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# Effect of posterior hypothalamic injection of procaine on the hippocampal theta rhythm in freely moving cats

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**Abstract.** Earlier *in vivo* studies conducted on freely moving and anesthetized rats demonstrated that the posterior hypothalamus (PH) comprises pathways critical for producing the synchronous hippocampal formation (HPC) theta rhythm. In addition, these findings suggested that the frequency of the HPC theta was encoded in the PH and then was fed *via* the medial forebrain bundle to the medial septum and HPC. In the present study we attempted to verify this hypothesis with use of a different *in vivo* model - freely moving cats. The microinjection of the local anaesthetic, procaine, into the PH region reversibly suppressed the spontaneous as well as sensory and electrically induced HPC theta. However, in contrast to rats, in freely moving cats microinjection of procaine into the PH reduced the amplitude of the HPC theta but had no effect on theta frequency. We conclude that in freely moving cats the PH region comprises a critical part of the ascending brainstem pathway, for production of the HPC theta rhythm. In contrast to rats, in freely moving cats ascending inputs from the brainstem to the PH contribute mainly to the amplitude of the HPC theta rhythm.

**Key words:** theta rhythm, rhythmical slow wave activity (RSA), EEG, posterior hypothalamic region, procaine, cats

There is a large body of research indicating that the occurrence of the hippocampal formation (HPC) theta rhythm (RSA – rhythmic slow activity) is critically dependent on the integrity of a number of structures localized at the level of the brainstem and diencephalon (Bland 1986, Vertes 1986, Bland and Colom 1993, Vertes et al. 1995). The existence of the ascending synchronizing pathway responsible for the production of the HPC theta has been well documented. Fibres forming this synchronizing system originate in the nucleus *pontis oralis* (NPO), ascend through the posterior and medial hypothalamus to the medial septum/vertical limb of the diagonal band of Broca (MS/vDBB), and from there project to the limbic cortex (Vertes 1982, 1984, 1988, Vertes et al. 1993). In addition to the MS region, the area of the posterior hypothalamus (PH) has been considered to be an important link between the brainstem and the HPC. Electrical stimulation of the PH in rats was shown to induce the HPC theta and rhythmic discharges of „*theta on*" cells both in the HPC and MS regions (Kawamura and Domino 1968, Bland and Vanderwolf 1972, Colom et al. 1987, Bland et al. 1990, Smythe et al. 1991, Oddie et al. 1994, Bland 2000). Electrolytic lesions of the PH, in contrast, abolished the HPC theta rhythm (Kawamura et al. 1961, Anchel and Lindsley 1972, Robinson and Wishaw 1974). It was also demonstrated that the injection of a local anesthetic, procaine, into the PH region in rats produced a typical pattern for recovery of the HPC theta rhythm: after the initial abolishment of theta, the frequency of the HPC theta recovered much slower than did its amplitude (Kirk and McNaughton 1991, 1993, Oddie et al. 1994, McNaughton et al. 1995, Oddie and Bland 1998). In addition, neurons in the PH region have also been shown to discharge rhythmically at theta frequencies (Kocis and Vertes 1994, Bland et al. 1995, Kirk et al. 1996) and repetitive bursts have been also recorded *in vitro* from the mammillary nucleus of the PH region (Alonso and Llinás 1992). These findings suggest that the frequency of the HPC theta is encoded in the PH and then is fed *via* the medial forebrain bundle to the MS (Bland et al. 1995, Bland 2000).

In the present study we attempted to verify this hypothesis with use of a different experimental model, freely moving cats. The key question to be answered in these experiments was whether the procaine reversible inactivation of the PH would produce a reduction of the HPC theta frequency in freely moving cats. A portion of these results have been previously reported in abstract form (Bocian et al. 1999).

