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Inhibition of stimulus-triggered and spontaneous epileptiform activity in rat hippocampal slices by the *Aconitum* alkaloid mesaconitine

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Abstract

The aim of the present study was to investigate if the plant alkaloid, mesaconitine, which has been reported to have antinociceptive effects via stimulation of the noradrenergic system, inhibits epileptiform field potentials. The experiments were performed as extracellular recordings on rat hippocampal slices. Epileptiform activity was induced by omission of Mg^{2+} from the bathing medium or by addition of bicuculline and stimulus-evoked population bursts were recorded in the CA1 region. Spontaneous epileptiform activity was elicited by perfusing a nominally Mg^{2+}-free bathing medium with high K^+ concentration (5 mM). Both stimulus-triggered and spontaneous epileptiform activity was attenuated in a concentration-dependent manner by mesaconitine (30 nM–1 μM). The inhibitory effect was rather variable in appearance when lower concentrations (30 and 100 nM) of mesaconitine were applied. Pretreatment of the slices with the α-adrenoceptor antagonist yohimbine (1 μM) prevented the effect of mesaconitine. It is concluded that the inhibitory action of mesaconitine at low concentration is mediated via α-adrenoceptors. © 1998 Elsevier Science B.V.

Keywords: Hippocampus; Epileptiform activity; Mesaconitine

1. Introduction

The C_{19} diterpenoid alkaloid mesaconitine is one of the predominant alkaloids contained in plants of the genera *Aconitum*. Together with aconitine, it occurs in a number of *Aconitum* species (Benn and Jacyno, 1983) and is the main alkaloid in the European subspecies *A. napellus*. These two alkaloids have very closely related chemical structures. Mesaconitine has a *N*-methyl function rather than the *N*-ethyl of aconitine. Mesaconitine has been reported to possess potent antinociceptive activity which is not mediated by stimulation of opioid receptors (Isono et al., 1994). Recently it has been shown that the antinociceptive effect of mesaconitine is blocked by α_2-adrenoceptor antagonists and 5-HT receptor antagonists (Isono et al., 1994) suggesting that the compound activates descending inhibitory α_2-adrenergic and serotonergic neurons which are known to inhibit nociception transmission at the spinal level (Dray et al., 1994).

The intention of the present study was to investigate if mesaconitine affects experimentally induced epileptiform activity in rat hippocampal slices and whether there is an involvement of the noradrenergic system. The hippocampus is known to receive a diffuse projection of noradrenaline containing fibers which originate in the locus coeruleus (Loy et al., 1980; Mongeau et al., 1997) and activation of these noradrenergic afferents has a profound influence on neuronal activity in the hippocampus (Olpe et al., 1986; Washburn and Moises, 1989). Noradrenaline, in turn, has been reported to interact with α-adrenoceptors to decrease pyramidal cell excitability, and with β-adrenoceptors to increase cell excitability (Mueller et al., 1981, 1982) and noradrenergic neurons are thought to be involved in the process of seizure development (Gundlach et al., 1995).

In the present study, the effect of mesaconitine on epileptiform activity in rat hippocampal slices was investigated by means of extracellular recordings. Epileptiform activity was induced either by omission of Mg^{2+} from the bathing medium or by addition of bicuculline and stimulus-triggered population spikes were recorded in area CA1. Spontaneous epileptiform activity occurred when the ex-

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periments were performed in absence of Mg^{2+} and in presence of 5 mM KCl and was recorded in area CA3.

2. Materials and methods

2.1. Slice preparation

Experiments were performed on hippocampal slices from 150 to 180 g male Wistar rats. The preparation of the hippocampus was performed as described previously (Ameri et al., 1996). The animals were decapitated under ether anaesthesia, the brains were removed and the hippocampi dissected free. Slices of 400 μm thickness were cut transversely to the longitudinal axis of the hippocampus with a McIlwain tissue chopper. In the recording chamber, the slices were kept submerged and held down on a nylon net by a U-shaped piece of flattened platinum wire. The standard artificial cerebrospinal fluid (ACSF) was gassed with 95% O_2 and 5% CO_2 and contained (in mM): NaCl 124, KCl 3, NaH_2PO_4 1.25, $NaHCO_3$ 26, $CaCl_2$ 2.5, $MgSO_4$ 2, glucose 10 at a pH of 7.4. It was superfused at flow rate of 3 ml min^{-1} and had a temperature of 32°C. After 2 min, the perfusion fluid reached the recording chamber which had a volume of 1.5 ml. In some experiments, a modified ACSF was used in which no $MgSO_4$ was added (low Mg^{2+} ACSF) in order to evoke epileptiform activity. For recording of spontaneously occurring epileptiform activity, a low Mg^{2+}/high K^+-ACSF was perfused. This solution was nominally Mg^{2+}-free and contained 5 mM KCl.

