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LOW-FREQUENCY OSCILLATORY ACTIVITIES INTRINSIC TO RAT AND CAT THALAMOCORTICAL CELLS

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SUMMARY

1. Low-frequency membrane potential oscillations recorded intracellularly from thalamocortical (TC) cells of the rat and cat dorsal lateral geniculate nucleus (dLGN) and of the rat ventrobasal nucleus (VB) maintained *in vitro* were investigated. On the basis of their electrophysiological and pharmacological properties, four types of activity were distinguished and named: the pacemaker oscillations, the spindle-like oscillations, the 'very slow' oscillations and the '*N*-methyl-D-aspartate' (NMDA) oscillations.

2. The pacemaker oscillations (95 out of 173 cells) consisted of rhythmic, large-amplitude (10–30 mV) depolarizations which occurred at a frequency of $1{\cdot}8 \pm 0{\cdot}3$ Hz (range, 0·5–2·9 Hz) and could often give rise to single or a burst of action potentials. Pacemaker oscillations were observed when the membrane potential was moved negative to -55 and positive to -80 mV, but in a given cell the upper and lower limits of this voltage range were separated by only $13{\cdot}1 \pm 0{\cdot}5$ mV. Above -45 mV tonic firing consisting of single action potentials was seen in the cells showing this or the other types of low-frequency oscillations.

3. The spindle-like oscillations were observed in thirty-nine (out of 173) TC cells and consisted of rhythmic ($2{\cdot}1 \pm 0{\cdot}3$ Hz), large-amplitude depolarizations (and often associated burst firing) similar to the pacemaker oscillations but occurring in discrete periods every 5–25 s and lasting for 1·5–28 s. The spindle-like oscillations were observed when the membrane potential was moved negative to -55 and positive to -80 mV and in two cells they were transformed into continuous pacemaker oscillations by depolarization of the membrane potential to -60 mV.

4. Pacemaker and spindle-like oscillations were unaffected by tetrodotoxin (TTX) or by selective blockade of NMDA, non-NMDA, $GABA_A$, $GABA_B$, nicotinic, muscarinic, α- and β-noradrenergic receptors.

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5. The 'very slow' oscillations consisted of a TTX-insensitive, slow hyperpolarization–depolarization sequence (5–15 mV in amplitude) which lasted up to 90 s and was observed in nine dLGN cells and in two VB cells. The pacemaker and the spindle-like oscillations were recorded in one cell each which also showed the 'very slow' oscillations.

6. The 'NMDA' oscillations were observed only in a 'Mg^{2+}-free' medium (0 mM-Mg^{2+}, 2–4 mM-Ca^{2+}; 64 out of 72 cells) and consisted of large-amplitude (10–25 mV) depolarizations that did not occur at regular intervals and were intermixed with smaller depolarizations present on the baseline and on the falling phase of the larger ones. The 'NMDA' oscillations were voltage dependent (observed in the range from -60 to -85 mV), insensitive to TTX and had a frequency of 1–4 Hz. Application of selective NMDA receptor antagonists reversibly transformed the NMDA into the pacemaker or the spindle-like oscillations while blockade of non-NMDA receptors as well as the other receptors mentioned above (paragraph 4) had no effect on the 'NMDA' oscillations.

7. The pacemaker, the spindle-like and the 'very slow' oscillations were never observed in electrophysiologically identified rat and cat dLGN interneurones ($n = 12$). Similarly, in a 'Mg^{2+}-free' medium, interneurones in the dLGN and cells in the ventral lateral geniculate nucleus did not show the 'NMDA' oscillations but only slow, small-amplitude (< 4 mV) depolarizations that were reversibly abolished by DL-2-amino-5-phosphono-valeric acid (25 μM).

8. These results indicate that (i) single TC cells in different thalamic nuclei of different species are capable of four types of low-frequency oscillatory activity that do not require the evoked rhythmic recruitment of other neurones and (ii) activation of the NMDA receptors by spontaneously released excitatory amino acid brings about the transformation of the pacemaker and the spindle-like oscillations into the 'NMDA' oscillations.

INTRODUCTION

Low-frequency membrane potential oscillations of thalamocortical (TC) cells and their often associated rhythmic burst firing play a major role in physiological functions (references in Andersen & Andersson, 1968; Purpura, 1970; Lamarre, Filion & Cordeau, 1971; Fourment, Hirsch & Marc, 1985; Steriade & Llinás, 1988) as well as in pathological conditions (Gloor & Fariello, 1988; Lenz, Tasker, Kwan, Dostrovsky & Murphy, 1988; Buzsaki, Smith, Berger, Fisher & Gage, 1990). These oscillatory activities have been mainly regarded as involving sensory and cortical excitatory drives as well as inhibitory postsynaptic potentials originating from the rhythmic recruitment of thalamic inhibitory cells, thus stressing the role of both intra- and extra-thalamic inputs in the mechanism responsible for their generation (Burke & Sefton, 1966; Andersen & Andersson, 1968; Purpura, 1970; Gloor & Fariello, 1988; Steriade & Llinás, 1988; Sumitomo, Takahashi, Kayama & Ogawa, 1988; Buzsaki *et al.* 1990). Recently, TC cells have been shown to possess a set of intrinsic membrane conductances (Deschenes, Paradis, Roy & Steriade, 1984; Jahnsen & Llinás, 1984*a*, *b*) which, it has been suggested, should make them capable of rhythmic electrical activity even in the absence of synaptic inputs (Jahnsen & Llinás, 1984*b*; Llinás, 1988; Steriade & Llinás, 1988). However, while repetitive

single action potential firing at 10 Hz has been observed *in vitro* (Jahnsen & Llinás, 1984*b*), attempts to record spontaneous membrane potential oscillations of TC cells at lower frequencies have so far proved unsuccessful.

In this paper we report that single rat and cat TC cells, recorded in different thalamic nuclei *in vitro*, are capable of three types of low-frequency (< 4 Hz) oscillations (i.e. the pacemaker, the spindle-like and the 'very slow' oscillations) which do not require the evoked rhythmic recruitment of other neurones nor the spontaneous release of transmitters. In addition, activation of the *N*-methyl-D-aspartate (NMDA) receptors by a spontaneously released excitatory amino acid transforms some of these oscillations into a fourth type, the 'NMDA' oscillations. In the accompanying paper we describe two of the voltage-dependent conductances necessary for these oscillations and their role in the transformation of the pacemaker into the spindle-like oscillations (Soltesz, Lightowler, Leresche, Jassik-Gerschenfeld, Pollard & Crunelli, 1991). Preliminary reports of some of the results described in this paper have been published (Leresche, Jassik-Gerschenfeld, Haby, Soltesz & Crunelli, 1990*a*, *b*).

METHODS

The preparation of rat brain slices containing the dorsal and the ventral lateral geniculate nucleus (dLGN, vLGN) has been described previously (Crunelli, Kelly, Leresche & Pirchio, 1987*a*). Briefly, male Wistar rats (200–250 g) were decapitated and a block of tissue containing the LGN was separated from the rest of the brain by two cuts made parallel to the plane of the optic tract, or a block of tissue containing the rat ventrobasal nucleus (VB) was cut in the frontal plane. Slices of the rat LGN or VB (300–400 μm thick) were then prepared from these tissue blocks using a Vibroslice (Campden Instruments). The preparation of cat LGN slices has also been described in detail elsewhere (Crunelli, Leresche & Parnavelas, 1987*c*) and involved the same procedures described above using tissue blocks dissected from the brain of anaesthetized (2:1 O_2:N_2O, 1·2% halothane) male and female cats (1·0–3·5 kg). The cats were killed by a coronal cut made at the level of the inferior colliculus to free the brain from the spinal cord and brain stem. In some experiments, cat and rat slices were prepared in such a way that they did not contain the perigeniculate nucleus (cat) and the nucleus reticularis thalami (rat), i.e. by removing the upper third of lamina A in the cat dLGN and the most medial third of the rat dLGN. Both rat and cat slices were then transferred to a recording chamber and perfused with a warmed (35 ± 1 °C), continuously oxygenated (95% O_2, 5% CO_2) medium of composition (mM): NaCl, 134; KCl, 2–5; KH_2PO_4, 1·25; $MgSO_4$, 2; $CaCl_2$, 2; $NaHCO_3$, 16; and glucose, 10. The slices were allowed to recover in this medium for at least 45 min before a medium of similar composition but containing either 0·5–0·8 mM-Mg^{2+} and 2–4 mM-Ca^{2+} or 0 mM-Mg^{2+}, 2–4 mM-Ca^{2+} (the 'Mg^{2+}-free' medium) was used. The Mg^{2+} concentration present in the 'Mg^{2+}-free' medium was measured by atomic absorption spectroscopy (Perkin-Elmer 2380) and found to be 0·75 ± 0·05 μM.

