Pharmacology Biochemistry & Behavior, Vol. 18, pp. 137–139, 1983. Printed in the U.S.A.

Amphetamine Effects on Long Term Potentiation in Dentate Granule Cells

RICHARD L. DELANOY, DEBARA L. TUCCI AND PAUL E. GOLD

Department of Psychology, Gilmer Hall, University of Virginia, Charlottesville, VA 22901

Received 11 March 1982

DELANOY, R. L., D. L. TUCCI AND P. E. GOLD. *Amphetamine effects on long term potentiation in dentate granule cells.* PHARMACOL BIOCHEM BEHAV **18**(1) 137–139, 1983.—Long term potentiation (LTP) has received considerable attention as a neurophysiological analog of memory. Amphetamine, as well as several other catecholamine agonists, can enhance behaviorally-assessed memory storage in a variety of training situations. The present experiments tested the effects of amphetamine on LTP produced by high frequency stimulation of the perforant path in rats. The results indicate that amphetamine can enhance the development of LTP under some but not all testing procedures. Studies of the neurobiological bases by which central and peripheral catecholamines modulate memory storage may be augmented by examinations of catecholamine effects on a specific form of long-lasting change in brain function. Similarly, the ability to manipulate LTP may prove to be an important aid in examinations of neurobiological correlates of this phenomenon.

Long term potentiation Amphetamine Catecholamines Memory modulation Perforant pathway Dentate granule cells

A VARIETY of evidence suggests that peripheral and central adrenergic systems can modulate memory storage processing. For example, peripheral posttraining injections of epinephrine or norepinephrine can enhance or impair later retention performance in an inverted-U dose-related manner [12,13]. Furthermore, under many conditions, retention performance appears to be well-correlated with posttraining release of peripheral epinephrine and norepinephrine and central norepinephrine [10,11]. Thus, the neuronal mechanisms underlying memory storage seem to be particularly sensitive to adrenergic influences.

A major question centers on the neurobiological mechanisms by which catecholamines modulate memory. Attempts to address this problem might be simplified if a specific example of long-term neuronal change could be modulated by aminergic agents. Recently, several laboratories have described long-lasting changes in monosynaptic evoked responses following brief high-frequency stimulation of the afferent pathway. This phenomenon, long-term potentiation (LTP), has been studied extensively for both hippocampal pyramidal cell and dentate granule cell responses to test stimuli administered after high frequency stimulation of their respective afferents (e.g., [2, 4, 6]). Because of the rapid initiation and relative permanence of these responses, LTP may be a useful analog with which to study the neurobiological mechanisms underlying memory [9,18].

In the present experiments, we examined the possibility that potentiation was susceptible to modulation by the catecholamine agonist, amphetamine. Amphetamine facilitates acquisition and retention of a variety of learned responses [5, 7, 15, 16]; like other adrenergic agonists, this drug exhibits a fairly broad inverted-U dose-response relationship with later retention performance [15,16]. Modulation of LTP with amphetamine may therefore facilitate investigations of the mechanisms by which catecholamines modulate memory. By analogy, such findings would also strengthen the view that the mechanisms of LTP are similar to those underlying memory.

Male Sprague-Dawley rats (Zivic-Miller and Flow Laboratories, 300–400 g) were housed individually and were maintained on a 12 hr light-dark cycle (on: 0800–2000). The experimental procedures were performed under Nembutal anesthesia. A twisted bipolar stimulating electrode (250 μm stainless steel) was placed stereotaxically just dorsal to the angular bundle (8.1 mm caudal, 4.4 mm lateral, 2.5 mm ventral from brain surface; horizontal skull). A monopolar recording electrode (250 μm) was positioned just above the dentate gyrus granule cell layer (3.5 mm caudal, 2.0 mm lateral, 2.5 mm ventral). Final electrode placements were adjusted ventrally under physiological control to maximize the evoked response amplitude to a test pulse (20 V, 100 μsec, monophasic square wave, Grass SD-9 stimulator). The evoked responses were amplified (Grass Wide Band AC EEG preamplifier Model 7P5B and DC amplifier 7DAF) and stored on an oscilloscope (Tektronix Model 5111); each population spike measurement was based on a visual average of 10 superimposed traces.