2.2. Extracellular recording and electrical stimulation

Extracellular recording electrodes were filled with 3 M NaCl (5–10 MΩ) and placed in CA1 stratum pyramidale for recording of stimulus-evoked population spikes. A bipolar concentric stimulation electrode (Rhodes Medical Instruments, USA) was positioned in the Schaffer collateral commissural pathway for orthodromic stimulation. The distance between the recording electrode and the stimulation electrode was approximately 0.5 mm. Electrical stimuli (200 μs in duration) were delivered every 15 s. The signal from the recording electrode was amplified by means of a DP 301 amplifier (Warner Instruments, USA). Analog data were digitized by use of the TIDA data acquisition system (HEKA electronic, Germany).

Recordings were commenced about 1 h after transfer of the slices to the chamber. Stimulus-triggered epileptiform activity was induced after a control period of 30 min in standard ACSF by means of two different experimental protocols. In one set of experiments, epileptiform activity was elicited by perfusion of a low Mg^{2+}-ACSF in order to activate of *N*-methyl-D-aspartate (NMDA) receptor-mediated responses (Coan and Collingridge, 1985; Anderson et al., 1986; Mody et al., 1987; Tancredi et al., 1990) or by addition of bicuculline in order to block GABA receptors

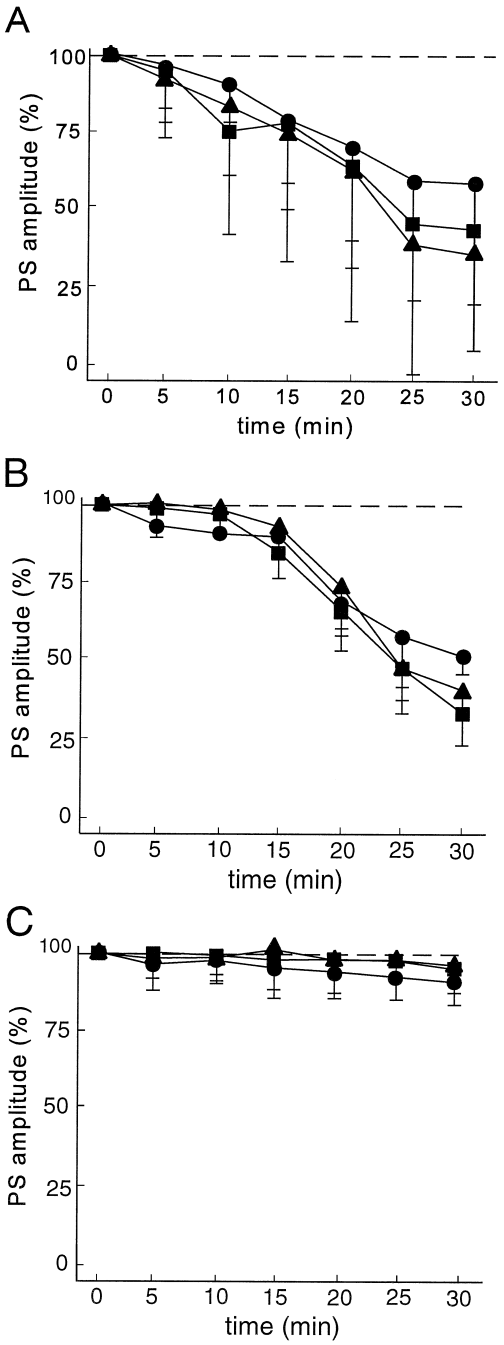

Fig. 1. Time-course of the effect of mesaconitine (30 nM) on the orthodromic response in nominal Mg^{2+}-free ACSF. The amplitude of the first (●), second (■) and third (▲) population spike (PS) were normalized with respect to the amplitudes achieved with perfusion of Mg^{2+}-free ACSF. In A, mesaconitine was applied alone to the Mg^{2+}-free ACSF. In B and C, the alkaloid was applied after a 15 min pretreatment and in combination with 1 μM timolol or 1 μM yohimbine, respectively. Note that yohimbine prevented the mesaconitine-induced attenuation of the spike amplitudes. Each data point represents the mean value ± S.D. recorded from 5 to 7 slices.

(Campbell and Holmes, 1984; Herron et al., 1985; Ault and Wang, 1986; Chagnac-Amitai and Connors, 1989). In standard ACSF, electrical stimulation elicits a single population spike superimposed on a field excitatory postsynaptic potential. During perfusion of the slices with the epileptogenic ACSF, however, the same stimulus evokes synchronized population bursts, each consisting of multiple spike discharges. Significant components of the epileptiform burst discharges include the presynaptic fiber spike, the first postsynaptic population spike and succeeding spikes which define epileptiform activity.

Spontaneously occurring epileptiform discharges were elicited with low Mg^{2+}/high K^{+}-ACSF and recorded in the pyramidal cell layer of CA3.

The experimental protocol consisted of 4 periods characterized as follows: period 1: perfusion with standard ACSF (control). Period 2: induction of epileptiform activity; perfusion of the epileptogenic ACSF. Period 3: test of the effect of mesaconitine; addition of mesaconitine to the epileptogenic ACSF used in period 2. Period 4: washout of mesaconitine with the epileptogenic ACSF. In all experiments, the individual amplitudes of the multiple population spikes were quantified as mean percentages of the change in response amplitude when compared to responses obtained during perfusion of the epileptogenic ACSF in period 2. In order to investigate an involvement of α- or β-adrenoceptors, the antagonists yohimbine and timolol, respectively, were added to the perfusate for the last 15 min of period 2 and for the entire period 3.

