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Interactions of Phencyclidine With Hippocampal Circuitry: Evidence for Neuronal Heterogeneity

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WANG, Y., K. PANG, A. E. JACOBSON, R. LESSOR, K. C. RICE AND B. HOFFER. *Interactions of phencyclidine with hippocampal circuitry: Evidence for neuronal heterogeneity.* PHARMACOL BIOCHEM BEHAV **24**(5) 1403–1407, 1986.—The discovery of phencyclidine (PCP) receptors has stimulated the search for specific PCP antagonists. A direct product of this research is metaphit, an irreversible PCP ligand, which has recently been synthesized. In this study we examined the effects of metaphit on the responses of hippocampal neurons to PCP. On the basis of unfiltered action potential durations, hippocampal cells were divided into two groups, complex-spike cells and theta neurons. Local application of PCP caused inhibitions of the spontaneous firing rates of complex-spike cells. Metaphit, locally applied, antagonized approximately 50% of these responses, while the remaining responses were unaffected. In contrast, PCP caused increases in the spontaneous firing rates of theta cells and in almost all cases, these responses to PCP were attenuated by metaphit administration. These effects of metaphit were specific for PCP as the responses to locally applied norepinephrine were not altered by metaphit. The data suggest two mechanisms of action of PCP in the hippocampus. In addition, these mechanisms may be localized in part to different cell types.

PCP Metaphit Hippocampus Complex-spike cell Theta cell

INTENSE research has been directed toward elucidating the actions of phencyclidine (PCP) (1-(1-phenylcyclohexyl)piperidine) because of its widespread abuse. Since PCP also produces abnormal behavior patterns resembling schizophrenia [5, 19, 32], this agent has been used as a model to learn more about the neurochemical basis of psychosis. Much of the controversy concerning the mechanisms of action of PCP is due to interactions of this agent with a number of neurotransmitter systems, including catecholamines [6, 10, 21, 22, 36, 38], acetylcholine [1, 13, 17, 18, 20], and opioids [3, 7, 14, 15, 16, 18, 30, 37, 40, 43, 44]. A major advance in the study of PCP has been the discovery of PCP receptors [41,45]. In addition, a specific PCP receptor affinity ligand has recently been synthesized. Metaphit (1-(1-(3-isothiocyanatophenyl)cyclohexyl)piperidine) is a PCP derivative which irreversibly acylates the PCP receptor [31]. Electrophysiological studies on cerebellar Purkinje cells have shown that the effects of PCP can be totally antagonized by prior application of metaphit [42]. Supporting these results are radioligand binding studies in which metaphit completely and irreversibly blocked the binding of PCP to its receptors in cerebellar preparations. Moreover, metaphit has also been observed to antagonize some of the behavioral effects of PCP in the rat [8].

The hippocampus has been suggested to mediate some of the dissociative anesthetic actions of PCP and other drugs of this class [2, 9, 24]. In area CA1 of the hippocampus, two different types of cells coexist, complex-spike cells and theta cells [11,33]. These two classes of cells have distinct electrophysiological properties and behavioral correlates. Complex-spike neurons generally have low spontaneous firing rates and can fire in multiple discharge bursts of 2–6 spikes of decreasing amplitude. These cells have been reported to increase their spontaneous firing rates when the animal occupies a specific location in space [25, 26, 27]. Theta cells, on the other hand, usually have higher basal firing rates than complex-spike cells and can only discharge in single action potentials. When rhythmical slow activity (RSA or theta rhythm) is present in the hippocampus, such as during walking and paradoxical sleep [39], theta neurons have been noted to increase their spontaneous firing rates [33]. In area CA1 it is generally believed that complex-spike cells are pyramidal cells and theta neurons are interneurons [11]. These two cell types can also be discriminated on the basis of unfiltered action potential duration with complex-spike neurons having much longer durations than theta cells [34]. Using the action potential duration to classify cell types, we have previously shown that local application of