Prior to investigating possible amphetamine effects on long-term potentiation, we examined the effects of amphetamine on the evoked response to test pulses. Two general procedures were employed. Procedure C used constant 0.5 Hz test pulses (20 V) throughout the experiment. After the optimal evoked response was achieved by adjusting electrode placement, 0.5 Hz pulses were administered over a 10 min period. The preinjection measurements were taken at the end of this phase. The animals then received an IP injection of d-amphetamine sulfate (0.3 or 1.0 mg/kg) or saline. The 0.5 Hz test pulses were continued for another 15 min;

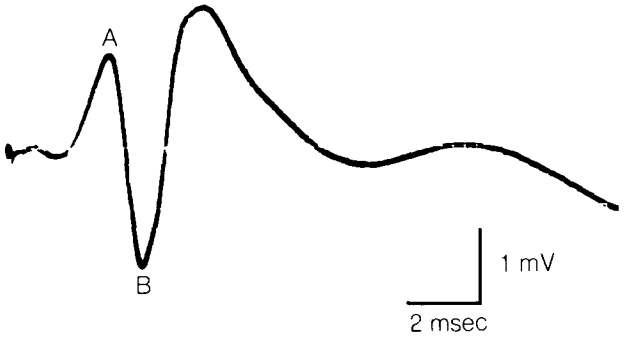

FIG. 1. Oscilloscope tracing of the evoked response. Population spike amplitude was measured from points A to B; potentiation was expressed as percent change from baseline.

post-injection measurements were taken during the final 5 min of this interval.

Procedure I used intermittent period of test pulses (1 pulse every 30 sec) administered only during times of evoked response measurements—i.e., the 5 min interval prior to injection and at 15–20 min after injection (saline or amphetamine, 0.3 mg/kg; IP). Furthermore, the test voltage was set for individual animals to 110% of the threshold voltage necessary to elicit a maximal population spike amplitude. With these procedures, test pulse intensities ranged from 16–33 V; these intensities did not differ across groups.

Population spike measurements were based on percent change in amplitude (points A to B on Fig. 1) (Before-After/Before × 100) from the preinjection values.

We also examined procedural and drug interactions with long-term potentiation in these experiments. After completing the measurements above, animals received high-frequency stimulation (20 V, 65 μsec, 100 Hz for 1 sec in Procedure C; test pulse voltage, 100 μsec, 100 Hz for 1 sec in Procedure I). Population spike ampltiude was then measured (3 or 10 min after the high-frequency train in Procedure C or I, respectively) and the percent change from the value obtained just prior to high-frequency stimulation was used as the dependent variable.

As shown in Fig. 2, prior to potentiation, the percent changes in population spike amplitude differed substantially depending on the specific test procedure employed. Using constant 0.5 Hz test pulses (Procedure C), the saline group exhibited a small but significant decrease in population spike amplitude (sign tests, $p<0.001$). Conversely, using intermittent 1 pulse/30 sec test probes (Procedure I), the amplitude of the population spike increased significantly (sign test, $p<0.005$). Notably, amphetamine injections resulted in significant attenuation of both effects although the direction of change was opposite in each case.

The results obtained by comparing the percent changes in population spike amplitude before and after high frequency stimulation are shown in Fig. 3. With both procedures, the saline animals exhibited small but significant increases in population spike amplitude after high frequency stimulation (sign test, p's<0.01). Under Procedure C, no significant differences were evident in the extent of the increase in the population spike after injection of saline or amphetamine. However, with Procedure I, the amphetamine-injected group exhibited a significantly ($p>0.001$) larger increase in amplitude. These results represent an interaction with the high-frequency stimulation train. Control animals (N=10) which