Impaled neurones in the rat and cat dLGN and in the rat VB were identified as TC cells by their location in the slice and by the presence of a low-threshold Ca^{2+} potential and of a depolarizing 'sag' in their voltage response to a hyperpolarizing pulse of current (Deschenes *et al.* 1984; Jahnsen & Llinás, 1984*a*; Kita & Kitai, 1986; McCormick & Pape, 1988; Sumitomo *et al.* 1988). Intracellular glass microelectrodes were filled with 1 M-potassium acetate and a tungsten bipolar electrode was used to stimulate the optic tract (20–100 μs, 1–40 V) in LGN slices when necessary. Intracellular voltage and current records were stored on a Racal 4D tape-recorder or a Biologic DAT recorder for subsequent analysis. The antagonists used in this study were dissolved in the perfusion medium while NMDA (20 mM in 150 mM-NaCl, pH 8) was applied ionophoretically from an independently mounted two-barrelled micropipette. The other barrel contained NaCl for current balancing and a retaining current (1–10 nA) was applied to the NMDA barrel when necessary.

Drugs were obtained from the following sources: tetrodotoxin (TTX), atropine, propranolol and

d-tubocurarine from Sigma; phaclofen, DL-2-amino-5-phosphono-valeric acid (APV), 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) and NMDA from Tocris Neuramin; bicuculline methiodide from Pierce. Phentolamine mesylate was kindly provided by Ciba-Geigy, UK and ketamine hydrochloride by Parke-Davis, UK. All quantitative data are expressed in the text as means ± S.E.M.

RESULTS

The experiments described in this and the accompanying paper are based on a total of 143 rat and 146 cat TC cells recorded in the dLGN (cat lamina A, A_1 and C), twenty-one cells recorded in the rat VB, fourteen cells recorded in the rat vLGN and three rat and nine cat dLGN interneurones.

Pacemaker oscillations

As reported by previous studies using thalamic slices (cf. Jahnsen & Llinás, 1984*a*; Crunelli *et al.* 1987*a*, *c*; McCormick & Prince, 1988; Thomson, 1988; Scharfman, Lu, Guido, Adams & Sherman, 1990), TC cells perfused with a medium containing 1–2 mM-Mg^{2+} and 2–2·5 mM-Ca^{2+} did not show any spontaneous firing activity or membrane potential oscillations but were quiescent (Fig. 1*A*; but cf. McCormick & Prince, 1988). Following a few (4–10) minutes perfusion with a solution containing 0·5–0·8 mM-Mg^{2+} and 2–4 mM-Ca^{2+}, however, TC cells began to show sporadic, small-amplitude (2–6 mV) depolarizations superimposed on a more 'noisy' baseline activity (visible as a thickening of the intracellular voltage record in Fig. 1*A*). After an additional 5–15 min a striking pattern of spontaneous activity, consisting of rhythmic, large-amplitude (10–30 mV) depolarizations lasting for 80–350 ms and occurring at a frequency of 0·5–2·9 Hz (1·8 ± 0·3 Hz, $n = 41$) developed (Fig. 1*A* and *B*). Each depolarization could give rise to single or a burst of two to seven action potentials (intraburst frequency, 100–450 Hz) thus giving an overall firing frequency of 0·5–20 Hz. For any given cell, once established, this activity often persisted as long as the intracellular recording lasted (4 h and 25 min being the longest impalement) and with very little change (< 5%) in their frequencies. This activity, which we have called the pacemaker oscillations, was observed in thirty-three (out of 67) rat and in sixty-two (out of 106) cat TC cells of the dLGN and VB: some of the remaining cells included those with a relatively low input resistance (< 55 MΩ; $n = 18$) and those which showed the spindle-like oscillations ($n = 39$) or the 'very slow' oscillations ($n = 11$) (see below). The pacemaker oscillations were observed more frequently, and their depolarizations were often larger, faster and more regular in cat than in rat TC cells (compare Figs 1 and 2 with Fig. 8*B*). No difference was found between the pacemaker oscillations recorded in TC cells of the rat VB and dLGN. In addition, no difference was observed in the pacemaker oscillations (or in the other types of oscillations described below) recorded in TC cells of slices that did or did not contain the perigeniculate nucleus (cat) and the nucleus reticularis thalami (rat). It is important to note that, though very rarely, the pacemaker oscillations could be observed in cat TC cells perfused with a solution containing 2 mM-Mg^{2+} and 2 mM-Ca^{2+}.

Pacemaker oscillations were voltage dependent and were observed only in the voltage range negative to −55 and positive to −80 mV. At membrane potentials

positive to −45 mV, the activity of the cell shown in Fig. 2, for instance, was characterized by continuous firing consisting of repetitive action potentials which showed little if any accommodation. At −50 mV, only small membrane potential oscillations were present and they disappeared, in this cell, between −55 and

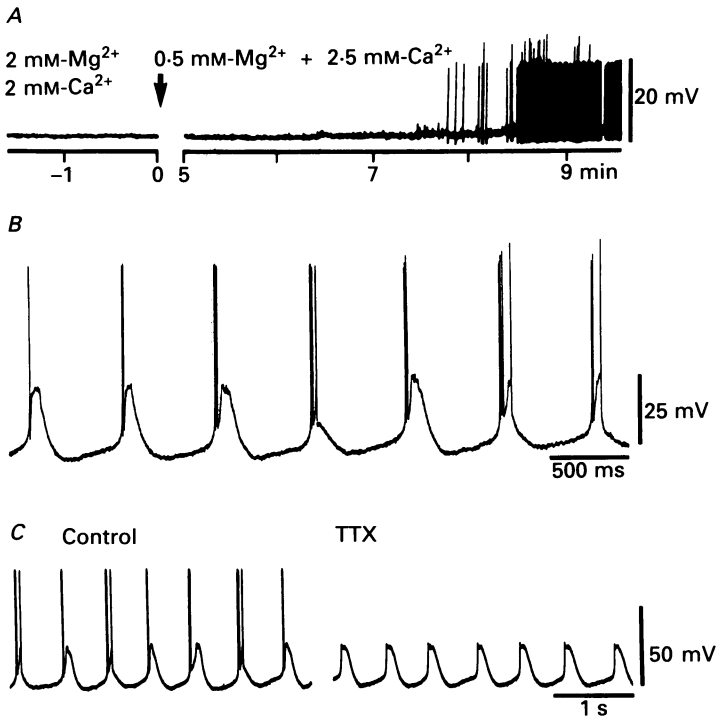

Fig. 1. The pacemaker oscillations. *A*, intracellular voltage recording shows the lack of any spontaneous activity in a TC cell of the cat dLGN when perfused with a medium containing 2 mM-Mg^{2+} and 2 mM-Ca^{2+} (resting membrane potential, −70 mV). About 5 min after the introduction of a medium containing 0·5 mM-Mg^{2+} and 2·5 mM-Ca^{2+} the cell started to show very small membrane potential oscillations visible as a thickening of the baseline voltage recording. At 8·5 min, the cell showed a striking pattern of oscillatory activity consisting of rhythmic, large-amplitude (10–25 mV) depolarizations occurring with a frequency of 0·8 Hz and shown at a faster time base in *B*. Here, the first large depolarization generates one action potential while the others generate a burst of two to four action potentials with an intraburst frequency of 190–320 Hz. Note that in the last two depolarizations the initial burst is followed, about 50 ms later, by a single action potential. *C*, intracellular recordings from a TC cell in the cat dLGN show that 15 min after the addition of TTX (1 μM) to the perfusion medium the action potentials were abolished but the large depolarizations underlying the pacemaker oscillations were still present. Note that in this cell, during perfusion with TTX, there is a slight increase in the frequency of the pacemaker oscillations and a shortening (20%) of the large depolarizations which now all have a similar duration. In *A*, action potential height has been reduced by the frequency response of the chart recorder. In *B* and *C*, the membrane potential at the peak of the hyperpolarizing phase of the oscillations is −75 mV.