Five adult cats (2.5-3.5 kg) were used in the present study. The animals were supplied from the breeding colony by the animal care service of the University of Łódź. The animals were prepared for the experiments by implanting them with intracerebral electrodes and cannulae (Fig. 1). The surgery was carried out under hexobarbital anesthesia (90 mg/kg, i.p.). Each animal was implanted with two guide cannulae (which were made of 22-gauge hypodermic needles) bilaterally into the posterior hypothalamus (Fr = 10.0; L = ±1.0; H = -3.5). For the administration of procaine, injection cannulae were positioned 1.5 mm lower (H= -5.0). Apart from the cannulae, the animals were also implanted bilaterally with bipolar recording electrodes (made of twisted stainless steel wires, 200-μm diameter coated with Teflon, except for a 0.5 mm tip) into the region of the stratum moleculare of the dentate gyrus (Fr = 4.0; L = ±5.5; H = +7.0) and a bipolar stimulation electrode (unilaterally, right side) into the area of the midbrain reticular formation (MRF, Fr = 2.0; L = 1.5; H = -2.0). Stereotaxic coordinates were adopted from a stereotaxic atlas of Jasper and Ajmone-Marsan (1954).

Two weeks after the surgery experiments were started. The cats were tested in a shielded cage (100 × 70 × 70 cm) placed in a soundproof chamber and were observed with closed circuit TV. This arrangement permitted the cats to move freely about the cage. The EEG signal recorded by the hippocampal electrodes was preamplified by a wide-band AC preamplifier with low and high filters set at 1 Hz and 1 kHz, respectively. Signals were digitalized using a computer interface (1401 plus, Cambridge Electronic Design, London, UK) and recorded to the computer hard disk. The specific experimental procedure was as follows: the cat was placed in the experimental cage and control EEG recordings (with epochs of theta) were taken for 120 s in spontaneous conditions as well as during sensory stimulation. Hippocampal formation field potential recordings were grouped into three categories: A) spontaneous theta, B) theta recorded during the presentation of sensory stimuli (hand claps, hand waves and whistles); C) theta elicited by electrical stimulation of the midbrain reticular formation (100 Hz pulses, 0.2 ms pulse duration, 0.4-0.8 mA, 20 s). In a given animal the stimulation intensity yielding the best response (i.e. almost continuous theta with minimal signs of the increased locomotor activity) during the preprocaine testing was kept constant during the postprocaine testing. The effect of PH reversible suppression by procaine on spontaneous, sensory, and elec-

