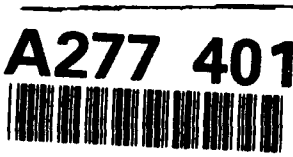
AD-A277 401



MENTATION PAGE

Approved for public release; distribution unlimited.

Form Approved
OMB No. 0704-0188

2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
31-DEC-93	~~INTERIM~~ ANNUAL 01-DEC-92 to 30-NOV-93

4. TITLE AND SUBTITLE
LONG-TERM POTENTIATION: ROLE OF HIPPOCAMPAL ADRENAL STEROID TYPE I & TYPE II RECEPTORS IN THE DIURNAL RHYTHM & THE IMPACT OF STRESS

5. FUNDING NUMBERS
F4920-93-1-0048
61102F
2312
BS

6. AUTHOR(S)
Dr. Bruce S. McEwen
Dr. Ana Maria Magarinos
Dr. Constantine Pavlides

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Rockefeller University
1230 York Avenue
New York, N.Y. 10021-6399

8. PERFORMING ORGANIZATION REPORT NUMBER
AFOSR-TR- 94 0111
AIR-I

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
AFOSR/NL
Building 410
Bolling AFB DC 20332-6448
Dr Haddad

48

94-09359

11. SUPPLEMENTARY NOTES

DTIC ELECTE MAR 28 1994 S B D

12a. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution unlimited.

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 words)

Adrenal steroid secretion during the sleep-waking cycle coordinates brain function and cognitive activity with metabolism and other basic body functions, and it also mediates the adaptive and restorative effects of stress. Jet lag represents a disordering of diurnal adrenocortical activity as well as a form of stress. We are studying the actions of adrenal steroids in hippocampus of living animals on long-term potentiation (LTP) and long-term depression (LTD), two forms of neurophysiological plasticity related to learning, and we are searching for some of the molecular and structural changes associated with it. Adrenal steroids biphasically modulate LTP via intracellular Type I and Type II receptors, and these effects are seen in both anaesthetized and awake-freely moving animals. LTP that is increased by Type I receptor activation lasts for at least 24h and is greater than in adrenalectomized rats. LTP is suppressed by Type II receptor activation, and LTD can also result from this activation. Current studies are investigating immediate early gene (mainly JUN) induction by steroids and LTP and LTD, and we also plan to look for changes in structural gene products such as GAP-43 that may be indicative of synaptogenesis.

94 3 25 035

14. SUBJECT TERMS
Hippocampus, adrenal steroids, receptors, long-term potentiation, learning, jet lag

15. NUMBER OF PAGES
4

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	SAR

Overview

Our work to date has focussed on electrophysiological measurements of long-term potentiation (**LTP**) in living animals in an attempt to establish the actions of adrenal steroids acting via Type I and Type II receptors. These investigations have revealed steroid potentiation via Type I receptors of LTP, as well as steroid potentiation via Type II receptors of long-term depression (**LTD**). During the past 6 months, we have moved from studies of anaesthetized animals to awake, freely-moving animals and have found comparable effects that strengthen the possible relevance to normal behavior. Currently we are beginning to determine effects of LTP and LTD on the expression of immediate early genes and of structural protein genes in order to assess the cellular changes that may accompany electrical changes and the actions of adrenal steroids.

Biphasic Effects of Adrenal Steroids on LTP In Vivo in Rats

Studies were performed in vivo on the dentate gyrus of anaesthetized rats to investigate the possible involvement of Type I and Type II adrenal steroid receptors in the mediation of reported adrenal steroid effects on long-term potentiation (LTP), through the use of specific Type I and Type II receptor agonists and antagonists. In adrenalectomized (ADX) rats, administration of aldosterone (ALDO), a specific Type I agonist, produced a marked enhancement in LTP, in comparison to either the ADX or sham operated controls. Administration of RU-28318, a Type I antagonist, which by itself had minimal effects, blocked the ALDO enhancement. In contrast, administration of the specific Type II agonist, RU 28362, produced a marked decrement in LTP induction. The RU-28362 effect was blocked by a prior injection of the Type II antagonist, RU-38486. Neither ADX nor administration of any of the steroid agonists or antagonists had noticeable effects on neuronal excitability (as determined both by the field potentials or using paired-pulse stimulation), nor on post-tetanic potentiation. These findings are consistent with other studies that have shown a biphasic effect of increasing levels of corticosterone on LTP or primed burst potentiation. Taken together, these various studies suggest that Type I receptors, with a high affinity for corticosterone, and Type II receptors, having a lower affinity for corticosterone, form a two-level recognition system to modulate induced synaptic plasticity in opposite directions in dentate gyrus and possibly also in Ammons horn.

