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THE EFFECTS OF HYPERGRAVIC FIELDS ON NEURAL SIGNALLING IN THE HIPPOCAMPUS

CONTENTS

A. Summary 1
B. Research Plan 2
  1. Introduction 2
  2. Background 2
  3. Specific questions 10
  4. Rationale and experimental procedures 10
  5. Data interpretation 14
C. Significance 15
D. References 16
E. Progress report (1985-1987) 19
  1. Hippocampal studies 19
  2. Vestibular and auditory system 20
  3. Thermoregulatory system 21
F. Biographical sketch of PIs 24
G. Budget 49
H. Budget justification 50
I. Available facilities 50
K. Appendix A Effects of pH and temperature on hippocampal population spikes A1
  Appendix B Temperature effects on evoked potentials of hippocampal slices from noncold-acclimated, cold-acclimated and hibernating hamsters . . . B1
  Appendix C Simulation of the effects of temperature on hippocampal neurons C1

A. SUMMARY

Experiments in this grant renewal have as a general long-term objective the elucidation of the effects of altered gravitational fields on neural regulatory mechanisms. More specifically, they focus on the effects of the neurotransmitter serotonin in the hippocampus. We have selected the hippocampus for study because rats flown on Spacelab-3 showed an increased number of serotonergic receptors in this region of the central nervous system after 7 days in space. A more recent study has shown that rats exposed to a hypergravic field of 2.0 G for 7 days show a decreased number of receptors. We propose to examine population and single cell electrical activity associated with these receptors using the *in vitro* hippocampal slice preparation. After development of experimental techniques, we will utilize centrifuges at the Chronic Acceleration Research Laboratory to expose animals to a hypergravic environment. Receptor numbers change relatively slowly so that altered activity can be studied in rats at 1 G following prolonged exposure to an increased gravitational field. This study will provide information on the modulation of signaling in the hippocampus by serotonin before and after exposure to hypergravic fields.

B. RESEARCH PLAN

1. Introduction

The goal of this grant is to study the effect of hypergravic fields on the modulation of hippocampal electrical activity by serotonin (5-HT). The proposed study represents a shift from our previous NASA grants covering three diverse areas in neurobiology (thermoregulation, vestibular and auditory brainstem evoked responses, and the hippocampus) to consideration of only one of these areas, the hippocampus. (Thus no experiments are proposed in the areas of thermoregulation or brainstem evoked responses, and the only continuing work in these areas will be to edit manuscripts covering work supported by our previous NASA grants.)

To place our proposed hippocampal experiments in context with relevant Spacelab-3 experiments and hypergravic experiments, two experiments on receptor changes in animals exposed to altered gravitational fields are first described. Our experiments build on these structural/biochemical observations and extend investigations to related electrical activity at 1 G and in hypergravic fields. The background continues with a review of past studies at 1G related to effects of serotonin on hippocampal electrical activity (i.e., population spikes, intracellular potentials).

2. Background

Increased number of serotonin receptors in rats aboard Spacelab-3. Miller et al. (1985) determined the number of receptors for several neurotransmitters in selected brain areas in animals after their return from space. Six male Sprague-Dawley rats were exposed to microgravity for 7 days aboard Spacelab-3. Twelve to 14 hours after return to 1 G, the rats were sacrificed and brain tissue was removed, frozen, and subsequently assayed for receptor number and affinity. Serotonin binding in the hippocampus of these rats was 49% greater compared to that from a control group maintained at 1 G (120 $\pm$ 5 in the flight group vs 81 + 11 fmoles/mg protein in the control group; $p<0.05$). The binding of serotonin in the lateral frontal cortex was unaffected by exposure to microgravity. Moreover, in the initial survey of other neural transmitters in different regions of the brain, changes in binding were not generally observed. Thus, the hippocampus was a region of the central nervous system that showed cellular changes attributable to exposure to a microgravity environment.