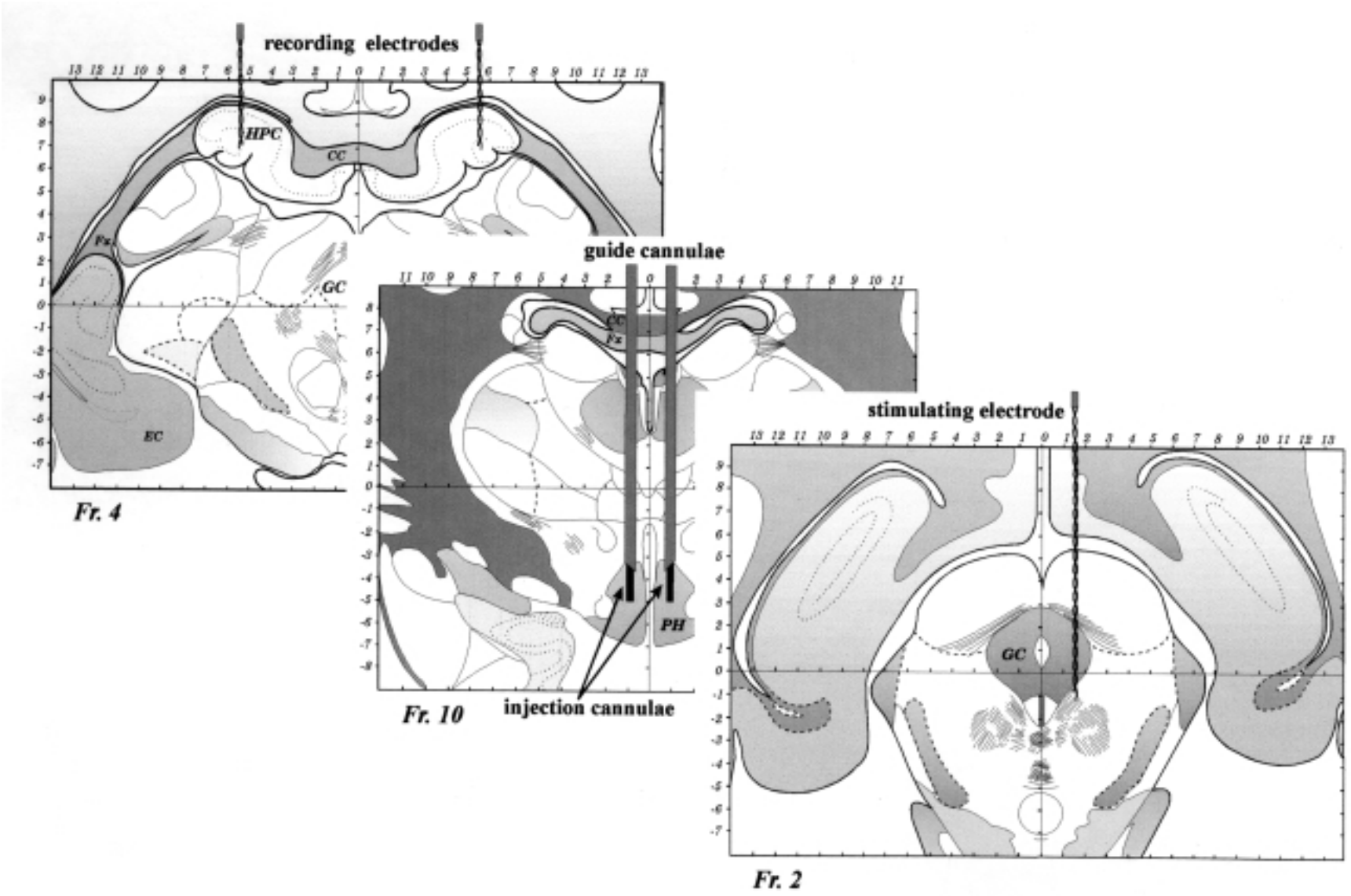


Fig. 1. Diagrammatic representation of the recording and stimulation electrodes and injection cannulae arrangement in the cat brain. Frontal plane (Fr) according to Jasper and Ajmone-Marsan (1954).

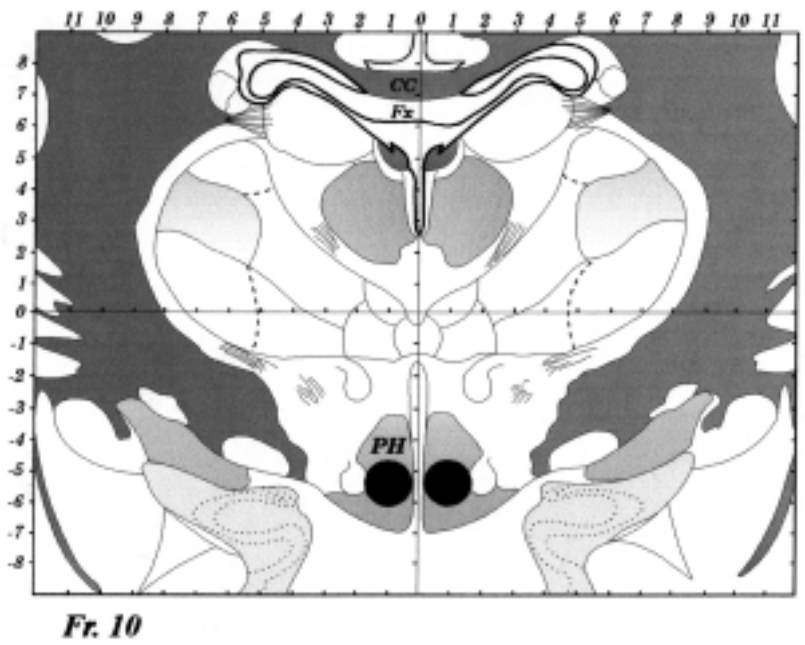


Fig. 2. Schematic representation of the typical location of procaine injection in the posterior hypothalamus region (frontal plane 10.0; according to Jasper and Ajmone-Marsan, 1954). Black filled circles indicate an assumed theoretical radius of procaine diffusion (0.8 mm; according to Myers, 1971).

trically induced hippocampal theta was determined in successive postprocaine time periods: 5, 15, 25, 35, 45, and 55min. For this purpose, 4 μl of 20% procaine HCl (Sigma Chemical Co., St. Louis, MO, USA) was bilaterally injected into the posterior hypothalamus at the rate of 1 μl/30s.