−57 mV. A slight hyperpolarization from this latter potential resulted in the appearance of pacemaker oscillations which were not large enough to reach threshold for generating action potentials (trace marked −60 mV in Fig. 2). Any additional hyperpolarization then decreased the frequency and increased the amplitude of the

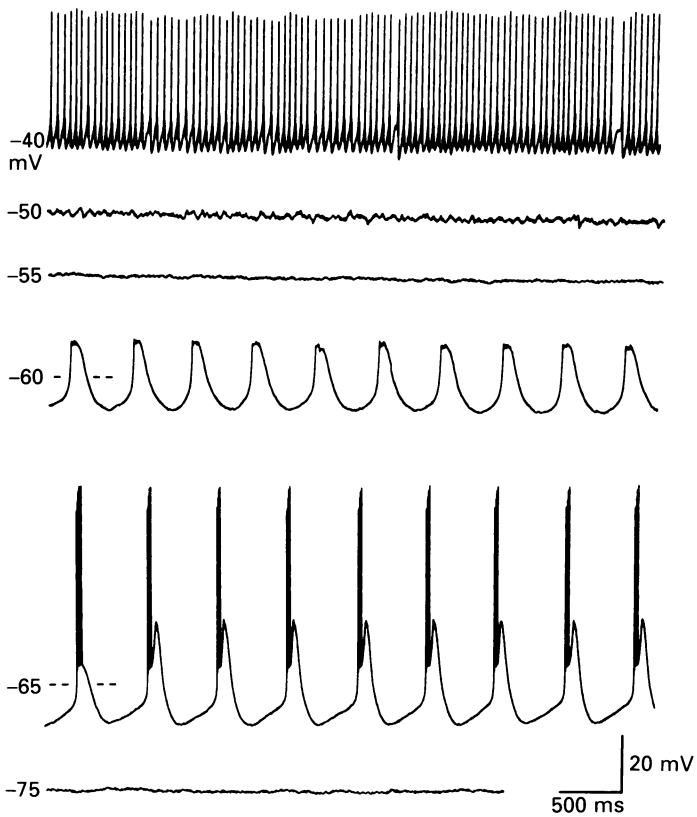

Fig. 2. Voltage dependence of the pacemaker oscillations. Intracellular voltage recordings from a TC cell in the cat dLGN show that the pacemaker oscillations were observed only when the membrane potential was moved (by steady DC current injection) to between −57 and −73 mV. Note that in the trace marked −60 mV the large depolarizations have a higher frequency and a smaller amplitude than those in the trace marked −65 mV. In addition, ramp-like (i.e. pacemaker) depolarizations were evident in the trace marked −65 mV but their absence at more depolarized potentials (traced marked −60 mV) gave the hyperpolarizing phase of the oscillations a more rounded shape. At potentials negative to −73 mV no activity was observed, while at potentials positive to −45 mV the activity of the cell was characterized by continuous firing consisting of single action potentials that showed no accommodation.

large depolarizations (which could now evoke a burst of action potentials) and made the hyperpolarized phase of the pacemaker oscillations more ramp-like (trace marked −65 mV in Fig. 2). When the cell was hyperpolarized below −73 mV, no activity was observed. In different cells, the upper limit of the voltage region where

the pacemaker oscillations were present ranged from −55 to −65 mV, while the lower limit was between −70 and −80 mV. In a given cell, however, the upper and lower limits of this voltage region were separated by only 13·1 ± 0·5 mV ($n = 15$).

Pacemaker oscillations are not synaptically generated

To investigate the relative contribution of synaptic *versus* intrinsic conductances in the mechanism responsible for the pacemaker oscillations, experiments were carried out in the presence of TTX (0·5–1 μM; $n = 10$). As shown in Fig. 1*C*, this toxin abolished the action potentials but left the underlying large depolarizations, and their frequency, unchanged. In a few cells, however, the frequency of the pacemaker oscillations was slightly decreased (by 0·3–0·5 Hz) in the presence of TTX. The lack of action of TTX, however, could not exclude the possibility that spontaneous (i.e. TTX-insensitive) release of transmitter(s) from nerve terminals present in the slice might contribute to the mechanism responsible for the pacemaker oscillations, and thus the effect of antagonists selective for the receptors known to be present on TC cells was also tested. Blockade of NMDA receptors (by 20–50 μM-APV, $n = 15$, and 10–25 μM-ketamine, $n = 5$; cf. Fig. 5; Watkins, Krogsgaard-Larsen & Honore, 1990), non-NMDA receptors (by 5–10 μM-CNQX, $n = 10$; Honore, Davies, Drejer, Fletcher, Jacobsen, Lodge & Neilsen, 1988; Soltesz, Haby, Jassik-Gerschenfeld, Leresche & Crunelli, 1989*a*), $GABA_A$ receptors (by 10–50 μM-bicuculline, $n = 24$), $GABA_B$ receptors (by 0·5–1 mM-phaclofen, $n = 7$) (Dutar & Nicoll, 1988; Soltesz, Haby, Leresche & Crunelli, 1988), cholinergic receptors (by 10 μM-atropine, $n = 6$, and 20 μM-*d*-tubocurarine, $n = 6$), α- and β-adrenoceptors (by 20 μM-phentolamine, $n = 6$, and 30 μM-propranolol, $n = 6$) had no effect on the pacemaker oscillations. These findings indicated that pacemaker oscillations recorded in a TC cell did not involve the activation of other neurones present in the slice nor the contribution of spontaneously released glutamate, GABA, noradrenaline and acetylcholine.

The spindle-like oscillations

A different type of oscillatory activity was observed in thirty-nine cat (but not rat) TC cells, and, because of similarities with the sleep spindles recorded in TC cells *in vivo* (Steriade & Llinás, 1988), will be referred to as the spindle-like oscillations. They consisted of rhythmic, large depolarizations (2·1 ± 0·3 Hz; range, 0·5–3·2 Hz) similar to the pacemaker oscillations, occurring, however, not continuously but in discrete periods (the intra-spindle) every 5–25 s (0·11 ± 0·05 Hz, $n = 18$) and lasting for 1·5–28 s (8·5 ± 1·3 s, $n = 18$) (Fig. 3*Aa* and *Ba*). In some cells the duration of the intra-spindle was relatively short and was associated with short periods where the cell showed no activity (the inter-spindle; Fig. 3*Ba* and *b*), while in other cells intra-spindles lasting up to 30 s (and associated with relatively long inter-spindles) were observed (Fig. 3*Aa* and *b*). Whatever its duration, the intra-spindle often started with a slow, small (2–5 mV) hyperpolarization that evoked a small depolarization followed by progressively larger and larger ones of shorter duration. These depolarizations then became smaller (and of longer duration) and the intra-spindle ended with a 'waxing and waning' of the membrane potential (Fig. 3*Ab* and *Bb*) similar to that observed for the spindles recorded *in vivo* (cf. Fig. $9B_1$ of Hu, Steriade & Deschenes, 1989*a* and Fig. 11*A* of Hu, Steriade & Deschenes, 1989*b*). Another

peculiar feature of the spindle-like oscillations was that the membrane potential at the end of the intra-spindle was slightly more depolarized (2–6 mV) than at the beginning, and from this depolarized level it then slowly hyperpolarized to the original potential before the next intra-spindle started (Fig. 3*Bb*, *C* and *D*): again a pattern similar to that observed *in vivo* (cf. Fig. $9B_1$ of Hu *et al.* 1989*a*).