Extension of Biphasic Effects to Awake, Freely-Behaving Animals

In the second study, we tested the ability of Type I receptors to prolong LTP, using awake, freely-behaving animals. Adrenalectomized (ADX) rats were implanted bilaterally with chronic recording electrodes in the dentate gyrus granule cell layer and stimulating electrodes in the medial perforant pathway. Following a 2d recovery period, field potentials were recorded bilaterally in freely behaving animals. Following baseline recording, the animals were administered aldosterone/vehicle (40ug/kg, s.c.) and high-frequency stimulation was applied to one hemisphere one hour later. Recording continued for one hour and again at 3h and at 24h. In comparison to controls, aldosterone produced an enhancement in LTP, as had been demonstrated previously. More importantly, while LTP in the control animals decayed to baseline levels within 3h, in the animals receiving aldosterone the field potentials were still enhanced (over baseline) not only at the 3h intervals but also at the 24h interval. Data on the ALDO effect to increase LTP and its duration is presented in **Figure 1**. In a few animals, recording was also performed at 72h and the animals injected with aldosterone still showed significant LTP. These findings provide the first hints that the enhancement of LTP by Type I receptor activation may have beneficial effects on behavioral processes dependent on LTP-like changes. We are presently conducting collaborative experiments with colleagues at the Hunter

College Psychology Department to assess the effects of aldosterone on radial maze learning and performance in ADX rats.

Adrenal steroids and long-term depression in anaesthetized rats

The effects of Type II adrenal steroid receptors on synaptic plasticity were investigated in the dentate gyrus of the hippocampus. Experiments were performed in either adrenalectomized (ADX) or intact (non-ADX), anesthetized rats. High-frequency stimulation was applied to the medial perforant pathway at three different frequencies, 100Hz, 200Hz and 400Hz, either pre-, post- or pre- and post-administration of the Type II adrenal steroid agonist RU-28362. High-frequency stimulation, prior to RU-28362 administration, produced a frequency dependent long-term potentiation (LTP) of the population spike, with 100Hz showing no LTP while 400Hz showing maximum potentiation. Conversely, following administration of RU-28362, high-frequency stimulation produced an immediate, long-term depression (LTD) of the population spike. This effect was also frequency dependent although opposite to the LTP effect. That is, 400Hz was the least effective frequency for inducing LTD while 100Hz was the most effective. The effectiveness of HFS in inducing LTD was not influenced by previous induction of LTP. In other words, LTD could be induced after LTP had been established. This could be seen as a form of depotentiation. As we had reported earlier, induction of LTP was substantially suppressed by RU-28362. However, in a number of experiments LTP could still be induced after RU-28362 administration, even after LTD had been established. In these cases, however, stimulation at the higher frequencies was necessary. These results demonstrate that glucocorticoids can have potent suppressive effects on hippocampal plasticity. The LTD effect could possibly help explain the behavioral deficits in aspects of cognitive function seen with elevations in glucocorticoids.