Hippocampal EEG was analyzed off-line using the Spike-2 software computing system (Cambridge Electronic Design). Sixty 2-s samples of EEG activity registered during the spontaneous and sensory stimulation procedures (in control as well as postprocaine periods) were subject to power/frequency (FFT) analysis. When theta was induced by electrical stimulation only ten 2-s samples of recordings were analyzed.

The hippocampal theta field activity was classified as semi-sinusoidal activity with a peak frequency of 3-7 Hz. The peaks were detected by a computer algorithm and were individually checked for accuracy and theta presence by the experimenter. Power was determined at the dominant (peak) frequency of the theta band. When no peak theta frequency occurred (irregular activity, postprocaine blockade), power was not measured. The mean peak-to-peak amplitude of theta was determined directly from epochs of theta.

Three measured theta parameters (frequency, amplitude and power) obtained from the control and successive postprocaine time periods were submitted to one-way Kruskal-Wallis analysis of variance. A detailed comparison was made by using Mann-Whitney U-test.

At the completion of the experiments, each animal was sacrificed with an overdose of hexabarbital and the brains were removed from the skull. The brains were prepared according to the paraffine technique and subsequently serially sectioned at 20 μm in the frontal plane. Sections were then stained with cresyl violet for the subsequent verification of the hippocampal electrodes and the hypothalamic cannulae placement.

Histological analysis revealed that procaine injection sites were typically positioned in the posterior hypothalamus area between frontal planes 9.0-10.0 (Fig. 2). The tips of bipolar electrodes implanted into the hippocampal formation were positioned in the stratum moleculare of the dentate gyrus of HPC (between frontal planes 4.0 and 4.5). The bipolar stimulation electrodes were localized in the midbrain reticular formation (frontal planes 2.0 - 2.5).

In our present experiments no apparent correlation between spontaneous overt behavior of cats and the presence of the hippocampal theta was observed. In all tested animals spontaneous theta was never observed to occur continuously. Typically, electrical activity recorded from the HPC of freely moving cats consisted of irregular activity separated by trains of regular theta epochs. The mean (± SE) frequency and amplitude of spontaneous theta was found to be 3.8 ± 0.1 and 216.6 ± 25.3 μV (respectively, Table I). Mean power of the dominant frequency in the theta band was 1812.8 ± 195.3 $\mu V^2$. Both sensory and electrical stimulation procedures increased the frequency, amplitude and power of theta (Table I). The power/frequency spectrographs of representative

TABLE I

Mean values (± SE) of frequency, amplitude and power of the hippocampal theta field activity before (control) and after procaine injection into the posterior hypothalamus area

| Preprocaine | | | Postprocaine ** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Parameters of theta* | Control | *n* | 5 min | 15 min | 25 min | *n* | 35 min | *n* | 45 min | *n* | 55 min | *n* |
| Power ($\mu V^2$) | | | | | | | | | | | | |
| A | 1812.8 ± 195.3 | 105 | No theta | No theta | 1021.2 ± 223.9 | 44 | 1289.7 ± 194.4 | 63 | 1408.9 ± 177.8 | 81 | 1752.1 ± 238.2 | 98 |
| B | 2118.9 ± 154.9 | 143 | No theta | No theta | 1325.5 ± 208.5 | 58 | 1562.6 ± 193.1 | 87 | 1754.9 ± 165.2 | 111 | 2189.9 ± 175.1 | 138 |
| C | 2415.2 ± 138.5 | 81 | No theta | No theta | 1598.8 ± 183.8 | 54 | 1876.4 ± 207.8 | 60 | 2216.6 ± 156.3 | 72 | 2460.6 ± 198.2 | 83 |
| Amplitude ($\mu V$) | | | | | | | | | | | | |
| A | 216.6 ± 25.3 | 105 | No theta | No theta | 149.9 ± 26.8 | 44 | 179.2 ± 22.5 | 63 | 1911.7 ± 20.7 | 81 | 220.0 ± 23.1 | 98 |
| B | 240.8 ± 29.7 | 143 | No theta | No theta | 170.7 ± 30.2 | 58 | 192.1 ± 27.0 | 87 | 221.2 ± 26.9 | 111 | 236.5 ± 19.0 | 138 |
| C | 267.1 ± 20.4 | 81 | No theta | No theta | 198.6 ± 17.9 | 54 | 219.0 ± 20.8 | 60 | 246.0 ± 18.3 | 72 | 261.3 ± 17.3 | 83 |
| Frequency (Hz) | | | | | | | | | | | | |
| A | 3.8 ± 0.1 | 105 | No theta | No theta | 3.7 ± 0.2 | 44 | 3.8 ± 0.1 | 63 | 3.8 ± 0.1 | 81 | 3.7 ± 0.2 | 98 |
| B | 4.1 ± 0.2 | 143 | No theta | No theta | 3.9 ± 0.1 | 58 | 4.0 ± 0.1 | 87 | 4.0 ± 0.1 | 111 | 4.1 ± 0.2 | 138 |
| C | 4.7 ± 0.2 | 81 | No theta | No theta | 4.9 ± 0.2 | 54 | 4.8 ± 0.1 | 60 | 4.9 ± 0.2 | 72 | 4.8 ± 0.1 | 83 |