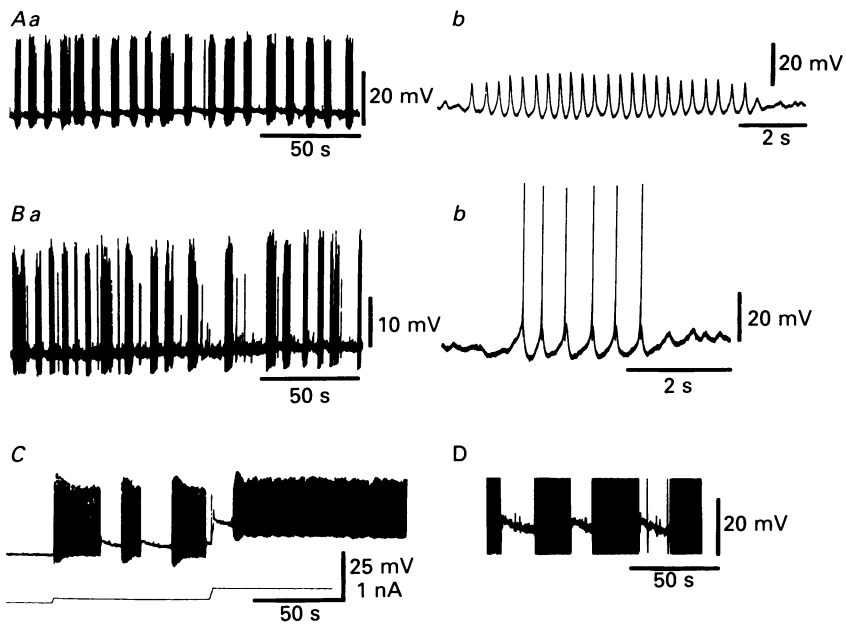

Fig. 3. The spindle-like oscillations. *Aa*, intracellular voltage trace shows the activity of a cat dLGN cell that is characterized by periods of activity (the intra-spindle) (occurring at a frequency of $0{\cdot}11 \pm 0{\cdot}02$ Hz and lasting for $4{\cdot}7 \pm 0{\cdot}3$ s) interrupted by periods of silence (the inter-spindle). Note the regularity of both the intra-spindle and the inter-spindle periods. In *Ab*, an intra-spindle (recorded from the same cell in *Aa* after 30 min perfusion with a solution containing 0·5 μM-TTX and 20 μM-bicuculline) is shown at a faster time base. The initial small depolarizations of the intra-spindle are followed by larger and larger depolarizations while, from the middle of the intra-spindle onwards, the depolarizations progressively start to decrease in amplitude and finally cease altogether in a way identical to the 'waxing and waning' described for the spindles recorded *in vivo* (Hu *et al.* 1989*a*, *b*). *Ba* shows the spindle-like oscillations recorded in another cat dLGN cell where relatively short inter-spindles were intermixed with relatively short intra-spindles, one of which is shown at a faster time base in *Bb*. The intra-spindle starts with a slow hyperpolarization and terminates with a 'waxing and waning' of the membrane potential. Note that at the end of the intra-spindle the membrane potential is more depolarized than at its beginning, as is also visible in *C* and *D*. *C*, intracellular voltage record (top trace) from one of the two TC cells where transformation of the spindle-like oscillations into the pacemaker oscillations could be achieved by depolarizing the membrane potential from −75 to −60 mV (right-hand side of the trace). At potentials negative to −80 mV (left-hand side of the trace) all spontaneous activity was blocked. In *D*, records from the same cell as in *C* are reproduced at higher amplification to show the slow hyperpolarization that characterized the inter-spindles. In *Aa*, *Ba* and *C*, action potential height has been reduced by the frequency response of the chart recorder. In *A* and *B* the membrane potential at the beginning of the intra-spindle was −65 mV.

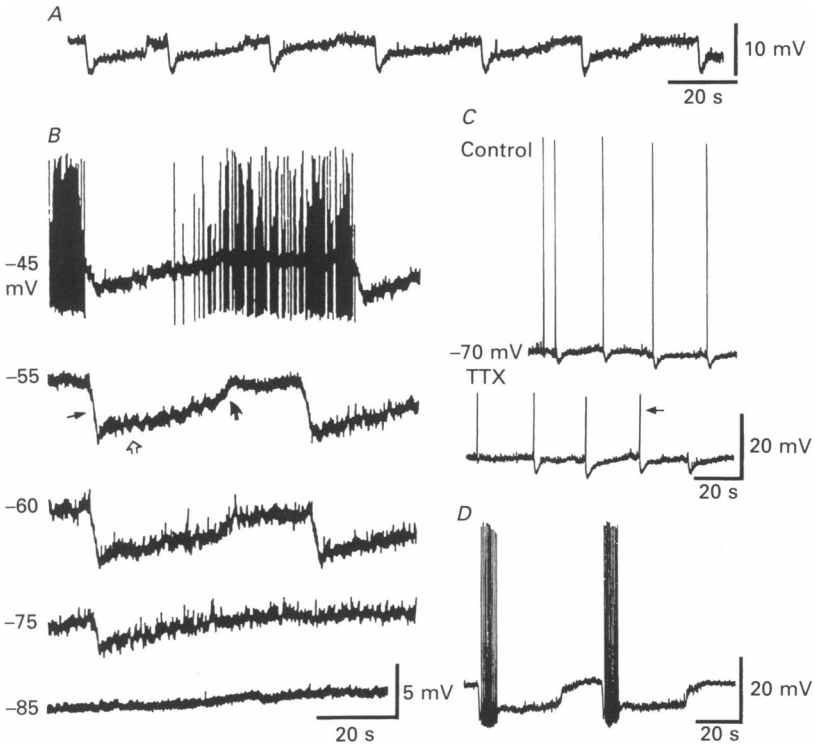

Fig. 4. The 'very slow' oscillations. *A*, intracellular voltage trace shows the 'very-slow' oscillations recorded in a TC cell of the cat dLGN at −60 mV, the most depolarized level reached by the membrane potential (same cell as in *C*). *B* shows the 'very slow' oscillations recorded in a TC cell of the rat VB at the different membrane potentials indicated. Note the decrease in the amplitude of the slow hyperpolarization (arrow) and depolarization (curved arrow) at membrane potentials outside the voltage region of −55 to −60 mV. *C*, intracellular voltage traces from the same cell as in *A* show the 'very-slow' oscillations recorded at −70 mV, a potential at which the depolarization of the 'very slow' was usually absent (cf. the trace marked −75 mV in *B*). At −70 mV in this cell the slow hyperpolarization of the 'very slow' oscillations was often preceded by a large depolarization (i.e. low-threshold Ca^{2+} potential) evoking one or two action potentials. Application of 1 μM-TTX (20 min) abolished the action potentials but left the 'very slow' oscillations and the low-threshold Ca^{2+} potentials (arrow) unaffected. Note that the last cycle of the oscillation recorded in TTX lacks a preceding low-threshold Ca^{2+} potential, while the first low-threshold Ca^{2+} potential in the 'Control' and 'TTX' traces is not followed by a hyperpolarization. *D*, intracellular voltage record from a TC cell in the cat dLGN where repetitive depolarizations (i.e. low-threshold Ca^{2+} potentials), and associated action potentials, were present during part of the 'very-slow' oscillations (membrane potential at the most depolarized potential, −60 mV). In *C* and *D*, action potential height has been reduced by the frequency response of the chart recorder.