LTP, adrenal steroids and immediate early gene expression

Neural activation is known frequently to induce the expression of immediate early genes (IEG). We are conducting an immunohistological study using specific antibodies to detect cFos, Jun B, c Jun and Jun D. after the induction of hippocampal LTP and LTD. One hour after the stimulation of the perforant path of adrenalectomized (ADX) rats, cFos immunoreactivity was not induced. Instead, Jun B, cJun and Jun D immunoreactivity was detected not only in the dentate gyrus of the hippocampus, but also in areas CA1, CA2 and CA3. The IEG immunoreactivity was also present throughout the hippocampus of rats pretreated with Aldosterone and RU 28362, type I and type II adrenal receptors agonists, respectively. As noted above, aldosterone seems to have a role in the maintenance of LTP, while RU 28362 has an inhibitory effect. We are presently performing the quantitative analysis to find out whether steroid treatment modifies IEG expression. These studies will be extended to measure IEG mRNA levels, which can be quantified on an individual cell basis, unlike the immunocytochemical labelling. We also plant to look at the expression of the structural protein gene, GAP-43, as a possible measure of synaptic sprouting.

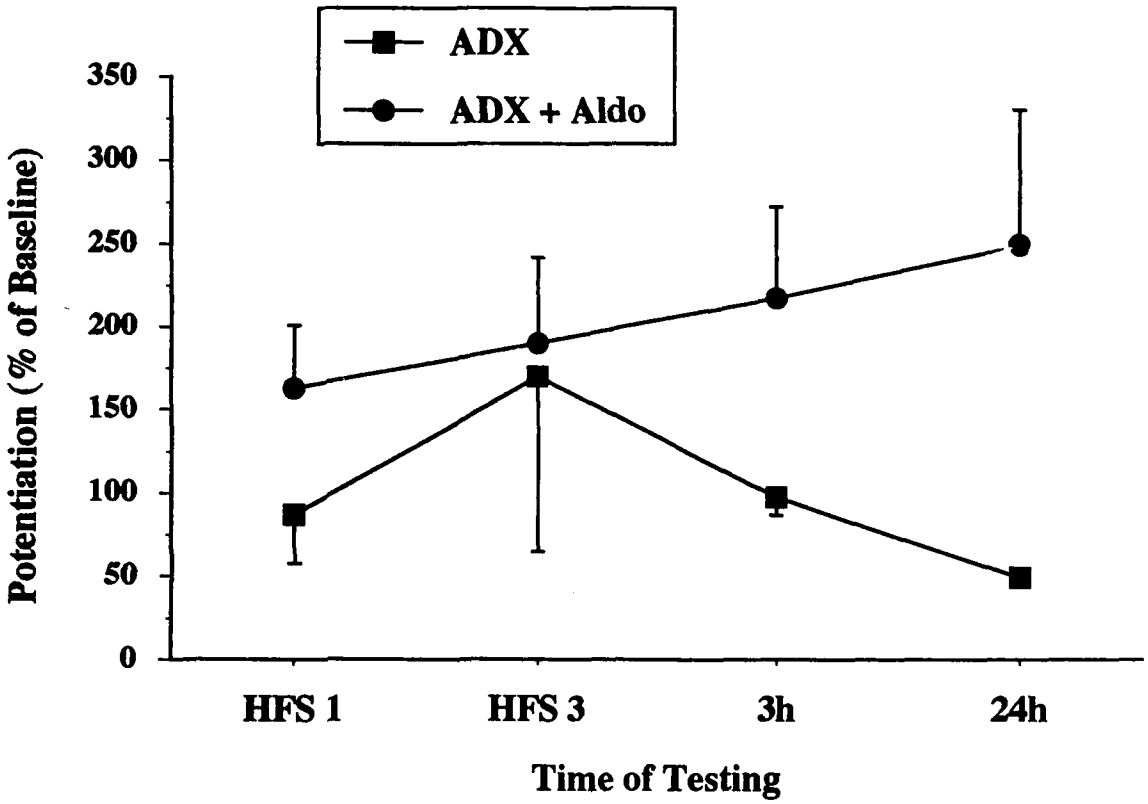


Fig. 1. Effects of aldosterone administration on LTP in the dentate gyrus. Following baseline recording, a set of three high-frequency stimuli (HFS) were applied and changes in the size of the population spike were determined, in comparison to baseline. The first HFS produced significantly higher LTP in the ADX+aldosterone in comparison to ADX+vehicle animals. By the third HFS, comparable LTP was obtained for both groups. However, while LTP decayed by 3 hours in the ADX+vehicle group, it persisted in the ADX+aldosterone animals not only at three but also at 24h following HFS.