* - A, spontaneous theta; B, sensory induced theta; C, electrically induced theta

** - tested at 5, 15, 25, 35, 45 and 55 min postprocaine

*n* - number of theta epochs

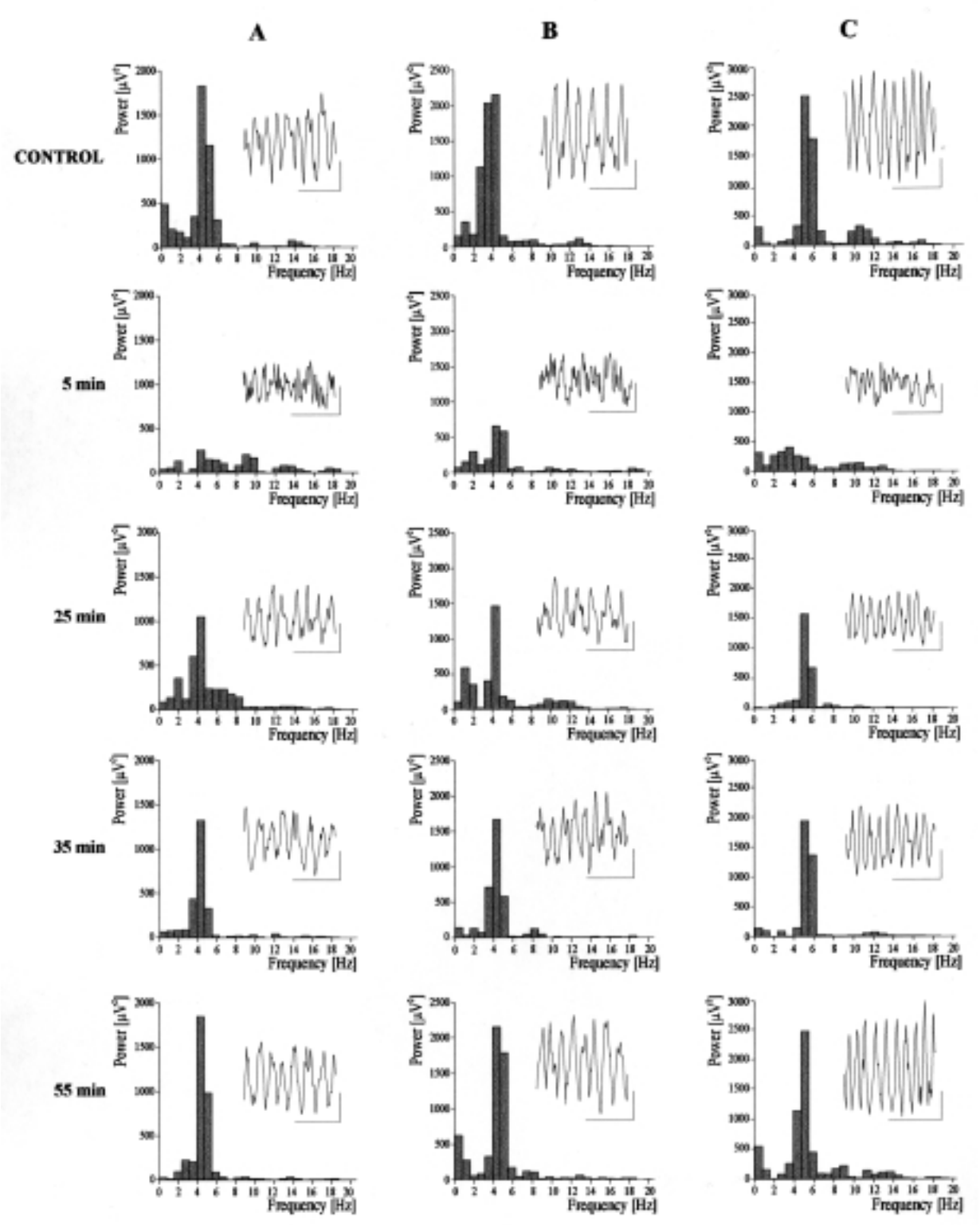


Fig. 3. The effect of procaine infusion into the posterior hypothalamus area on the hippocampal theta rhythm. (**A**) spontaneous theta, (**B**) sensory induced theta, (**C**) electrically induced theta. Each of the spectrographs was taken from 2-s epochs of the hippocampal field activity shown in the right inserts. The panels show data taken during the control (preprocaine) conditions and data taken 5, 25, 35 and 55 min after the intrahypothalamic injection of procaine in the representative experiments. Calibration: 1s and 100 μV.

analogue samples of hippocampal spontaneous theta field activity, as well as theta recorded during sensory and electrical stimulations are shown in Fig. 3A, B, C, respectively.

Inactivation of the HP by the bilateral injection of 4 μl of 20 % procaine HCl completely abolished the spontaneous HPC theta field activity. Procaine suppression of the posterior hypothalamus area also blocked theta elicited by sensory and electrical stimulation of the MRF. The hippocampal theta blocking effect was observed for at least 15 min (Table I, Fig. 3A, B, C and Fig. 4). Illustrative examples of the power/frequency spectrographs with representative analogue samples of the hippocampal field potential recorded in the successive postprocaine time periods are shown in Fig. 3A, B, C. At 5- and 15 min postprocaine, a peak frequency in the theta band was no longer present. The spontaneous (Fig. 3A) and evoked (Fig. 3B, C) hippocampal theta field activity gradually recovered at 25-, 35- and 55 min postprocaine (a peak within the theta frequency band could again be detected). There was a substantial difference in the recovery time course between frequency *vs.