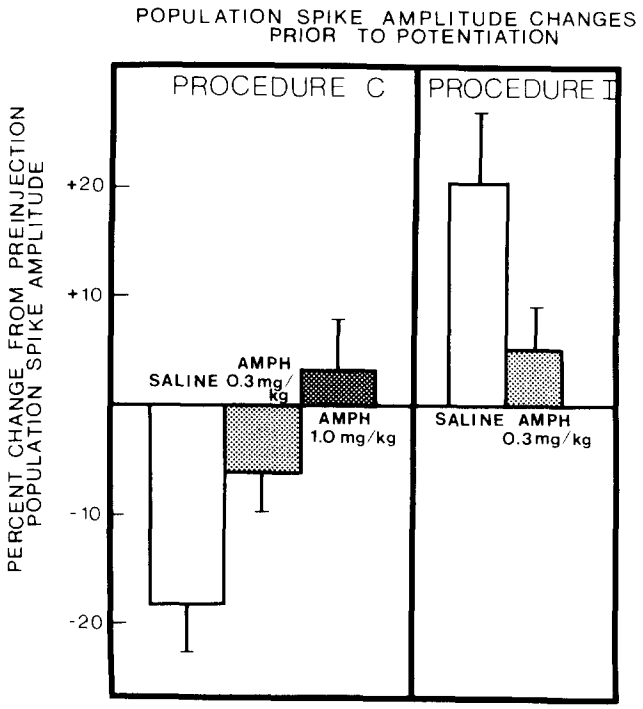

FIG. 2. Percent change (mean±s.e.m.) in population spike amplitude following injection but prior to potentiating stimulation. Note that the amplitude decreased with constant 0.5 Hz stimulation (Procedure C) but increased when the pulses were given intermittently during 5 min test periods (Procedure I). Amphetamine injections attenuated both of these effects.

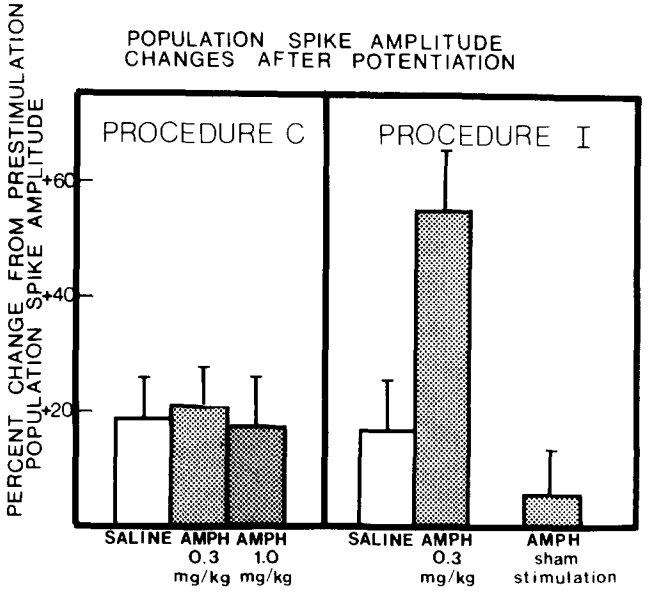

FIG. 3. Percent increase (mean±s.e.m.) in population spike amplitude after a high-frequency train. Amphetamine did not significantly alter the extent of potentiation seen under Procedure C. However, the drug significantly enhanced the extent of potentiation observed with Procedure I. The control group on the far right received amphetamine but did not receive a high frequency stimulation train.

did not receive the potentiating train showed no significant change over this time interval. Thus, under Procedure I, amphetamine significantly augmented the development of the increase in population spike amplitude.

The results of this experiment indicate that population spike amplitude is quite sensitive to the test stimulation schedule. Continued 0.5 Hz stimulation results in attenuation of the population spike amplitude; this response has been observed previously [14,19]. In contrast, intermittent application of 1 pulse every 30 sec results in augmentation of the population spike amplitude. Furthermore, both effects are absent in animals pretreated with amphetamine, an unexpected result for which we have no explanation.

Our findings also support the view that, with some procedures (e.g., Procedure I) amphetamine can modulate long-term potentiation. Thus, the present findings suggest that it may be possible to examine catecholamine modulation of a specific form of neuronal plasticity in a manner analogous to that used in experiments which study modulation of behaviorally-assessed memory. However, these initial findings also impose an important cautionary note regarding the attention one must pay to the specific methods used to examine LTP and its modulation. The ability to modulate LTP will be an important tool in examinations of the neural mechanisms underlying LTP. Currently, there is evidence for both neurochemical and anatomical changes after LTP [1, 3, 8, 17]. The interpretation of such correlational studies suffers from an inability to manipulate LTP or the correlate. The promise of a set of agents and procedures with which to modulate LTP will enhance the strength of correlational studies aimed at determining the neural bases of LTP.

