sensory impulses and by iontophoresis of ACh. Anatomical (Scheibel & Scheibel, 1972; Szentágothai, 1972), and physiological observations (Hotta & Kameda, 1963; Meulders *et al.*, 1966; Godfraind & Meulders, 1969; Meulders & Godfraind, 1969; Sumitomo, Nakamura & Iwama, 1976) suggest that the perigeniculate area may contain the inhibitory interneurones of the LGN. Such an organization is

similar to that in the thalamic somato-sensory relay nucleus (Angel, 1964; Massion, 1968; Schlag & Waszak, 1970; 1971; Ben-Ari, Dingledine, Kanazawa & Kelly, 1976; Dingledine & Kelly, 1977).

The aim of the present work was to see whether or not perigeniculate neurones are inhibited by somatic sensory impulses and by iontophoretically applied ACh, and to test the differential effect of anaesthetics. These results have been briefly presented elsewhere (Godfraind, 1976a, b).

Methods

Experiments were performed on 10 cats, 5 of which were anaesthetized with intravenous α-chloralose (80 mg/kg), 2 with intravenous urethane (1 g/kg), 2 with 1% fluothane in a (1:1) mixture of N_2O/O_2 (v/v), and 1 was unanaesthetized with a midpontine pretrigeminal transection (Batini, Moruzzi, Palestini, Rossi & Zanchetti, 1959). Except for the animals anaesthetized with fluothane, all cats were paralyzed with an intravenous infusion of succinylcholine (Fluka) at an approximate rate of 1 mg/min and artificially ventilated. All cats also received atropine methylnitrate (4 mg/kg). The grey and white matter overlying the LGN region was removed by suction to the level of the hippocampal fornix. Routine care of animals was similar to that previously described (Godfraind, 1975). Conventional techniques were used for extracellular recordings and drugs were applied by iontophoresis (Krnjević & Phillis, 1963a). The central barrel was filled with a dye (4% pontamine in a 0.5 M NaCl solution), the ejection of which permitted the recording sites to be localized (Godfraind, 1969). The other barrels were filled with the following substances: sodium-L-glutamate (Fluka) 1 M, pH 7 to 7.4; acetylcholine chloride (Fluka) 1 M, pH 4.9; atropine sulphate (Pharmacie Centrale de Belgique) 10 mM in 165 mM NaCl, pH 5.5; mecamylamine hydrochloride (Merck, Sharp & Dohme) 10 mM in 165 mM NaCl, pH 6.6.

Peripheral somatic stimulation of all 4 limbs was performed by delivering electrical stimuli through needles inserted under the skin of the paws. Electrical stimulation consisted of a train of two to three impulses of 0.1 ms in width, delivered at a frequency of 5 kHz and repeated every 3, 4 or 6 s; the voltage was adjusted, before paralysis, to just elicit the flexor reflex.

Techniques for visual stimulation were similar to those used previously (Godfraind & Meulders, 1969; Godfraind, Meulders & Veraart, 1972). One eye was covered and accommodation of the other paralyzed with a few drops of an atropine methylnitrate solution. The cornea was covered with a +3 D contact lens to prevent drying and ensure accommodation at 30 cm. The visual axis of that eye was centred on a hemispherical translucent perimeter (Gambs, Lyon); spots (6–14 candela/m^2) were projected onto the perimeter against a background luminance of 0.5 candela/m^2.

During the experiments, the discharge rate of the neurones was displayed on a pen recorder. Spikes were also recorded on magnetic tape, and later played back for photographic recordings.

At the end of the experiments, the brain was perfused with 10% formaldehyde in 9% w/v NaCl solution, removed and cut in serial sections for histological control and reconstruction of electrode tracks.

Results

The entire perigeniculate region was explored between the frontal planes AP 7 to about AP 4.5, according to the atlas of Jasper & Ajmone-Marsan (1954), and studies on 58 neurones showed little variation to occur in relation to the recording sites. When the electrode reached the LGN, the sensitivity to drugs changed dramatically. Although LGN neurones were less sensitive to glutamate than perigeniculate cells, they were easy to excite with ACh. This change in sensitivity was always clearcut and proved to be a reliable indicator of the border between perigeniculate and LGN (Table 1). Thus the differential sensitivity to glutamate and ACh constitutes a further criterion to distinguish the two neuronal populations of the perigeniculate and LGN, and may be added to the list of the other physiological criteria previously described (Negishi, Lu & Verzeano, 1962; Mukhametov, Rizzolatti & Tradardi, 1970).