* amplitude and power of the hippocampal theta. While frequency of theta was almost at the control, preprocaine level upon the first appearance (Fig. 3A and 4), amplitude and power showed a gradual recovery (Table I, Fig. 3A, B, C and 4). After 55 min, amplitude and power also reached the control preprocaine levels.

No changes in the overt behavior of the cats were observed after the posterior hypothalamic procaine injections. The animals did not exhibit symptoms of immobility or cataleptic state. In response to external stimuli (sensory or electrical) cats appeared to be in an agitated condition, sometimes walking around the experimental cage.

Following bilateral microinjection of physiological saline (4 μl) into the PH both the hippocampal EEG and cats' behavior did not differ from that commonly observed in the preinjection conditions (data not shown).

In the present report the effect of the PH procaine injection on the HPC theta rhythm was assessed in freely moving cats. Reversible procaine inactivation of the PH region, which combines the posterior hypothalamic and supramammillary nuclei, abolished all HPC theta induced caudal to the PH (spontaneous theta, sensory-induced theta and theta rhythm produced by electrical stimulation of the brainstem reticular formation). This finding generally confirms the earlier hypothesis that midline posterior region of the hypothalamus comprises a critical part of the ascending synchronizing pathway that originates in the *nucleus pontis oralis* (NPO) and provides afferents to the limbic cortex (Bland and Colom 1993, Kirk and McNaughton 1993, Oddie et al. 1994, Oddie and Bland 1998).