The spindle-like oscillations were observed in the voltage range from −60 to −75 mV and, once established, they sometimes continued for as long as the impalement of the cell lasted. Small depolarization of the cell by steady DC current injection slightly decreased the frequency of intra- and inter-spindles and in two

cells, at around −60 mV, resulted in their transformation into the pacemaker oscillations (Fig. 3*C*). At membrane potentials positive to −45 mV the cells showed repetitive single action potential firing while at membrane potentials negative to −75 mV the spindle-like oscillations were blocked and no other underlying activity

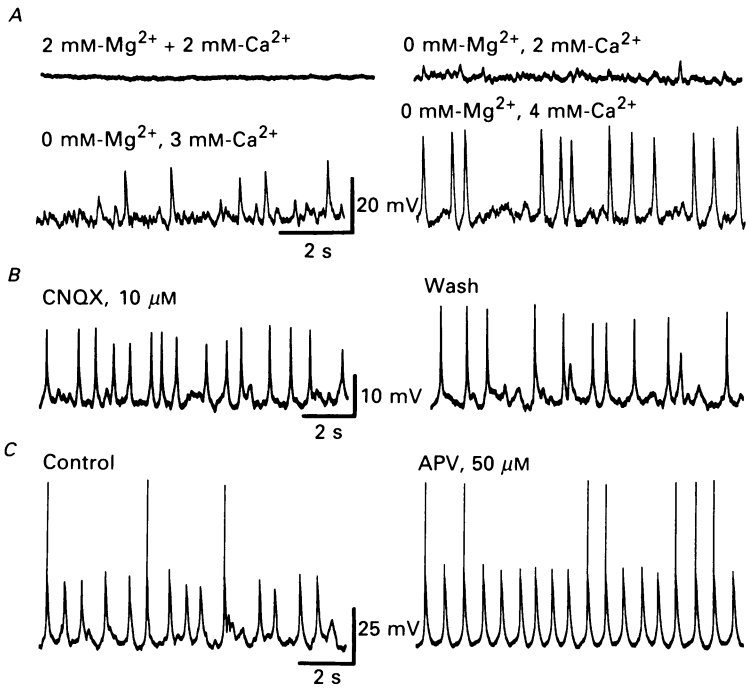

Fig. 5. The 'NMDA' oscillations and their transformation into the pacemaker oscillations by a selective NMDA antagonist. *A*, intracellular voltage recordings from a TC cell in the rat dLGN show membrane potential oscillations in a 'Mg^{2+}-free' medium containing different Ca^{2+} concentrations (membrane potential, −70 mV). Note that the depolarizations became larger and larger by increasing the Ca^{2+} concentration. Each trace was recorded about 40 min after switching to the appropriate test solution. The flow rate throughout this experiment was close to 0·8 ml/min (slice bath volume, 1·8 ml) and when 1 μM-TTX was applied at the end of the recording session action potentials were abolished in 6 min. *B*, this rat dLGN cell showed the typical pattern of the 'NMDA' oscillations even after 40 min perfusion with a medium containing 10 μM-CNQX (membrane potential at the peak of the hyperpolarization, −75 mV; 'Mg^{2+}-free' medium with 3 mM-Ca^{2+}). Following wash-out of CNQX (75 min; Wash), no marked differences were observed in the pattern of the 'NMDA' oscillations. TTX (0·5 μM) was present throughout the course of this experiment. *C* shows the 'NMDA' oscillations recorded in a cat dLGN cell perfused with a 'Mg^{2+}-free' medium containing 3 mM-Ca^{2+}. Addition of 50 μM-APV, a selective NMDA receptor antagonist, transformed the 'NMDA' oscillations into the pacemaker oscillations. In *C*, action potential height has been reduced by the frequency response of the chart recorder and the membrane potential at the peak of the hyperpolarization phase of the pacemaker oscillations is −80 mV.

was observed (Fig. 3*C*). Application of TTX (0·5–1·0 μM, $n = 5$) on cells that showed the spindle-like oscillations abolished the action potentials but left the underlying activity and their frequency unchanged (Fig. 3*Ab*). In addition, APV, ketamine,

CNQX, bicuculline (Fig. 3*Ab*), phaclofen, atropine, *d*-tubocuranine, phentolamine and propranolol (at the concentrations previously mentioned) had no effect on the spindle-like oscillations.

The 'very slow' oscillations

A third type of oscillatory activity (referred to as the 'very slow' oscillations) was observed in two rat and seven cat TC cells in the dLGN and in two TC cells in the rat VB, with no obvious difference between rat and cat cells (Fig. 4*A* and *B*). They consisted of a rhythmic sequence of slow hyperpolarizations and depolarizations, the duration of each cycle being constant in a given cell but ranging from 15 to 90 s in different cells. As shown in the trace recorded at −55 mV for instance (Fig. 4*B*), the 'very slow' oscillations started with a slow hyperpolarization (2–3 mV/s, 5–10 mV in amplitude; arrow) followed by a slow depolarization of about 2–6 mV (open arrow). Following a variable period of time (5–40 s) another depolarization (curved arrow) brought the membrane potential back to its original level where it remained for tens of seconds until the next cycle began. Injection of steady DC current showed that the 'very slow' oscillations had a maximal amplitude at around −60 mV, but decreased in size at more depolarized and hyperpolarized membrane potentials and were abolished at potentials close to −85 mV. At −45 mV, action potentials were generated at the most depolarized potential reached during a cycle, resulting in a pattern of single action potential firing similar to the one observed in some vLGN cells (cf. Fig. 2*C* of Soltesz, Lightowler, Leresche & Crunelli, 1989*b*). In some cells, depending on the membrane potential, a few, repetitive, large-amplitude depolarizations (i.e. low-threshold Ca^{2+} potentials, see Soltesz *et al.* 1991) were observed during the first depolarization (Fig. 4*D*) or following the second depolarization of the 'very slow' oscillations.

The 'very slow' oscillations were unaffected by TTX (1 μM, $n = 2$; Fig. 4*C*), APV (50 μM, $n = 2$), bicuculline (50 μM, $n = 2$) and phaclofen (1 mM, $n = 2$), but the limited number of observations restricted a more detailed investigation of the possible contribution of other, spontaneously released, transmitters to this type of oscillation. While in the majority of TC cells that displayed the 'very slow' oscillations these were the only spontaneous oscillations observed, in one cell each they were seen following and preceding the pacemaker and the spindle-like oscillations, respectively. It is worth noting that the 'very slow' oscillations were also observed in two dLGN cells perfused with a 'Mg^{2+}-free' medium, and in one rat VB cell in the presence of 2 mM-Mg^{2+} and 2 mM-Ca^{2+} following 1 h perfusion with a 'Mg^{2+}-free' medium.

The 'NMDA' oscillations

During perfusion with a 'Mg^{2+}-free' medium a different type of low-frequency membrane potential oscillations (called the 'NMDA' oscillations) was observed in thirty-eight out of forty-three rat and twenty out of twenty-two cat dLGN cells and in six out of seven rat VB cells (Figs 5, 6 and 8*C*). Compared to the pacemaker oscillations, the main differences in the 'NMDA' oscillations were the absence of rhythmic, pacemaker properties and the presence of smaller depolarizations on the baseline and on the falling phase of the large ones (Figs 5, 6, 8*C* and 9). The 'NMDA'

oscillations were often faster and had larger depolarizations in cat than in rat TC cells although in the presence of 3–4 mM-Ca^{2+} rat cells showed 'NMDA' oscillations similar to those observed in cat cells. Indeed, the full spectrum of the 'NMDA' oscillations described above could be recorded in the same rat cell by simply raising the extracellular Ca^{2+} concentration (Fig. 5*A*).