Under chloralose anaesthesia, most perigeniculate units were clearly influenced by sensory stimuli, but no clear effect could be observed upon iontophoretic application of ACh. However, under fluothane and urethane anaesthesia, somatic sensory stimulation was without effect, but ACh was clearly shown to depress perigeniculate neuronal activity. The ACh inhibitory effect was also observed in the midpontine pretrigeminal preparation.

Chloralose anaesthesia

Thirty neurones were investigated under chloralose anaesthesia and, with few exceptions, these could be divided into two main groups with regard to their spontaneous activity, glutamate sensitivity and reactions to sensory inputs.

The first group of 16 neurones was glutamate-sensitive, and diffusion of glutamate from the electrode was often sufficient to increase neuronal activity (Figure 1). An increase of the glutamate retaining current from 15 to 30 nA was sufficient to suppress the

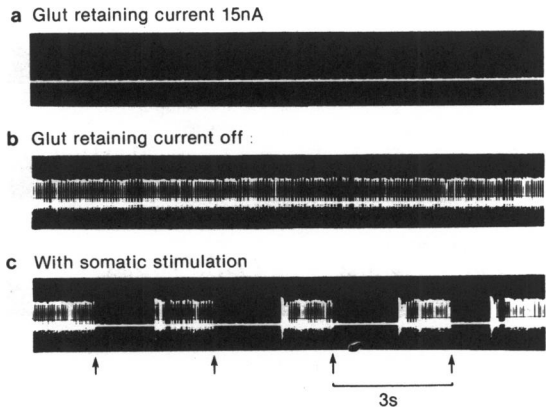

Figure 1 Somatically evoked inhibition. Perigeniculate neurone recorded under chloralose anaesthesia. Glut: glutamate; calibration time: 3 seconds. (a) The perigeniculate cell has no spontaneous activity; the retaining current applied to the glutamate channel is 15 nA; (b) the glutamate retaining current is switched off, and the diffusion of the amino-acid is sufficient to discharge the cell; (c) somatic sensory stimulation is delivered every 3 s at arrow; it evokes inhibition of the glutamate-induced activity (the retaining current being off).

apparent spontaneous firing rate of these 16 cells. The other 14 neurones, in the second group, exhibited a low spontaneous firing rate (range 3–10 spikes/second). These could not be silenced by increasing the glutamate retaining current to 30 nA or more. Although some of these neurones were as sensitive to glutamate as cells of the first group, they often required a greater amount of glutamate in the range of 30 to 40 nA to reach a firing level of about 50 spikes/second.

The glutamate-induced activity of 15 out of the 16 neurones in the first group was clearly inhibited by somatic sensory stimulation (Figure 1). There was a preferential projection, stimulation of one or another paw being more effective than excitation of the others. Fourteen of these 15 cells could not be fired by visual stimulation.

Thirteen of the 14 spontaneously active neurones in the second group responded to visual stimulation and could be separated into 5 ON, 3 OFF and 5 ON–OFF cells. As previously noted (Godfraind & Meulders, 1969; Meulders & Godfraind, 1969; Sanderson, 1971), visually evoked responses were often 'fatiguable'; after a few presentations of the stimulus, responses became irregular and waned. Nevertheless, some of the units could follow stimulation frequencies of 0.5 hertz. Most neurones responded to light over the entire field of vision, and some had a restricted visual receptive field of 7 to 8 degrees of arc situated in the half-field of vision contralateral to the thalamic region under examination. Twelve of the 14 neurones were not inhibited by somatic stimulation. On only one occasion did paw stimulation seem to facilitate the visual responses.

ACh applied with iontophoretic currents between 20 and 90 nA for 35 to 90 s had no clear and systematic effect on most of the neurones firing either spontaneously or excited by glutamate. Only two neurones in the second group, recorded in different experiments, were excited by ACh (40 nA for 10 s); one was an ON and the other an ON–OFF cell.