The marked difference in the postprocaine time course of recovery of the amplitude and power *vs.* frequency of theta recorded in the current experiments suggests that in freely moving cats the PH region contributes to the amplitude of the HPC theta but not to its frequency. This suggestion is in direct contrast to the results obtained earlier in rats. Oddie et al. (1994) demonstrated in anesthetized rats that after PH procaine infusion the recovery of theta frequency was slower than the recovery of theta amplitude. According to Oddie et al. (1994) slower recovery of frequency suggested that this region contributed more substantially to frequency than amplitude of the HPC recorded theta rhythm. In addition, Kirk and McNaughton (1993) also reported that in anesthetized rats, an injection of procaine into SuM (supramammillary nucleus) itself reduces both frequency and amplitude of the HPC theta. They also concluded that the major contribution of the posterior hypothalamic region to the HPC theta was involved in determining its frequency. Similar data were also obtained by Thinschmidt et al. (1995). However, in separate experiments conducted on freely moving rats Thinschmidt et al. (1995) also reported that the electrolytic lesions of the SuM did not eliminate theta induced by stimulation of the brainstem and did not appear to reduce its frequency. These findings may suggest that the experimental model (anesthetized *vs.* freely moving rats) and technique of lesion *per se* (procaine reversible blockade *vs.* electrolytic permanent lesion) may determine the pattern for recovery of the amplitude and frequency of the HPC theta rhythm after PH inactivation. However, McNaughton et al. (1995) demonstrated in freely moving rats that reduction of the frequency of HPC theta produced by PH procaine injection was in fact present, but was less than 50% of the control value. These authors suggested that even with RPO stimulation, as a means of producing the HPC theta, there seems to occur an anesthetic-sensitive contribution to the frequency of theta which is not dependent on the SuM (McNaughton et al. 1995, Thinshmidt et al. 1995).

It appears that subcortical control of the HPC theta frequency and amplitude is more complex then previously thought (McNaughton et al. 1995, Thinshmidt et al. 1995). For example, in separate experiments Oddie et al. (1994) demonstrated that complete inactivation of the