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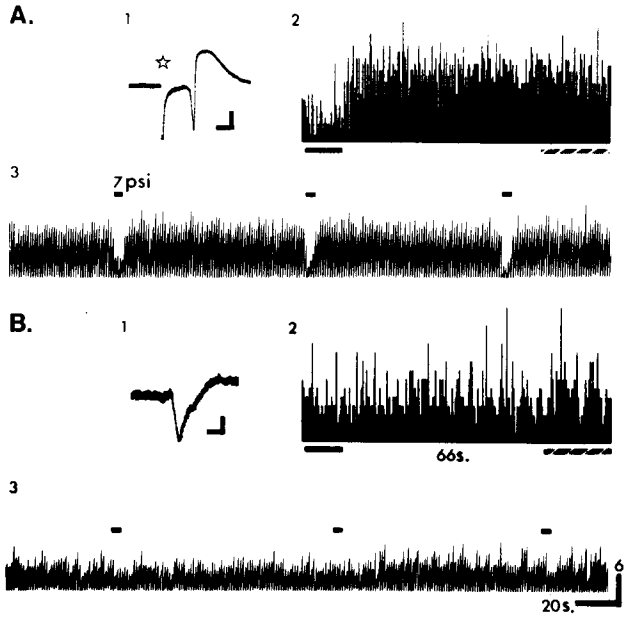

FIG. 1. Metaphit antagonized the effects of PCP on some complex-spike cells. Evoked response (A1) to hippocampal commissural stimulation with the pipette recording from a complex-spike cell (B1) shows the classical triphasic wave confirming that the recording electrode is in area CA1. Histogram (A2) and ratemeter record (A3) shows the effects of local application of PCP (62.5% inhibition calculated using the histogram). Metaphit was administered at 10 psi for 3 minutes. The effects of PCP are markedly reduced fifteen minutes after metaphit application (22.6% inhibition; histogram—B2; ratemeter record—B3). In the histograms the solid bar marks the time period used to calculate the drug response, while the striped bar indicates the control period. In the ratemeter records the numbers indicate the ejection pressure in pounds per square inch (psi) with the width of the bars representing the length of drug application in seconds. The calibration bar in B3 applies to A3 as well. Calibration bars: A1: vertical—1 millivolt; horizontal—5 milliseconds, B1: vertical—0.2 millivolt; horizontal—0.5 milliseconds, B3: vertical—6 spikes per two seconds; horizontal—20 seconds.

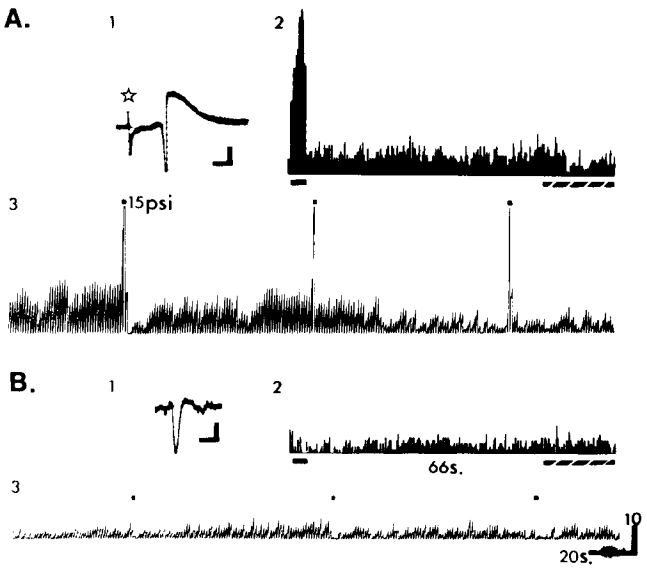

FIG. 2. Metaphit antagonized the actions of PCP in almost all theta neurons. The commissural evoked response (A1) with the recording electrode at the location of a theta cell (B1) verifies that the pipette is in area CA1. Local application of PCP caused a pronounced elevation of the spontaneous firing rate (725% excitation; histogram—A2; ratemeter record—A3). Metaphit application of 8 psi for 5 minutes reduced the effects of PCP twenty minutes after metaphit administration (41.4% inhibition; histogram—B2; ratemeter record—B3). Calibration bars: A1: vertical—1 millivolt; horizontal—5 milliseconds, B1: vertical—0.2 millivolt; horizontal—0.5 milliseconds, B3: vertical—10 spikes per two seconds; horizontal—20 seconds.