In order to determine input–output functions for the epileptiform response, the amplitude of the presynaptic fiber spike as well as the amplitude of the first and the following population spikes was measured at different stimulation intensities. Stimulation intensity was varied from subthreshold to maximal response, each of the evoked potentials described above was measured at each intensity and each response was plotted as an input–output curve. The stimulation intensity was plotted against the fiber spike and the fiber spike was plotted against the first and the second population spike.

2.3. Data analysis

Data are expressed as means $\pm$ standard deviation (S.D.). Statistical evaluation was performed by means of Student's *t*-test. Significance was assumed when $P \leq 0.05$. The amplitude of the population spike was determined from the negative peak to a tangent drawn between the preceding maximum and that following. The number of population bursts occurring during 1–5 min before and after a 30 min application of mesaconitine was counted in order to determine the average firing rate which was used for the quantification of the depressions.

2.4. Drugs

All drug solutions were prepared immediately before application to the slices and added to the perfusion medium. Mesaconitine (obtained from O. Krishtal, Bogomoletz Institute Kiev, Ukraine) was dissolved in dimethylsulfoxide (DMSO) to give stock solutions of 1 mM. These solutions were diluted with ACSF to yield final concentrations varying between 10 nM and 1 μM. Phenytoin (Sigma, Deisenhofen) was dissolved in DMSO to give a stock solution of 100 mM and was applied in a final concentration of 100 μM. The final concentration of DMSO never exceeded 0.1%, a concentration which did not affect any of the parameters measured as shown in control experi-

Table 1
Effects of drugs on the epileptiform population spikes induced by a nominally Mg^{2+}-free bathing solution

Drug	Amplitude of the population spike (PS) in % of control		
	1st PS	2nd PS	3rd PS
TIM (1 μM)	97.90 $\pm$ 3.2 (n.s.)	99.55 $\pm$ 2.8 (n.s.)	99.57 $\pm$ 4.1 (n.s.)
YOH (1 μM)	97.35 $\pm$ 3.6 (n.s.)	97.65 $\pm$ 4.7 (n.s.)	99.87 $\pm$ 6.9 (n.s.)
MES (30 nM)	55.73 $\pm$ 20.2[a]	36.81 $\pm$ 18.6[b]	26.21 $\pm$ 29.9[a]
MES (30 nM) + TIM (1 μM)	50.03 $\pm$ 7.2[b]	32.80 $\pm$ 12.3[b]	38.48 $\pm$ 3.9[b]
MES (30 nM) + YOH (1 μM)	92.03 $\pm$ 2.9[a]	95.91 $\pm$ 2.9 (n.s.)	97.40 $\pm$ 10.3 (n.s.)
MES (100 nM)	40.47 $\pm$ 15.6[b]	20.45 $\pm$ 16.7[b]	9.73 $\pm$ 9.5[b]
MES (100 nM) + TIM (1 μM)	34.70 $\pm$ 6.9[b]	8.96 $\pm$ 11.85[b]	—
MES (100 nM) + YOH (1 μM)	63.85 $\pm$ 8.9[b]	58.65 $\pm$ 12.12[a]	59.45 $\pm$ 22.1[a]
PHEN (100 μM)	91.75 $\pm$ 3.6[a]	83.20 $\pm$ 15.4 (n.s.)	78.35 $\pm$ 16.3 (n.s.)

Data represent mean values $\pm$ S.D. of 5–7 experiments and are normalized with respect to the values measured at the end of perfusion of low Mg^{2+}-ACSF. The amplitudes of the first three spikes in the epileptiform burst were determined at the end of the drug-application. Timolol (TIM) and yohimbine (YOH) were applied 15 min. Mesaconitine (MES), alone or in combination with one of the antagonists as well as phenytoin (PHEN) was applied 30 min. No data are given when the spike was completely suppressed. All comparisons made by use of the paired Student's *t*-test.
[a] $P \leq 0.05$.
[b] $P \leq 0.001$.
n.s.; not significant.

ments. Bicuculline methiodide, timolol–HCl and yohimbine–HCl (Sigma, Deisenhofen) were dissolved in distilled water and applied to the ACSF.

3. Results

Only data from the hippocampal slices which showed normal field potentials (i.e. no second population spike by maximal stimulation intensity) in response to electrical activation of Schaffer collaterals in standard ACSF were used for calculations. Furthermore, population spikes had to be stable during a control period of at least 30 min prior to application of drugs.

3.1. Effects of mesaconitine on the stimulus-triggered population spikes

The slices were bathed in standard ACSF and after stable potentials had been recorded from the pyramidal cell layer for at least 20 min, the perfusion medium was switched to the low Mg^{2+}-ACSF. After 15–20 min an epileptiform discharge of population spikes was induced in area CA1, which reflects synchronous discharges of the neurons in the vicinity of the recording electrode (Anderson et al., 1986). The elicited epileptiform burst activity became manifest as 5–8 negative population spikes of declining amplitude on top of a positive postsynaptic field potential of 50–70 ms in duration. The amplitudes of these spikes became stable after another 15–20 min and were observed in control experiments to persist during the entire recording time of up to 6 h.