Table 1 Variation in neuronal sensitivity to glutamate and acetylcholine

	Perigeniculate region			*Lateral geniculate nucleus*		
Animal preparation	*Cell code*	*Glutamate*	*Acetylcholine*	*Cell code*	*Glutamate*	*Acetylcholine*
Chloralose No. 4	C5	↑ 17	No effect	C6	Not tested	↑ 5
				C7	Not tested	↑ 5
				C8	↑ 70	↑ 40
Chloralose No. 8	C7	↑ 40	No effect	C8	↑ 50	↑ 32
					↑ 40	↑ 15
Fluothane No. 12	C9	↑ Diffus.	↓ 20	C10	↑ 75	↓ 40
Pretrigeminal No. 14	C7	↑ 10	No effect	C8	↑ 65	↑ 40
Urethane No. 16	C5	↑ 5	↓ 40	C6	↑ 45	↑ 15
Urethane No. 17	C14	↑ Diffus.	↓ 80	C15	↑ 40	↑ 18

Each horizontal row corresponds to a penetration performed during separate experiments with either chloralose, fluothane, urethane or pretrigeminal preparation, to show that in general more glutamate is needed to excite the LGN cells, and that acetylcholine excites LGN neurones but depresses or does not affect perigeniculate neurones. The letter C followed by a number refers to the code attributed to each cell. 'Glutamate' and 'Acetylcholine' show the amount of iontophoretic current applied, which is expressed in nA. The signs ↑ and ↓ show excitation and depression respectively.

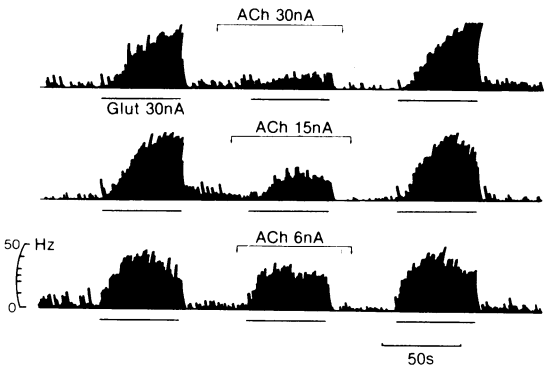

Figure 2 Acetylcholine-evoked inhibition. Perigeniculate neurone recorded under fluothane anaesthesia. Calibration time on abscissa scale: 50 s; on the ordinate scale; firing frequency per second. The records (in counts per s) have been interrupted for about 1 min 20 seconds. The cell is discharged by intermittent applications of glutamate (Glut) 30 nA (black bars under traces indicate the time of application). Acetylcholine (ACh) applied successively with 30, 15 and 6 nA (period of application indicated by black bars between arrows) inhibits the glutamate-evoked firing in a dose-dependent manner.

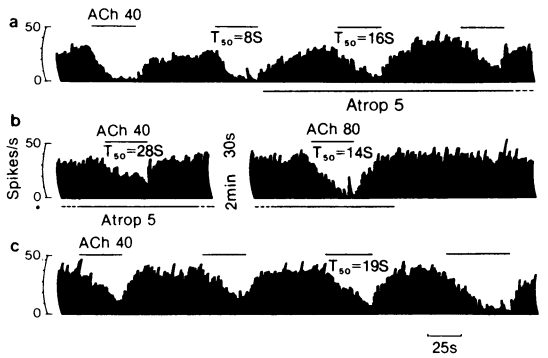

Figure 3 Antagonism of acetylcholine inhibition by atropine. A perigeniculate cell recorded under fluothane anaesthesia is fired at an approximate rate of 25–30 spikes/s by continuous iontophoresis of glutamate (10 nA). Acetylcholine (ACh, 40 nA, 30 s) is regularly applied with about 60 s pauses between successive applications. Almost complete depression of firing is reached within 15 s after the start of ACh application; the control value of the T_{50} is indicated in the figure (T_{50} is the time necessary to reach 50% of the depression; Simmonds, 1974). Atropine (Atrop) is then applied with a current of 5 nA for 9 min 50 seconds. Atropine antagonism is surmountable: 80 nA ACh produces a 100% depression as tested about 9 min after the start of atropine; note the T_{50} value. Atropine application is then discontinued and 40 nA ACh applied for 30 s cannot provoke complete firing depression. ACh is then applied for 45 s; almost complete depression is obtained after 30 seconds. Estimates of T_{50} give the same values 9 min and 15 min (trace not shown) after atropine was discontinued; recovery is thus incomplete. Calibration time on abscissa scale: 25 s; on the ordinate scale: firing frequency per second. The records have been interrupted for 2 min 30 s between (a) and (b), and for 4 min 15 s between (b) and (c).