PCP inhibited the spontaneous firing rates of complex-spike cells while theta neurons were excited [36].

The hippocampal region has been shown to contain very large amounts of PCP binding sites [30,45]. Recent radioligand binding studies have suggested a heterogeneity of PCP receptors in the hippocampus. Evidence for this has come from binding studies in which metaphit, at doses (10 μM) which completely blocked cerebellar PCP receptors, irreversibly antagonized only about 50% of the hippocampal PCP receptors [31]. In the present study, we sought to determine if metaphit would selectively block the effects of locally applied PCP on the spontaneous discharge of identified complex-spike and theta cells. Were PCP-induced electrophysiological responses of complex-spike cells and theta neurons differentially sensitive to metaphit in a manner that could provide a cellular basis for the binding studies cited above?

METHOD

Male Sprague Dawley rats (280–400 g) were anesthetized with urethane (1.25 g/kg), intubated and placed in a stereotaxic apparatus. The skin overlying the skull was retracted, and the bone and dura above the dorsal hippocampus were removed. Recording electrodes were lowered into the hippocampus at a point 4.0 mm posterior and 2.5 mm lateral to bregma. A stimulation electrode was placed in the contralateral ventral hippocampal commissure 2.0 mm posterior and 1.0 mm lateral to bregma. Body temperature was maintained at 37°C using an electric heating pad.

Three- or four-barrel micropipettes were constructed and used to record extracellular action potentials [29]. The recording barrel contained 5 M NaCl and 50 mM sodium glutamate. The remaining barrels of the pipette were filled with drugs to be locally applied. Glutamate was used in the recording barrel in order to enhance the spontaneous firing rate of the normally slow firing hippocampal neurons. Recordings from 6 cells using electrodes without glutamate showed that the responses of cells to the locally applied drugs were not altered by the presence of glutamate. Area CA1 of the hippocampus was located using the characteristic response to hippocampal commissural stimulation [4] (Fig. 1-A1). Hippocampal cells were categorized as complex-spike cells or theta neurons based on their unfiltered action potential duration ($\leq$0.4 msec for theta cells and $\geq$0.6 msec for complex-spike neurons).

Action potentials were amplified and both filtered and unfiltered waveforms were displayed on a digitizing oscilloscope. This facilitated the determination of unfiltered action potential durations. A window discriminator was used to separate the signal of the cell from background "noise." The spontaneous activity was integrated over two second inter-

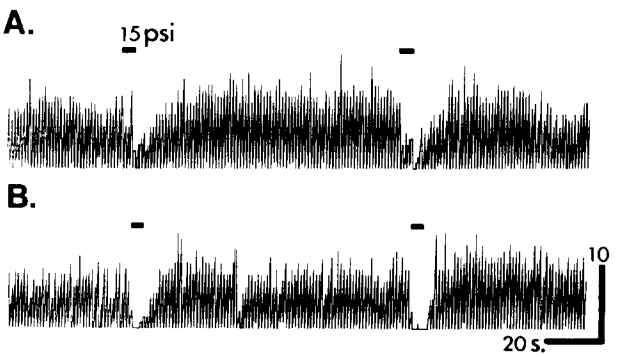

FIG. 3. Some complex-spike neurons were not sensitive to metaphit. Ratemeter record shows an example of a metaphit-insensitive complex-spike cell. PCP caused an inhibition of the spontaneous firing rate before a metaphit application of 5 psi for 4 minutes (A). Seventeen minutes after metaphit administration, the complex-spike cell was still depressed by PCP (B). Calibration bars: vertical—10 spikes per two seconds; horizontal—20 seconds.

vals by a ratemeter and displayed on a strip chart recorder. Besides being recorded on strip chart paper, drug responses were also analyzed using histograms [12] on an Apple IIe computer. With the use of histograms, the responses of cells could be summed during several drug applications. This process was necessary because of the very low firing rate seen in hippocampal cells after metaphit application. In addition, the drug effects were quantitated on the computer by comparing the counts per address during the control and drug response time periods.