At concentrations of 30 nM to 1 μM, mesaconitine reversibly attenuated the stimulus-triggered epileptiform burst discharges elicited by omission of Mg^{2+} from the perfusate. At higher concentrations (300 nM and 1 μM), complete suppression of the multiple population spikes was observed 10–15 min after starting the drug-application. The diminution of the epileptiform activity evoked by lower concentrations (30 and 100 nM) was highly variable in appearance (Fig. 1A, Table 1). When mesaconitine was applied at a concentration of 30 nM, it failed to alter the burst activity in 3 out of 7 slices, whereas in the other 4 slices the amplitudes of the multiple population spikes were decreased. In order to investigate the possibility if mesaconitine might exert differential effects via α-adrenoceptors and β-adrenoceptors, experiments have been performed with either β-adrenoceptor antagonist timolol ($n = 6$) or the α-adrenoceptor antagonist yohimbine ($n = 6$). For this purpose, slices were first pretreated with timolol (1 μM) or yohimbine (1 μM) for the last 15 min of period 2 in order to observe if any change in the pattern of epileptiform activity occurs. After that, a combination of either timolol or yohimbine with mesaconitine was applied. The results of these experiments are summarized in Table 1. Both timolol and yohimbine did not affect the amplitudes of the multiple population spikes when added to the low Mg^{2+}-ACSF at the end of period 2. When mesaconitine (30 nM) was applied after pretreatment of the hippocampal slices with timolol (1 μM), low Mg^{2+}-induced epileptiform activity was reduced in all slices tested (Fig. 1B and Fig. 2A). In contrast, when applied at the same concentration after pretreatment with the α-adrenoceptor antagonist, yohimbine (1 μM), mesaconitine completely failed to significantly change the amplitudes of the second and third population spikes in the burst (Fig. 1C and Fig. 2B) suggesting an involvement of α-noradrenergic receptors in the drug-evoked inhibition of the epileptiform activity. When mesaconitine was applied at a concentration of 100 nM together with yohimbine, the inhibitory action of mesaconitine was reduced as compared to its action in

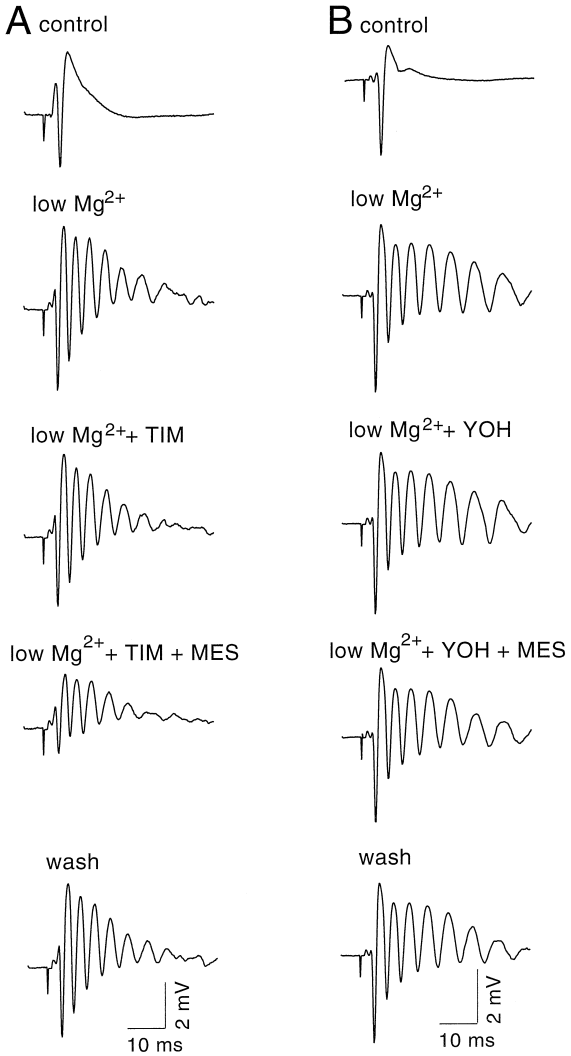

Fig. 2. Effect of mesaconitine (MES, 30 nM) in combination with (A) timolol (TIM, 1 μM) and (B) yohimbine (YOH, 1 μM) on the orthodromic response in CA1 elicited with nominal Mg^{2+}-free ACSF. Neither timolol nor yohimbine affected the extracellularly recorded population spikes prior to the addition of mesaconitine.