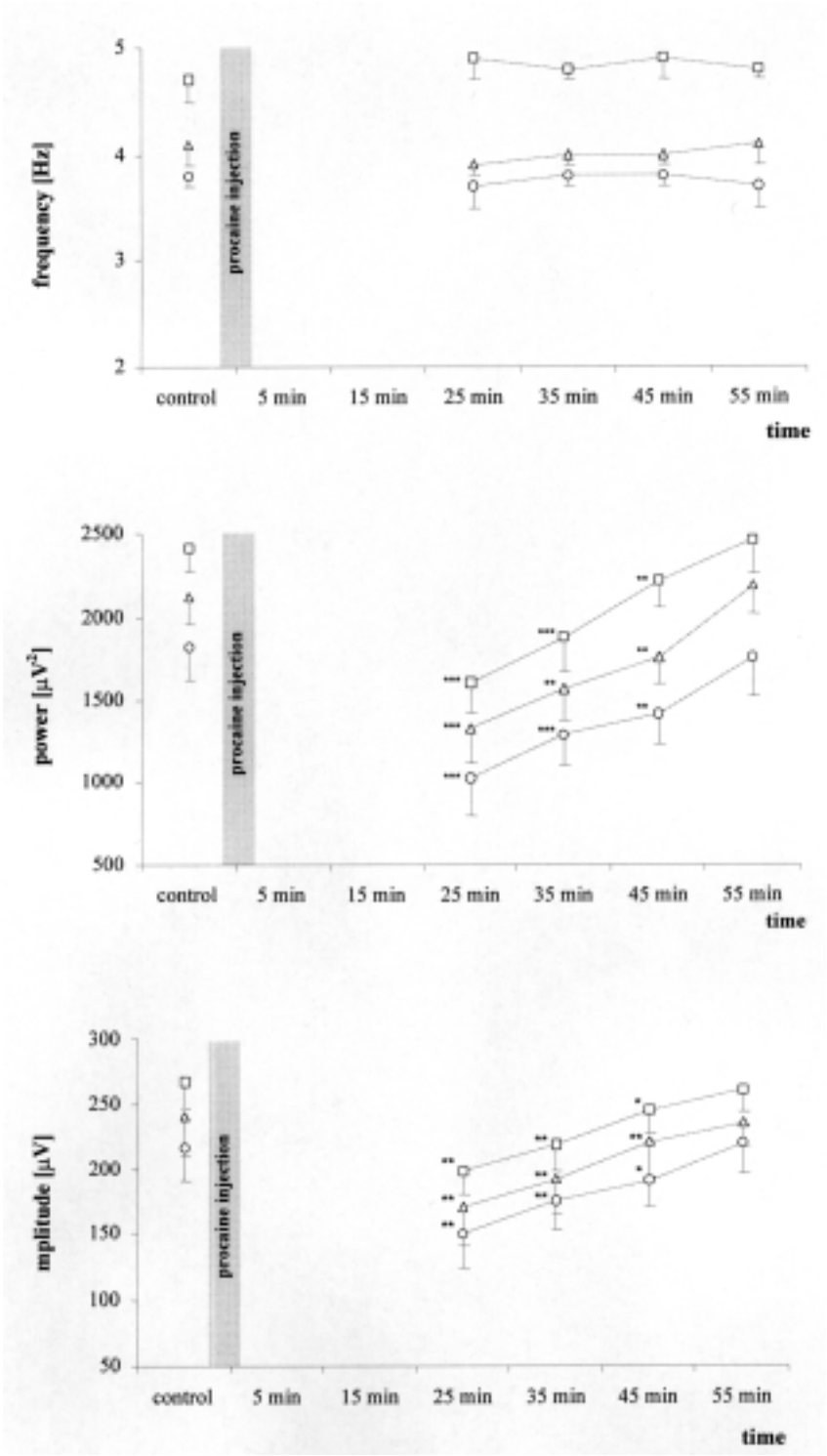


Fig. 4. Graphs displaying the effects of procaine injection into the posterior hypothalamus area on hippocampal theta parameters: frequency (Hz), power ($\mu V^2$), and amplitude ($\mu V$) of spontaneous theta, o; sensory-induced theta, $\Delta$; and electrically-induced theta, □. Preprocaine (control) and postprocaine - (tested at 5, 15, 25, 35, 45, and 55min) - mean (± SE) values of measured theta parameters are shown. Note the total abolishment of the hippocampal theta activity at 5 and 15 min after the intrahypothalamic procaine injections. The recovery of theta was characterized by an unchanged frequency, however, amplitude and power showed a gradual recovery reaching the control levels after 55 min postprocaine (*$P$<0.05; **$P$<0.01; ***$P$<0.001 in comparison to the control level).

PH by the microinfusion of procaine had no effect on frequency of the ongoing theta elicited by the intraseptal microinfusion of carbachol but did markedly decrease its amplitude. In current experiments procaine was injected into the PH region of freely moving cats. In contrast to rats, this species has only one type of the theta rhythm which pharmacologically resembles type 2 theta observed in freely moving and anesthetized rats (Sainsbury 1985, Gołębiewski et al. 1993, Gołębiewski et al. 1999). Using the same technique of the local procaine blockade of the medial septum, we have recently replicated findings obtained earlier in freely moving rats (Kirk and McNaughton 1991, Lawson and Bland 1993, Bland and Oddie 1998, Kirk 1998): theta frequency exhibited a rapid reappearance with shallow slope in contrast to gradual recovery with a steeper slope of theta amplitude and power. Interestingly, the same pattern of recovery was obtained in our present experiments after procaine injection into the PH region (i.e. caudal to the MS). Our results indicate that in a freely moving cats, in contrast to a freely moving or anesthetized rats, not only the MS region but also the PH itself is engaged in modulation of hippocampal theta amplitude. The question arises as to the locus of the neuronal substrate of the ascending synchronizing system responsible for the frequency of the HPC theta encoding. Further experiments using microinjection of procaine more caudally - i.e. directly into the pathways from the NPO to PH are necessary to answer this question.

In summary, the present experiments demonstrated that in freely moving cats the PH region comprised a critical part of the ascending brainstem pathway for production of theta rhythms. In contrast to rats, in freely moving cats ascending inputs from the brainstem to the PH contribute mainly to the amplitude of the HPC theta rhythm. These results imply that there is a difference (in addition to the frequency band and pharmacology) in neuronal substrates responsible for production of theta rhythms between rats and cats. Future work must be carried out to determine the exact location of the area of the ascending synchronizing system responsible for the frequency programming of theta in freely moving cats.

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