All drugs were locally applied by pressure ejection from multibarrel micropipettes. Drug administration using this method has previously been shown to be reproducible and linearly related to pressure and time of drug ejection [29]. The drugs used were as follows: PCP, 10^{-5} M, metaphit, 6×10^{-3} M; norepinephrine, 5×10^{-3} M. All drugs were dissolved in 154 mM NaCl and adjusted to pH 6.5–7.

RESULTS

A total of thirty-three hippocampal CA1 neurons from 19 animals, using 25 pipettes, were suitable for analysis. Twenty-three cells were classified as complex-spike cells with action potential durations ranging from 0.7 to 1.2 msec (Fig. 1-B1). These cells were frequently observed to fire in multiple discharge bursts. The remaining 10 cells had durations of 0.3 to 0.4 msec and were therefore classified as theta neurons (Fig. 2-B1). These theta cells were always observed to discharge in single spikes.

Local application of PCP depressed the spontaneous unit activity of complex-spike cells (Fig. 1-A2 and 1-A3), while the spontaneous firing rates of theta cells were elevated (Fig. 2-A2 and 2-A3). Both types of responses were reversible and reproducible. At very high application pressures PCP was also observed to cause nonspecific effects, which were manifested as decreases in action potential amplitude. These responses were probably due to pressure artifacts or the local anesthetic effects of PCP [28]. In all cases these nonspecific effects were seen at much higher pressures than the effects of PCP on spontaneous firing rates. The responses suspected of resulting from pressure or anesthetic artifacts have not been included in the data analysis.

Metaphit was usually applied at low pressures for long time periods (2–5 minutes). During this application the spontaneous firing rates of both cell types were depressed and metaphit frequently caused a complete cessation of spontaneous activity. It was generally observed that an almost complete inhibition of firing rate by metaphit was necessary before the irreversible blockade of PCP was seen. Cells normally resumed firing 5–20 minutes after metaphit application, but spontaneous firing rates were usually less than before metaphit administration (compare Fig. 1-A3 and 1-B3). After the spontaneous activity had recovered, the effects of metaphit were tested by applying PCP to the cell.

TABLE 1

METAPHIT-INDUCED BLOCKADE OF PCP IN HIPPOCAMPAL CELLS

Cell type:	Number of Cells: Complete Block	Partial Block	No Block
Complex-spike	10	4	9
Theta	9	0	1

Metaphit caused a total blockade of the effects of PCP in 44% of the complex-spike cells (Fig. 1B), 17% of the complex-spike cells had their responses to PCP partially antagonized, and the remaining 39% of complex-spike cells had their PCP-induced responses unaltered (Fig. 3, Table 1). Interestingly, the initial and reversible metaphit-induced depression of complex-spike cell discharge was similar in all three groups of complex-spike neurons. In marked contrast to the diverse effects of metaphit on complex-spike cells, metaphit totally blocked the response to PCP in 9 of 10 theta cells (Fig. 2, Table 1). The remaining theta cell was not affected by metaphit.

The specificity of metaphit was tested by applying norepinephrine, a putative inhibitory hippocampal transmitter, and PCP from the same pipette assembly before and after metaphit application. Metaphit selectively antagonized the effects of PCP without altering the response to norepinephrine in all four complex-spike and theta neurons tested.

As a final control for variable sensitivities to metaphit between animals, the effects of metaphit were tested in the hippocampus and cerebellum of the same animal. A number of hippocampal complex-spike cells were found in which the effects of PCP were not antagonized by metaphit. In the same animal, three cerebellar Purkinje cells were recorded and in all three cells, metaphit completely blocked the actions of PCP.