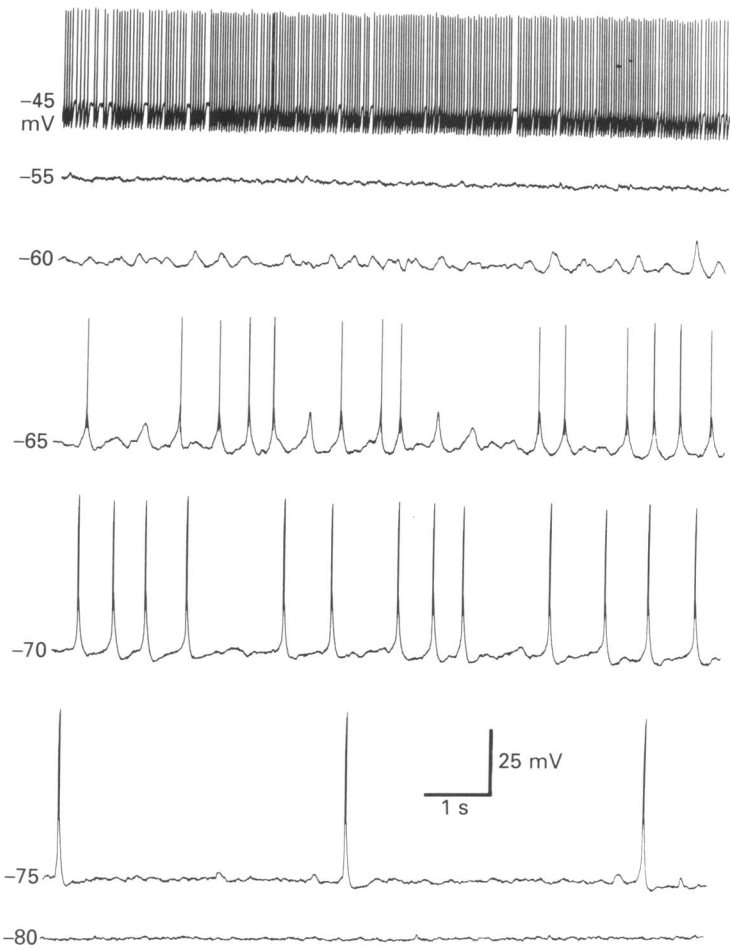

Fig. 6. Voltage dependence of the 'NMDA' oscillations. Intracellular voltage recordings from a TC cell in the rat VB (0 mM-Mg^{2+}, 3 mM-Ca^{2+}) show that at −70 mV the 'NMDA' oscillations occurred with a frequency of 1·3 Hz and each depolarization reached threshold for action potentials. Depolarization of the cell to −65 mV decreased the amplitude of the depolarizations, not all of which were now capable of triggering action potentials, while at −55 mV little spontaneous activity was present. Further depolarization to −45 mV resulted in repetitive action potential firing with no accommodation. Hyperpolarization of the cell to −75 mV markedly decreased the frequency of the 'NMDA' oscillations and at −80 mV all types of spontaneous activity were abolished. Action potential height has been reduced by the frequency response of the chart recorder.

The 'NMDA' oscillations were observed from between −60 and −85 mV (Fig. 6), a voltage region with a lower limit more hyperpolarized than the one for the pacemaker and the spindle-like oscillations. For the cell shown in Fig. 6, for instance, at −60 mV the 'NMDA' oscillations consisted of slow, small-amplitude (3–5 mV)

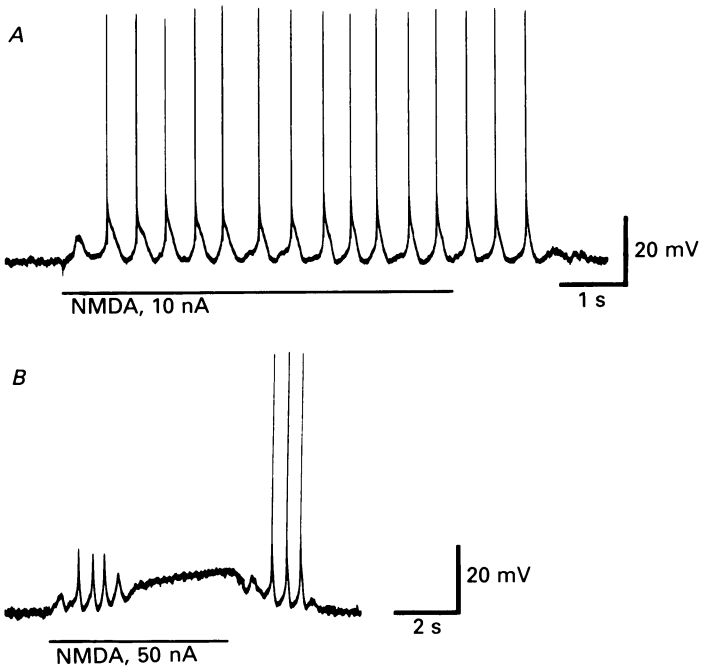

Fig. 7. Oscillation evoked by NMDA in the presence of 2 mM-Mg^{2+}. *A* shows the repetitive oscillations evoked in a TC cell of the rat dLGN by ionophoretic application of NMDA (membrane potential, −75 mV). *B*, increasing the ejection current of NMDA resulted in a larger depolarization with repetitive oscillations present on its rising and falling phase.

depolarizations, while at −45 mV the activity of the cell was characterized by repetitive firing consisting of single action potentials and identical to the one observed at this membrane potential in the presence of Mg^{2+} (cf. Fig. 2). At potentials more hyperpolarized than −70 mV the frequency of the 'NMDA' oscillations became slower and slower and at around −80 mV they were absent, partly because of the large decrease in input resistance present at these hyperpolarized membrane potentials.

TTX (0·5–1 μM) had no effect on the 'NMDA' oscillations ($n = 13$) (cf. Fig. 5*B*) nor did the addition to the perfusion medium of bicuculline ($n = 5$) (but see below), phaclofen ($n = 5$), atropine ($n = 3$), *d*-tubocurarine ($n = 2$), phentolamine ($n = 4$), propranolol ($n = 4$) (each at the concentration previously mentioned) and 20 μM-strychnine ($n = 3$). However, blockade of NMDA receptors by APV (20–50 μM) reversibly transformed the 'NMDA' into the pacemaker (or the spindle-like) oscillations in all cat ($n = 27$) and in the majority of rat (11 out of 18) TC cells (Fig. 5*C*). In the remaining rat cells, the 'NMDA' oscillations were blocked and no other