Fluothane and urethane anaesthesia

Out of 28 cells examined in these series, 14 were recorded under fluothane and 14 others under urethane anaesthesia. The spontaneous activity of cells under fluothane was less than that under urethane anaethesia and, except for one neurone, cells were not discharged by visual stimulation. On the other hand, under urethane anaesthesia, almost all neurones responded to visual stimulation. There were 4 ON, 1 OFF and 6 ON–OFF cells. The effect of glutamate, ACh and somatic stimulation on all 28 cells tested was the same.

Except for one silent neurone all cells were spontaneously active. In 15 cells (10 cells under fluothane, 5 under urethane), the mean level of spontaneous activity was about 10 spikes/s, or below and, in 12, it was approximately 20 to 25 spikes/second. Some cells were readily excited by withdrawal of the glutamate retaining current or application of small iontophoretic currents of 3 to 5 nanoamperes. For comparison with 14 cells tested under chloralose anaesthesia, the amount of glutamate necessary to induce firing levels of about 50 spikes/s was determined in 18 cells. Approximately half of these neurones were excited to this level with application of less than 10 nanoamperes.

Out of 25 neurones tested, no effect of somatic sensory stimulation was observed.

Almost all neurones (20 out of 24 examined) were depressed by ACh. In many cases, the spontaneous activity was low, and ACh was tested on discharges evoked either by intermittent or continuous iontophoretic applications of glutamate. In 4 cases, the depression was slight, i.e. 25%. In the other 16 neurones, a minimum of 50% depression of the mean firing rate was observed following ACh administration with 20 to 40 nA applied for 30 to 90 seconds. As shown in Figure 2, ACh often exerted a dose-dependent inhibitory effect on the firing evoked by regular applications of glutamate. Occasionally burst activity

similar to that described by Ben-Ari *et al.* (1976) occurred during the ACh-induced depression. In only 3 of the 16 neurones did recording conditions remain stable long enough to permit tests with cholinoceptor antagonists. Atropine had a clear antagonistic action on the depressant effect of ACh (Figure 3), whereas mecamylamine, applied with similar iontophoretic parameters, was not very effective.

Midpontine pretrigeminal preparation

The 6 neurones tested in this preparation were all spontaneously active. The firing level was about 25 spikes/s, except in one case in which the rate was less than 10 spikes/second. Discharge rates of about 40 spikes/s were obtained following glutamate application ranging from 5 to 55 nanoamperes. Four of the 6 cells responded to visual stimulation with ON–OFF responses, the OFF component being predominant. Four were depressed by ACh applied with 70 nA for 30 to 40 seconds.

Discussion

Acetylcholine effects

The present data bring additional support to the hypothesis that presence of inhibitory cholinoceptors is a common feature of the cells of the thalamic reticular system of which the perigeniculate area is a part. In the pretrigeminal preparation, as well as in animals anaesthetized with fluothane or urethane, ACh depressed almost all perigeniculate neurones. This is in full agreement with recent observations showing the same effect, with similar iontophoretic doses, on reticular units surrounding the thalamic somatosensory relay nucleus (Ben-Ari *et al.*, 1976). This pharmacological action of ACh may be significant in the facilitation of synaptic transmission in the thalamic sensory relay nuclei following activation of midbrain reticular structures. In the case of the LGN, most recent experiments support the idea that perigeniculate neurones play the role of inhibitory interneurones for the LGN cells (Sumitomo *et al.*, 1976; Tsumoto & Suzuki, 1976). Furthermore, midbrain reticular structures, which are believed to exert their influence via the mediation of ACh (references in Krnjević, 1974), have been shown to send fibres to the perigeniculate (Szentágothai, 1972). Therefore, the fact that iontophoretically applied ACh inhibits perigeniculate neurones, is consistent with this scheme.

As described by others (Ben-Ari *et al.*, 1976), the ACh-induced inhibitions were quite sensitive to a muscarinic antagonist. However, ACh effects were not antagonized by mecamylamine applied with similar iontophoretic parameters to those used in the administration of atropine.