DISCUSSION

Hippocampal CA1 neurons were divided into two cell types based on their unfiltered action potential duration. Local application of PCP caused a depression of the spontaneous firing rate in complex-spike cells and an elevation of the spontaneous activity of theta neurons. These results confirm previous findings of a differential response of PCP on these two hippocampal cell types [36].

Metaphit, an irreversible PCP ligand [31], caused a total or partial antagonism of the effects of PCP in 61% of the complex-spike cells with 39% remaining unaffected by metaphit. On the other hand, 9 of 10 theta cells had their

PCP-induced responses antagonized by metaphit, while the remaining theta cell was unaltered. High and low affinity binding sites for PCP have been found in biochemical studies [23]. It is unclear from the present study if hippocampal complex-spike cells are associated with two specific PCP receptors, where one receptor is sensitive to metaphit and the other is not, or if PCP is interacting with a specific PCP receptor and a second non-PCP (metaphit-insensitive) receptor.

In addition to the differential sensitivities of metaphit on hippocampal neurons, the heterogeneous effects of metaphit on hippocampal complex-spike neurons are different from the results obtained in the cerebellum. In 100% of the cerebellar Purkinje cells studied, metaphit completely antagonized the effects of PCP [42]. Radioligand binding studies have also found differences in metaphit sensitivity between these two brain areas. In the cerebellum virtually all of the PCP binding sites were irreversibly blocked by metaphit at a concentration of 10 μM. In contrast, radioligand binding studies in the hippocampus showed that only about 50% of the PCP receptors were sensitive to metaphit at 10 μM [31], although a larger proportion of PCP receptors could be inactivated by 60–100 μM metaphit.

The observation that hippocampal complex-spike cells fall into 2 groups based on metaphit sensitivity suggests the possibility that metaphit-sensitive and metaphit-insensitive PCP binding sites may be interacting with different complex-spike neurons. Thus, complex-spike cells, which show similar electrophysiological characteristics [11,33], behavioral correlates [25, 26, 27] and pharmacological profiles [35,36], may be further divided into subclasses based on their sensitivity to metaphit. Alternatively, all complex-spike cells may be interacting with both types of PCP binding sites, but by chance, the pipette tips could be adjacent to regions rich in metaphit-sensitive PCP binding sites or metaphit-insensitive PCP receptors.

The specificity of metaphit was demonstrated by administering PCP and norepinephrine from the same pipette. Metaphit selectively antagonized the effects of PCP while it did not affect the responses to norepinephrine. In addition, the variable effects of metaphit on hippocampal complex-spike cells were not due to differential sensitivities between animals. This was demonstrated in cases where complex-spike cells with metaphit-sensitive and metaphit-insensitive PCP responses were found in the same animal preparations. Moreover, the effects of PCP were also blocked by metaphit in cerebellar Purkinje cells from the same animal in which hippocampal complex-spike cells were not affected by metaphit.

Several important technical considerations were derived from our previous cerebellar work with metaphit [42]. These were of immense value in the present investigation and appear to be important for the successful application of metaphit in electrophysiological studies in general. First, it is necessary to use drug barrel concentrations of 3–6 mM. This range allows irreversible blockade of PCP responses to occur but does not depress neurons for so long a duration that recovery is difficult. Secondly, it is necessary to apply enough metaphit to reversibly eliminate spontaneous discharge for several minutes in order to subsequently show irreversible antagonism of PCP. Finally, metaphit has a "shelf-life" of only several weeks at −20°C. Storage in a dessicant chamber at lower temperatures is needed for more prolonged usage.

In summary, PCP caused excitations of theta neurons and inhibitions of complex-spike cells. Metaphit, an irreversible PCP antagonist, totally or partially antagonized 61% of the complex-spike cells, while 39% were unaffected by metaphit. In contrast, virtually all theta neurons had their PCP-induced responses antagonized by metaphit. These findings indicate a diversity of PCP mechanisms in the hippocampus and suggest that various neuronal subtypes may, in part, underlie this heterogeneity.

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