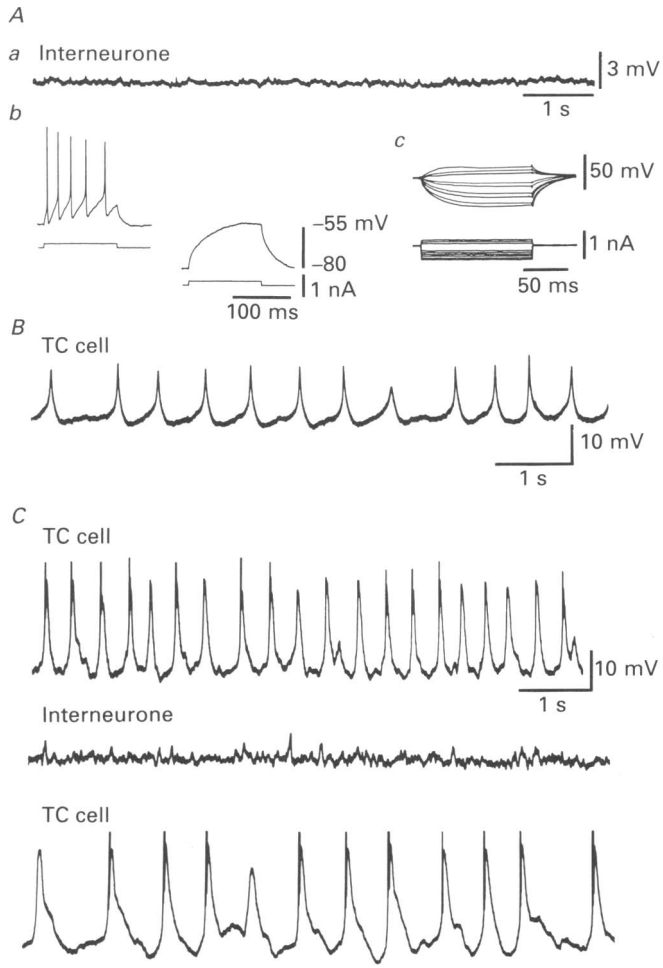

Fig. 8. Absence of the pacemaker and the 'NMDA' oscillations in rat (*A*) and cat (*C*) dLGN interneurones. *A a*, intracellular voltage recordings (0·5 mM-Mg^{2+} + 4 mM-Ca^{2+}) show the lack of any low-frequency oscillatory activity in a rat dLGN cell that on the basis of its electrophysiological properties (shown in *A b* and *A c*) was identified as a dLGN interneurone (membrane potential, −70 mV). *A b* depolarizing electrotonic potentials (top traces) recorded at two membrane potentials show the lack of low-threshold Ca^{2+} potentials when the cell was hyperpolarized to below −70 mV (right trace). *A c* shows some of the hyperpolarizing and depolarizing electrotonic potentials used to calculate the steady-state voltage–current relationship of the cell. Note the absence of any depolarizing 'sag' in and of low-threshold Ca^{2+} potentials at the end of, respectively, the largest hyperpolarizing electrotonic potentials. *B*, shows the pacemaker oscillations observed in a TC cell of the rat dLGN that was impaled, in the same slice, 15 min after the interneurone in *A* (membrane potential at the peak of the hyperpolarization, −75 mV). Note the less regular pattern of the pacemaker oscillations in this rat TC cell as compared to those observed in the cat (cf. Figs 1, 2 and 5*C*). *C*, intracellular voltage recordings from neurones in a cat slice perfused with a 'Mg^{2+}-free' medium containing 2 mM-Ca^{2+}. The spontaneous activity recorded from the interneurone showed only small depolarizations

spontaneous low-frequency activity was observed possibly because the pacemaker oscillations are weaker in this species. Transformation of the 'NMDA' oscillations into the pacemaker oscillations was also obtained in five cat TC cells perfused with ketamine (10–25 μM), though with a longer and never complete recovery, and with low concentrations of Mg^{2+} (50–300 μM; $n = 25$; Nowak, Bregestovski, Ascher, Herbet & Prochiantz, 1984; Mayer & Westbrook, 1987; Watkins *et al.* 1990). We also examined the effect of the non-NMDA antagonist CNQX (5–10 μM) and found that it had no effect on the 'NMDA' oscillations (Fig. 5*B*; $n = 7$).

In a few TC cells of the cat dLGN some of the small depolarizations observed in the 'NMDA' oscillations were reversed (i.e. depolarizing) spontaneous $GABA_A$ IPSPs, since they were blocked by bicuculline (20 μM) and appeared as hyperpolarizing potentials at membrane potentials positive to −60 mV. In these cells, application of this $GABA_A$ receptor antagonist decreased the number of smaller depolarizations and thus the overall frequency of the 'NMDA' oscillations.

It is important to note that what we have so far described as the 'NMDA' oscillations were not the only type of activity that could be evoked in TC cells by activation of the NMDA receptors. In fact, in the presence of 2 mM-Mg^{2+} ionophoretic application of small amount of NMDA evoked rhythmic oscillations which closely resembled the pacemaker oscillations (Fig. 7*A*). Using higher ejection current, instead NMDA evoked a larger, sustained depolarization that on the rising and falling phase produced repetitive membrane potential oscillations with or without single or a burst of action potentials (Fig. 7*B*).

Absence of low-frequency oscillations in interneurones and in cells of the vLGN

In the course of this study we impaled three rat and nine cat dLGN cells that showed electrophysiological features identical to those described for local circuit cells (i.e. interneurones; Fig. 8). These included (i) the lack of low-threshold Ca^{2+} potentials following a depolarizing electrotonic potential evoked from a resting potential of −80 mV (Fig. 8*Ab*), and (ii) a relatively linear steady-state voltage–current relationship, as indicated by the lack of a prominent depolarizing 'sag' in their hyperpolarizing electrotonic potentials (Fig. 8*Ac*; cf. McCormick & Pape, 1988). These cells never showed the pacemaker, the spindle-like or the 'very-slow' oscillations (Fig. 8*Aa*), although, in the same slices, TC cells showing one of these types of low-frequency oscillations were recorded either just before or after the impalement of the interneurones (Fig. 8*B*). In addition, we recorded the spontaneous activity of one rat and three cat dLGN interneurones perfused with a 'Mg^{2+}-free' medium and did not observe the 'NMDA' oscillations but only small-amplitude depolarizations (Fig. 8*C*). Before and after the interneurones were impaled. TC cells in the rat and cat dLGN showing the typical pattern of 'NMDA' oscillations with large depolarizations (up to 20 mV in amplitude) were recorded in the same slices (Fig. 8*C*).

(membrane potential, −75 mV). A TC cell showing the typical pattern of the 'NMDA' oscillations (with small and large depolarizations) was impaled, in the same slice, 20 min before (upper trace) and another one 10 min after (lower trace) the interneurone (membrane potential for both TC cells, −75 mV).

Similar results were obtained in cells of the vLGN that, though unique among thalamic projecting cells in lacking low-threshold Ca^{2+} potentials (Crunelli *et al.* 1987*a*), can still be distinguished from interneurones because they show a depolarizing 'sag' in their voltage response to large hyperpolarizing pulses of current (cf. Fig. 1 of

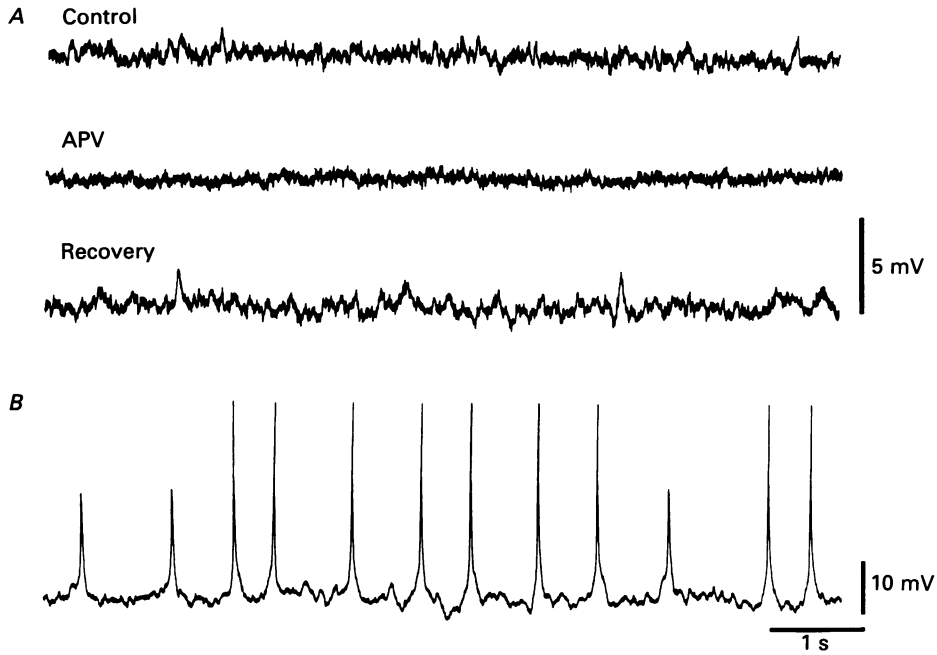

Fig. 9. Absence of the 'NMDA' oscillations in the rat vLGN. *A*, intracellular voltage recordings from a cell in the rat vLGN perfused with a 'Mg^{2+}-free' medium containing 4 mM-Ca^{2+} (Control) show the lack of depolarizations larger than 3 mV in its spontaneous activity. Application of 25 μM-APV reversibly blocked this spontaneous activity (membrane potential, −70 mV). *B* shows the typical pattern of the 'NMDA' oscillations seen in 'Mg^{2+}-free' medium in a TC cell of the rat dLGN that was impaled 20 min after the vLGN cell in the same slice. The membrane potential at the peak of the hyperpolarization was −75 mV and action potential height has been reduced by the frequency response of the chart recorder.