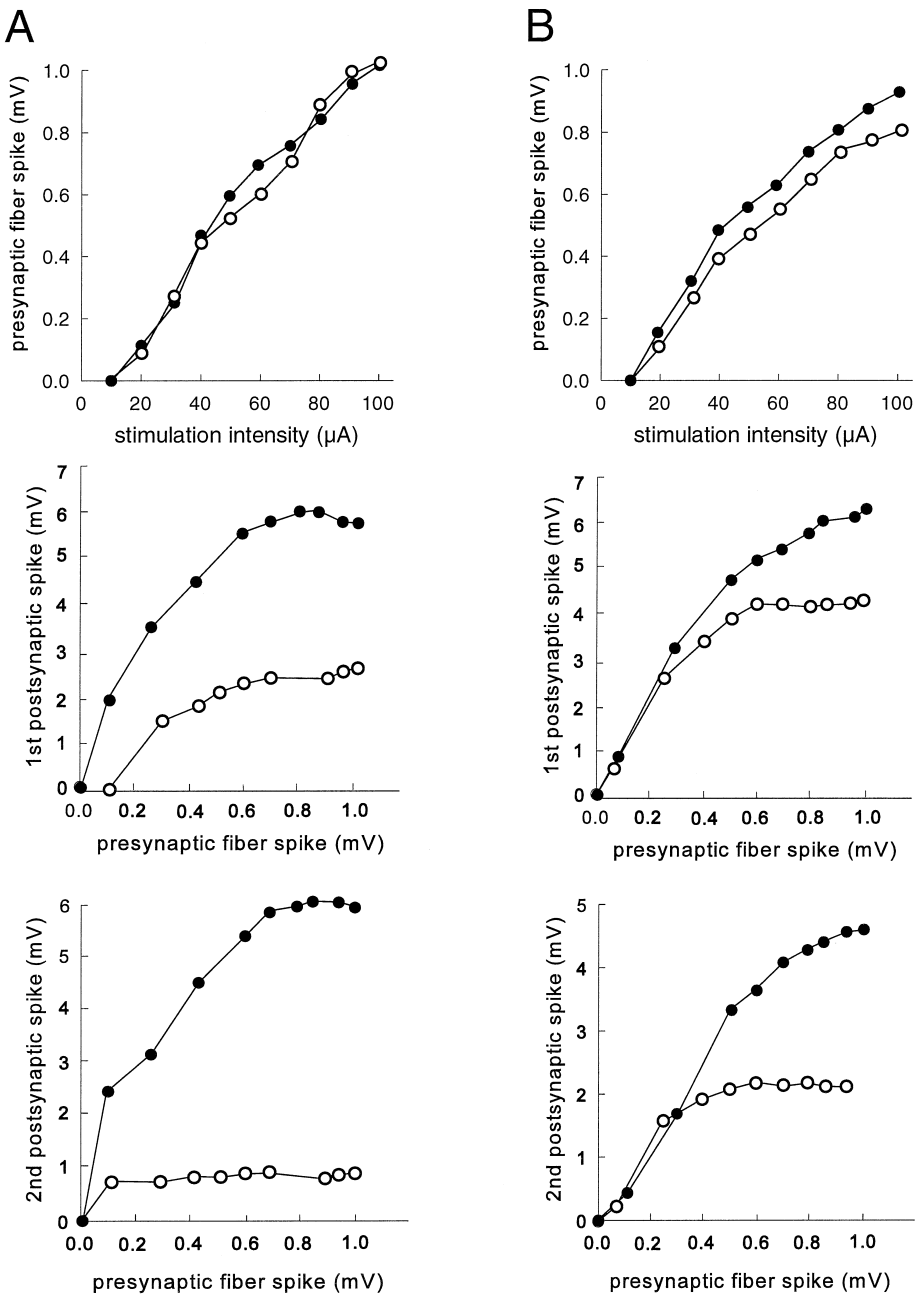

Fig. 3. Input–output curves for the orthodromically evoked response elicited with (A) low Mg^{2+}-ACSF and (B) 10 μM bicuculline. After epileptiform activity was stable, 100 nM mesaconitine was applied. Slices were stimulated with intensities ranging from subthreshold to maximal. For each response, the amplitudes of the presynaptic fiber spike, the first population spike, and the second population spike were measured after perfusion of the epileptogenic ACSF (●) and 30 min after addition of mesaconitine (○). The fiber spike is related to the stimulation intensity (top), the first population spike is related to the fiber spike (middle), and the second population spike is related to the fiber spike (bottom). Both in A and B, a representative experiment out of 6 or 7 other ones is shown.

low Mg^{2+}-ACSF. Yohimbine failed to affect the inhibitory effect of higher concentrations of mesaconitine (300 nM and 1 μM).

When epileptiform activity was elicited with bicuculline (10 μM), no difference in the sensitivity to mesaconitine (100 nM) was observed when applied either alone or in combination with timolol or yohimbine. Compared with low Mg^{2+}-evoked epileptiform activity, the inhibitory action of mesaconitine was lower when tested in the bicuculline model (Fig. 3). At concentrations less than 100 nM, there was no effect of mesaconitine on the bicuculline-induced multiple population spikes.

In order to determine the relationship of the presynaptic fiber spike to stimulation intensity, the first postsynaptic population spike to the fiber spike, and the second population spike to the first one, input–output functions were

measured as described in Section 2. The effect of mesaconitine (100 μM) on the input–output curve obtained during perfusion with low Mg^{2+}-ACSF and bicuculline is shown in Fig. 3A and B, respectively. It is obvious that mesaconitine showed only a slight or no effect on the presynaptic fiber spike which reflects the compound action potential of the afferents, whereas the first and second postsynaptic population spike in the stimulus-triggered burst are markedly reduced at all stimulation intensities.