REFERENCES

1. Baudry, M. and G. Lynch. Hypothesis regarding the cellular mechanisms responsible for long-term synaptic potentiation in the hippocampus. *Exp Neurol* **68:** 202–204, 1980.
2. Bliss, T. and T. Lomo. Long-lasting potentiation of synaptic transmission in the dentate area of the anesthetized rabbit following stimulation of the perforant path. *J Physiol (Lond)* **232:** 331–356, 1973.
3. Browning, M., T. Dunwiddle, W. Bennett, W. Gispen and G. Lynch. Synaptic phosphoproteins: Specific changes after repetitive stimulation of the hippocampal slice. *Science* **203:** 60–62, 1979.
4. Deadwyler, S. A., V. Gribkoff, C. W. Cotman and G. Lynch. Long lasting changes in the spontaneous activity of hippocampal neurons following stimulation of the entorhinal cortex. *Brain Res Bull* **1:** 1–7, 1976.
5. Doty, B. A. and L. A. Doty. Facilitative effects of amphetamine on avoidance conditioning in relation to age and problem difficulty. *Psychopharmacologia* **9:** 234–241, 1966.
6. Douglas, R. and G. Goddard. Long-term potentiation of the perforant path granule cell synapses in the rat hippocampus. *Brain Res* **86:** 205–215, 1974.
7. Evangelista, A. M. and I. Izquierdo. The effect of pre- and posttrial amphetamine injections on avodiance responses of rat. *Psychopharmacologia* **20:** 42–47, 1971.
8. Fifkova, E. and A. van Harreveld. Long-lasting morphological changes in dendritic spines of dentate granular cells following stimulation of the entorhinal area. *J Neurocyto* **6:** 211–230, 1977.
9. Goddard, G. V. Component properties of the memory machine: *Hebb revisited. In: The Nature of Thought: Essays in Honour of D. O. Hebb,* edited by P. W. Jusczyk and R. M. Klein. Hillsdale, NJ: Lawrence Erlbaum Associates, 1980.
10. Gold, P. E., R. McCarty and D. B. Sternberg. Peripheral catecholamines and memory modulation. In: *Neuronal Plasticity and Memory Formation,* edited by C. Ajmone Marsan and H. Matthies. New York: Raven Press, 1982. pp. 327–338.
11. Gold, P. E. and J. L. McGaugh. Endogenous modulators of memory storage processes. In: *Clinical Psychoneuroendocrinology in Reproduction,* edited by L. Carenza, P. Pancherra and L. Zichella. New york: Academic Press, 1978, pp. 25–46.
12. Gold, P. E. and R. B. van Buskirk. Facilitation of time-dependent memory processes with posttrial epineprhine injections. *Behav Biol* **13:** 145–153, 1975.
13. Gold, P. E. and R. B. van Buskirk. Effect of posttrial hormone injections on memory processes. *Horm Behav* **7:** 509–517, 1976.
14. Harris, E. W., S. S. Lasher and O. Steward. Analysis of the habituation-like changes in transmission in the temporodentate pathway of the rat. *Brain Res* **162:** 21–32, 1979.
15. Haycock, J. W., R. B. van Buskirk and P. E. Gold. Effects on retention with posttraining amphetamine injections in mice: Interaction with pretraining experiences. *Psychopharmacology (Berlin)* **54:** 21–24, 1977.
16. Krivanek, J. A. and J. L. McGaugh. Facilitating effects of pre- and posttrial amphetamine administration on discrimination learning in mice. *Agents Actions* **1:** 36–42, 1969.
17. Lee, K. S., F. Schottler, M. Oliver and G. Lynch. Brief bursts of high-frequency stimulation produce two types of structural change in rat hippocampus. *J Neurophysiol* **44:** 247–258, 1980.
18. Lynch, G., M. Browning, and W. F. Bennett. Biochemical and physiological studies of long-term synaptic plasticity. *Fed Proc* **38:** 2117–2122, 1979.
19. Teyler, T. J. and B. E. Alger. Monosynaptic habituation in the vertebrate forebrain: The dentate gyrus examined in vitro. *Brain Res* **115:** 413–425, 1976.