Crunelli *et al.* 1987*a*). The spontaneous activity recorded in projecting cells of the vLGN in a 'Mg^{2+}-free' medium did not show the typical pattern of the 'NMDA' oscillations but consisted exclusively of small-amplitude (2–4 mV) depolarizations that were reversibly abolished by 25 μM-APV (Fig. 9).

DISCUSSION

The main conclusions of this investigation are (i) that single TC cells (in different thalamic nuclei of different species) are capable of generating three types of low-frequency oscillatory activities (i.e. the pacemaker, the spindle-like and the 'very slow' oscillations) that do not require the evoked rhythmic recruitment of other

neurones nor the spontaneous release of neurotransmitters, and (ii) that activation of the NMDA receptors is responsible for the reversible transformation of the pacemaker and the spindle-like oscillations into the 'NMDA' oscillations.

Low-frequency oscillations are generated by single TC cells

The different types of low-frequency oscillations described in this paper are characteristic of TC cells and not of interneurones. The studies of Deschenes *et al.* (1984) and Jahnsen & Llinás (1984*a*) clearly indicated that thalamic local circuit cells in various thalamic nuclei do not display low-threshold Ca^{2+} potentials. Later, McCormick & Pape (1988) confirmed and enlarged these findings by showing that morphologically identified dLGN interneurones do not display low-threshold Ca^{2+} potentials and are characterized by a relatively linear, steady-state, voltage–current relationship. In this study, cat and rat dLGN cells that were identified on the basis of these electrophysiological properties as interneurones never showed any of the four types of low-frequency oscillations. On the other hand, the majority of the recorded cells that displayed a marked rectification in their voltage–current relationship below −70 mV and low-threshold Ca^{2+} potentials showed one or more of the four types of low-frequency oscillations.

The pacemaker and the spindle-like oscillations are generated solely by the interplay of voltage-activated conductances intrinsic to single TC cells since they are unaffected by TTX (i.e. they do not require the evoked rhythmic recruitment of other neurones) or by selective blockade of the excitatory and inhibitory amino acids, noradrenaline and acetylcholine receptors present on these cells. In particular, the lack of action of bicuculline and phaclofen, a $GABA_A$ and $GABA_B$ receptor antagonist respectively, on the low-frequency oscillations rules out the possibility of a local synaptic interaction at the interneurone–TC cell synapses as well as at the perigeniculate cell–TC cell synapses. In addition, the lack of any dye-coupled TC cells in studies using intracellular injection of Lucifer Yellow and horseradish peroxidase (Friedlander, Lin, Stanford & Sherman, 1981; Jahnsen & Llinás, 1984*a*; Kita & Kitai, 1986; Crunelli *et al.* 1987*a*, *c*) and the absence of electrical coupling in pairs of simultaneously recorded TC cells (Jahnsen & Llinás, 1984*a*) are evidence against the possibility that a direct interaction between TC cells might be involved in the generation of the low-frequency oscillations. As far as the mechanism of the 'very-slow' oscillations is concerned, because of the relatively few cells in which this activity has been observed, at present we can only exclude with certainty the need of evoked synaptic activity from other neurones present in the slice and of the spontaneous release of amino acid neurotransmitters (i.e. glutamate and GABA).

Recordings in the dLGN and VB showed that the four types of low-frequency oscillations were identical in TC cells from these two thalamic nuclei, suggesting that these oscillatory activities are not peculiar to the dLGN but are common to TC cells in other thalamic nuclei. This suggestion is supported by the fact that the low-frequency oscillations are not generated by synaptic inputs (some of which vary between different thalamic nuclei) but by their intrinsic membrane conductances that are similar in TC cells of different thalamic nuclei (Jahnsen & Llinás, 1984*a*, *b*; Steriade & Llinás, 1988), except in projecting neurones of the vLGN (Crunelli *et al.* 1987*a*). In addition, the low-frequency oscillations are not peculiar to a particular

species since they were observed in rat and cat (and in guinea-pig, cf. McCormick & Prince, 1988). Indeed, the 'very slow' oscillations were similar in the two species, while the pacemaker and the 'NMDA' oscillations observed in the cat were often of a relatively larger amplitude, more regular and faster than those in the rat.

The 'NMDA' oscillations were the only type of low-frequency oscillations described in this paper that, although they did not involve the evoked recruitment of other neurones, required the spontaneous release of an excitatory amino acid (probably glutamate) and its interaction with the NMDA receptors. This conclusion is based on the lack of action of TTX and the blockade by selective NMDA receptor antagonists and channel blockers. The existence of a spontaneous release of excitatory amino acid(s) *in vitro* is supported by biochemical evidence (Johnson, 1978) as well as by the finding of a TTX-insensitive, inward current generated by the tonic activation of the NMDA type of excitatory amino acid receptors (Sah, Hestrin & Nicoll, 1989). The presence of the 'NMDA' oscillations in cat and rat dLGN and in the rat VB indicates that these oscillations are found in TC cells from different species and from different nuclei where afferents containing glutamate-like immunoreactivity (Ottersen & Storm-Mathisen, 1984) and NMDA receptor-mediated responses have been observed (Kemp & Sillito, 1982; Crunelli, Kelly, Leresche & Pirchio, 1987*b*; Salt, 1987; Soltesz *et al.* 1989*a*; Heggelund & Hartveit, 1990; Juhasz, Kekesi, Emri, Soltesz & Crunelli, 1990; Scharfman *et al.* 1990; Sillito, Murphy, Salt & Moody, 1990). The mechanism likely to be responsible for the generation of the 'NMDA' oscillations is described in the accompanying paper (Soltesz *et al.* 1991).

Different types of low-frequency oscillations as a continuum of TC cell activity

The addition of NMDA antagonists to TC cells showing the 'NMDA' oscillations did not abolish all types of oscillations, but reversibly transformed them into the pacemaker and the spindle-like oscillations. This finding and the possibility of recording more than one type of low-frequency oscillations in the same TC cell in the absence of any pharmacological manipulation indicates that these activities are not peculiar to a particular group of TC cells but represent a *continuum* of electrical activity common to each TC cell (cf. Fig. 11 of Soltesz *et al.* 1991).

The results of the present paper have described the electrophysiological properties of spontaneous low-frequency oscillations observed in TC cells *in vitro*, the differences and similarities between thalamic nuclei in different species and how activation of synaptic receptors can disrupt their rhythm and change their frequency. The accompanying paper (Soltesz *et al.* 1991) describes some of the voltage-activated conductances involved in their generation and how transmitter-induced changes in the amplitude of a slow, Na^+–K^+ inward rectifying current are responsible for the reversible transformation of the pacemaker into the spindle-like oscillations, stressing the inter-relationship between the various types of spontaneous low-frequency oscillations present in a single TC cell.

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