3.2. Effects of mesaconitine on spontaneously occurring epileptiform field potentials

The experiments reported above indicate a depressant effect of mesaconitine on stimulus-triggered epileptiform activity in hippocampal area CA1. The CA1 subfield is known to receive powerful excitatory projections from the CA3 region via the Schaffer collaterals. Accordingly, the effects induced by mesaconitine in the CA1 area could result from a change first occurring in CA3. Therefore a

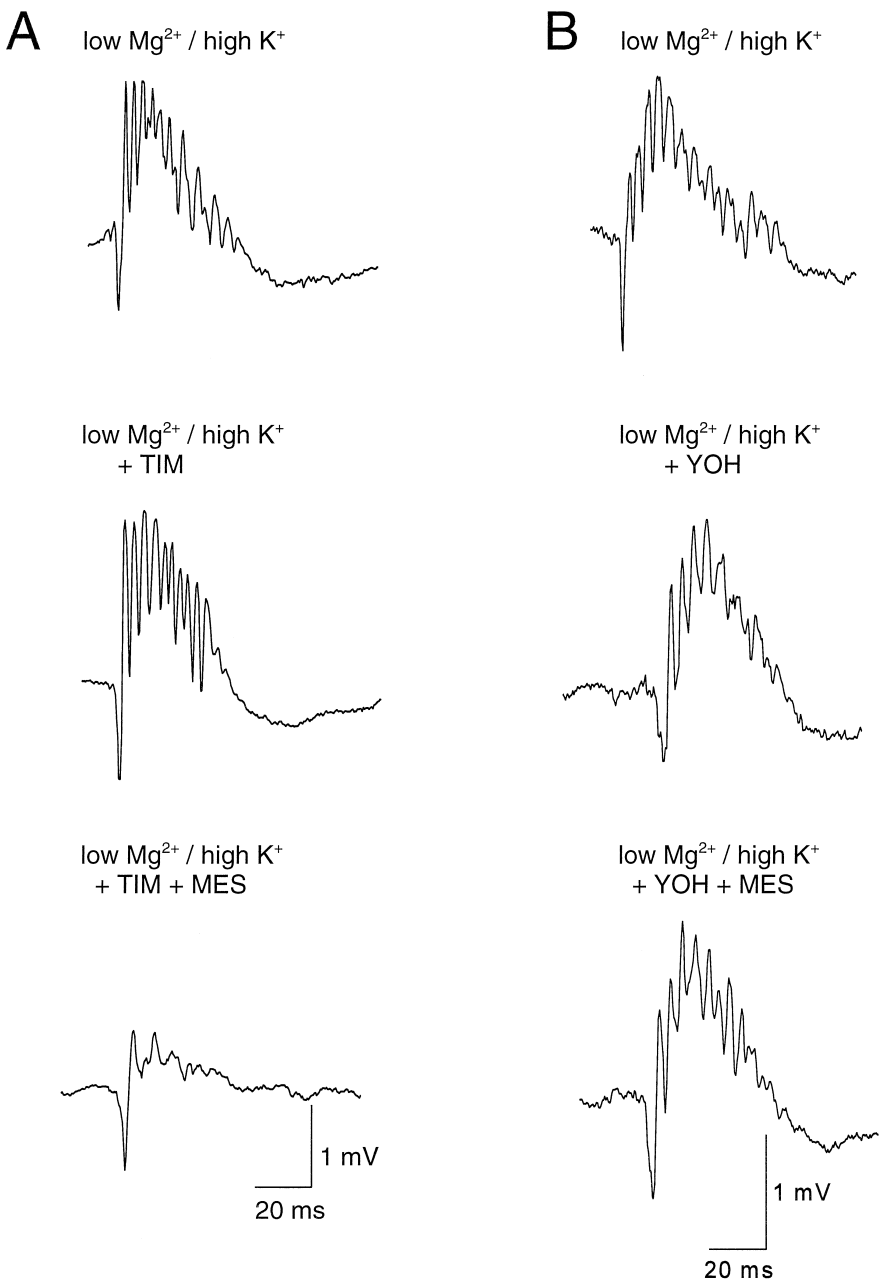

Fig. 4. Effect of mesaconitine (MES, 30 nM) in combination with (A) timolol (TIM, 1 μM) and (B) yohimbine (YOH, 1 μM) on the spontaneously occurring epileptiform activity in CA3 elicited with nominal Mg^{2+}-free ACSF with elevated K^+ concentration (5 mM). Neither timolol nor yohimbine affected the extracellularly recorded population spikes prior to the addition of mesaconitine. After pretreatment with yohimbine, mesaconitine failed to affect the spontaneous epileptiform discharges.