Under chloralose anaesthesia, the inhibitory effect of ACh was very weak. This result suggests that chloralose affects the cholinergic sensitivity of perigeniculate reticular neurones more profoundly than the sensitivity of neurones in other regions (Biscoe & Krnjević, 1963; Krnjević & Phillis, 1963b; De France, Yoshihara, McCrea & Kitai, 1975), As suggested earlier by Krnjević (1971), an anti-inhibitory action of chloralose, like that seen here, could be one of the ways by which this anaesthetic acts on the central nervous system. This action could also account for its convulsive effects (Albe-Fessard & Fessard, 1963).

Somatic effects

Somatic sensory stimulation inhibited only a certain group of perigeniculate neurones and only under chloralose anaesthesia. It is tempting to suggest that the facilitatory effect exerted by somatic sensory impulses on the LGN are brought about by inhibition of these perigeniculate neurones. However, the fact that these neurones exhibit no spontaneous activity in this experimental situation casts some doubts on their intervention in such a disinhibitory circuit, at least under chloralose. It is therefore possible that the influence exerted by direct pathways linking midbrain structures to the LGN (Bowsher, 1970) may be more pronounced under chloralose. This could agree with physiological data suggesting that facilitation of LGN transmission after midbrain reticular stimulation may be partly caused by postsynaptic excitation (Nakai & Domino, 1968; Singer, 1973a). A direct excitatory effect associated with an indirect disinhibitory effect on the LGN would certainly be compatible with the proposition of a 'push-pull arrangement' of the cholinergic ascending system proposed by Krnjević (1974) and already supported by the results of Kelly and associates (Ben-Ari *et al.*, 1976; Dingledine & Kelly, 1977) in the somato-sensory area of the thalamus.

The failure of somatic stimulation to inhibit perigeniculate cells under fluothane and urethane anaesthesia may be the result of a depressant effect of these drugs on synaptic transmission (Angel & Unwin, 1970; Angel & Knox, 1970; Richards, 1973). Fluothane appears to be more depressive than urethane since the former also causes a relatively greater reduction in the cell's responses to visual stimuli and lowers the mean firing rate. Under urethane anaesthesia, it has been shown previously that thalamic neurones lying around the somatic relay nucleus are influenced by somatic sensory stimuli (Angel, 1964); but this was observed only when using very strong stimuli, more intense than the ones used here. The present stimuli

were intended not to stimulate the nociceptive, slowly conducting fibres of the peripheral nerves.

The hypothesis that perigeniculate neurones lacking spontaneous activity are a link in the inhibitory loop responsible for the facilitation observed in LGN, is consistent with other experimental observations: (i) The reduced activity in the perigeniculate may result in continuous disinhibition of LGN cells. Such a phenomenon could account for the greater surface area of the visual receptive fields of LGN neurones observed in the chloralose-anaesthetized animals when compared to that observed in non-anaesthetized animals (Godfraind & Meulders, 1969; Meulders & Godfraind, 1969). (ii) Units remaining silent for long periods in 'encéphale isolé' preparations have been described by others (Schlag & Waszak, 1970; 1971) in the reticular region surrounding the nucleus ventralis lateralis; and it has been proposed that neurones of this region play a role identical to that of the perigeniculate cells. Unfortunately, experimental conditions which were most suitable to observe the somatic influences were not favourable for the ACh effects and *vice versa*. This not only limits further analysis but also leaves open the question as to whether or not other ascending projection systems are involved in the control of excitability of neurones in the LGN region (Laurent, Guerrero & Jouvet, 1974; Nakai & Takaori, 1974). Recent experiments on the thalamic reticular neurones (Dingledine & Kelly, 1977), which show good correlation between inhibition induced by reticular stimulation and the inhibitory action of iontophoretically applied ACh, are undoubtedly, but not exclusively, in favour of a cholinergic innervation.

Footnote

As kindly pointed out to the author by Prof. Dr Holländer (Munich), the term 'perigeniculate' should be restricted to a thin layer (200 microns thick) of cells lying close to the lateral geniculate nucleus. Above these cells, are the neurones of the thalamic reticular nucleus. According to Szentágothai (1972), the perigeniculate cells resemble very closely the reticular nucleus of the thalamus; in fact one gets the impression that this nucleus is nothing but a geniculate part of the thalamic reticular nucleus. In these experiments, neurones were recorded in these two very similar reticular areas, and no difference in physiological properties (ACh effect; somatic sensory influence) was noticed.

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