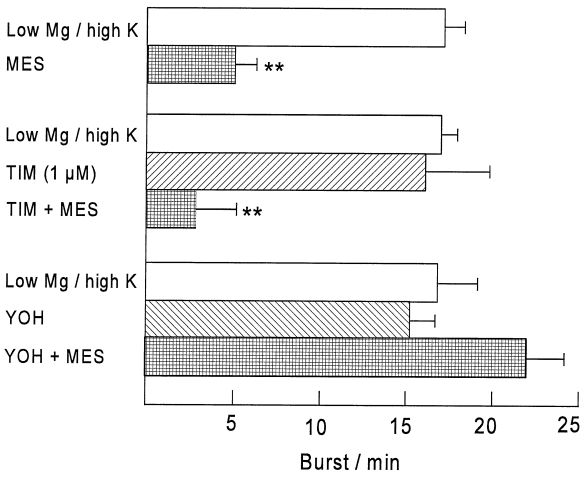

Fig. 5. Effect of mesaconitine (MES, 30 nM) alone and in combination with timolol (TIM, 1 μM) or yohimbine (YOH, 1 μM) on the frequency of spontaneously occurring burst discharges in hippocampal area CA3. The bars represent the mean $\pm$ S.D. of 5–6 experiments. When mesaconitine was applied alone or in combination with timolol the frequency was significantly ($P < 0.01$) reduced. Mesaconitine failed to change the frequency when it was applied together with yohimbine. The combined application of mesaconitine with a noradrenergic receptor antagonist was preceded by a 15 min application of the antagonist alone. Neither timolol nor yohimbine significantly altered the burst frequency.

subsequent series of experiments was carried out in which slices were perfused with low Mg^{2+}/high K^{+}-ACSF. During these experiments no electrical stimuli were given. Spontaneously occurring epileptiform activity was recorded in the pyramidal cell layer of the CA3 region. When mesaconitine was added to the low Mg^{2+}/high K^{+}-ACSF the frequency of burst discharges was reduced (30 nM) or fully suppressed (100 nM) within 30 min of drug-application. According to the results obtained with stimulus-triggered epileptiform activity recorded in CA1, pretreatment of the slices with yohimbine (1 μM) abolished the inhibitory action of mesaconitine (Fig. 4) and even enhanced the frequency of the spontaneously occurring burst discharges when mesaconitine was applied at a concentration of 30 nM, whereas timolol (1 μM) did not affect the action of the alkaloid. There was no significant effect of timolol and yohimbine on the spontaneously occurring epileptiform activity when applied before mesaconitine. Fig. 5 summarizes the effects of these drugs on the frequency of the low Mg^{2+}/high K^{+}-ACSF bursting.

Furthermore, control experiments were performed with phenytoin (Fig. 6). While phenytoin (100 μM) failed to reduce the second and third low Mg^{2+}-evoked population spikes in CA1 (Table 1), it reduced the frequency of bursting in CA3 from 17.6 ± 2 burst/min in low Mg^{2+}/high K^{+}-ACSF to 6.6 ± 2 ($n = 5$, $P < 0.01$).

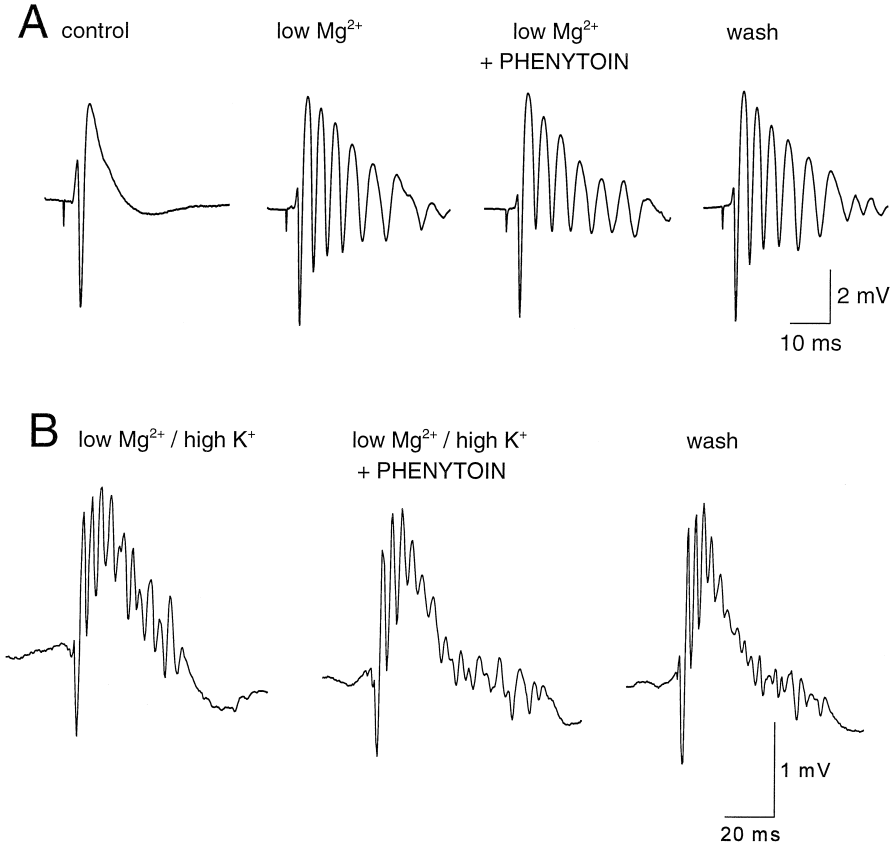

Fig. 6. Effect of phenytoin (100 μM) on the epileptiform activity elicited with nominal Mg^{2+}-free ACSF. (A) Stimulus-triggered population spikes recorded in the pyramidal cell layer of area CA1. (B) Spontaneously occurring burst discharges recorded in the pyramidal cell layer of area CA3.

4. Discussion

The aim of the present study was to investigate the effect of mesaconitine, a plant alkaloid of *Aconitum* species, on experimentally evoked epileptiform activity in rat hippocampal slices. The present results demonstrate that mesaconitine diminished both stimulus-triggered epileptiform activity and spontaneously occurring epileptiform discharges.

Mesaconitine has been reported to possess antinociceptive properties in rat (Benn and Jacyno, 1983; Isono et al., 1994). It has been demonstrated that the antinociceptive action of mesaconitine is not antagonized by naloxone suggesting that it is not mediated by a stimulation of opioid receptors, but seems to be due to an activation of descending inhibitory noradrenergic pathways which project from the brainstem to the spinal cord (Isono et al., 1994). Noradrenaline has a variety of effects at α- as well as β-adrenoceptors in the hippocampus. In the CA1 region of the hippocampus, extracellular studies have demonstrated that noradrenaline has both α-adrenoceptor mediated inhibitory and β-receptor mediated excitatory actions (Mueller et al., 1981, 1982). This is consistent with the observation that stimulation of locus coeruleus increases the amplitudes of the evoked population spike in the CA1 area of anesthetized rats (Olpe et al., 1986; Washburn and Moises, 1989). Moreover, there is mounting evidence of a role for noradrenaline in long-term plasticity and epileptogenesis by enhancing activation of glutamate receptors of the *N*-methyl-D-aspartate (NMDA) subtype (Stanton et al., 1992; Gundlach et al., 1995). NMDA, in turn, has been reported to stimulate ^{3}[H]noradrenaline release in hippocampal slices (Snell et al., 1987).

The main purpose of the present study was to investigate whether or not there is an interaction of mesaconitine with the noradrenergic system and a consequence of its pharmacological intervention for epileptiform activity in rat hippocampus. The present results provide evidence that the mesaconitine-induced suppression of epileptiform activity which was elicited by omission of Mg^{2+} is sensitive to the α-adrenoceptor antagonist yohimbine. These findings imply an involvement of α-adrenoceptors in the inhibitory action of mesaconitine. This is in line with the rather large variances seen when mesaconitine was applied in absence of both α- and β-adrenoceptor antagonists and with the blockade of effect in presence of yohimbine. However, the antagonizing effect of yohimbine on the mesaconitine-evoked attenuation of epileptiform activity could be overcome, when higher concentrations of mesaconitine (300 nM and 1 μM) were applied. These findings suggest that different mechanisms of action might be involved in the inhibitory effects induced by low and high concentrations of mesaconitine. Mesaconitine is closely related with aconitine, bearing a *N*-methyl group rather than the *N*-ethyl of aconitine. Due to this structural relationship, it seems likely that the depressant effects evoked by high concentrations of mesaconitine are mediated by an activation of Na^{+} channels as previously described for aconitine (Schmidt and Schmitt, 1974; Catterall, 1980). As reported for aconitine this action leads to excessive depolarization (Schmidt and Schmitt, 1974) with final inexcitability (Ameri et al., 1996).

In contrast to the low Mg^{2+}-elicited epileptiform activity, mesaconitine had a lower inhibitory effect when investigated in the bicuculline-model. Interestingly, no change in the action of mesaconitine was observed when it was applied together with either timolol or yohimbine. The different results obtained with both epilepsy models might be due to an interaction between the NMDA receptor and β-adrenoceptors. As recently reported, stimulation of β-adrenoceptors during excitatory synaptic transmission can increase charge transfer and ion influx through NMDA receptors (Raman et al., 1996), thereby exerting a facilatory effect on the induction of long-term potentiation (Thomas et al., 1996).

Although the present study provides evidence that the antiepileptiform activity of mesaconitine involves an activation of α-adrenoceptors, the question remains in which manner the alkaloid interacts with this receptors. Assuming that mesaconitine, like aconitine and veratridine, is capable to activate voltage-dependent Na^{+} channels (Catterall, 1980) it is possible that it can induce exocytotic release of noradrenaline and outward transport of noradrenaline by the noradrenaline transporter as shown for veratridine (Bönisch et al., 1983; Bönisch and Trendelenburg, 1987). In fact, it has been demonstrated that mesaconitine-induced contractions of the guinea-pig vas deferens is due to neuronal release of noradrenaline (Sato et al., 1979).

Taken together, the antiepileptiform activity of mesaconitine which became obvious in the low Mg^{2+}-model was not blocked by the β-adrenoceptor antagonist timolol, but was blocked instead by the α-adrenoceptor antagonist yohimbine. These findings indicate that noradrenergic inhibitory actions in the CA1 and CA3 subfield of the hippocampus are involved in the antiepileptiform action of the plant alkaloid mesaconitine which are likely to be α-receptor mediated.

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