Decreased number of serotonin receptors in rats exposed to 2 G. The experiments reported by Miller et al. (1985), while demonstrating an effect at microgravity, left open the question of whether hypergravic fields had any effect on serotonergic receptors. Very recently, Miller et al. (1986) reported at a Tokyo conference the results of studies in which they measured serotonergic binding in rats afer exposure to a 2 G field for seven days. Twelve rats were exposed to chronic accleration on an 18 foot diameter centrifuge and then binding was determined using the ligand [^{3}H]-5-hydroxytryptamine. A 27% decrease in receptor number was observed in rats exposed to the 2 G field.

These studies by Miller et al. (1985, 1986) show that hypergravic and microgravity environments have opposite effects on hippocampal 5-HT receptor number. In both environments the effects appear to be terminal field specific, since changes in serotonin binding were not observed in the lateral frontal cortex. Although receptor changes have been described in both microgravic and hypergravic environments, there are no parallel electrophysiological studies of serotonergic effects on neural activity. It is therefore unknown if the changes in receptor number alter the functional characteristics of the neurons. It is this issue that this grant will address.

Neurochemistry and multiple serotonergic receptors. The population of 5-HT receptors in rat cerbral cortex and hippocampus can be divided into two types denoted 5-HT_1 and 5-HT_2 receptors (Peroutka and Synder,1979; Creese and Synder, 1978), and recent studies (Pedigo et al.,1981) suggested a further subdivision of 5-HT_1 receptors into two subtypes, 5-HT_{1A} and 5-HT_{1B}, a classification based on the biphasic inhibition of spiroperidol (or spiperone) on serotonin binding. Binding inhibited by low concentrations of spiroperidol defined the 5-HT_{1A} site, whereas the component that was unaffected by low concentrations of spiroperidol defined the 5-HT_{1B} site. Beck et al. (1985), De Vivo and Maavani (1986), Mauk et al. (1985), and Andrade and Nicoll (1985) have identified serotonergic receptors found on hippocampal pyramidal cells as 5-HT_{1A} receptors. This grant covers effects of binding of serotonin to 5-HT_{1A} receptors.

The effect of serotonin on population spikes. We plan experiments on changes in hippocampal electrical activity and the effects of serotonin using both extracellular and intracellular procedures. Extracellular methods (described in this section) allow assessment of the system as a whole, while intracellular methods allow a closer look at the cellular mechanisms underlying serotonin's effects. The results of the proposed experiments would provide baseline data for future studies using rats exposed to microgravic environments.

Several studies have shown that serotonin decreases the amplitude of a population response of hippocampal neurons (Beck et al., 1985; Beck and Goldfarb, 1985; Rowan and Anwyl, 1985; Mauk et al., 1985). (The decrease in amplitude is often preceded by a small transient increase.) When Schaffer collaterals, axons forming a fiber tract in the hippocampus, are stimulated, pyramidal cells are excited and generate a synchronous burst of action potentials. The electrical fields of the action potentials add to produce an easily detected potential, a population spike. In experiments where serotonin was superfused over the tissue and then washed out with buffer, Beck and Goldfarb (1985) showed that serotonin reversibly decreased the amplitude of the population spike. The magnitude of this decrease was concentration dependent and was greater on submaximal than on maximal population spikes. The EC_{50} for serotonin was 3.2 μM. Repeated applications of a maximal dose of serotonin did not produce tachyphylaxis. Beck and Goldfarb (1985) concluded that the reversibility, reproducibility, and concentration dependence of the serotonergic response in the rat hippocampal slice preparation make the hippocampus useful for pharmacological experiments on the modulatory role of serotonin.

Recent pharmacological studies involving measurement of hippocampal population spike amplitudes have indeed further characterized serotonergic mechanisms. Thus Beck et al. (1985) were among the first to suggest that the decrease in population spike amplitude involved a 5-HT_{1A} receptor because spiperone at 100 nM shifted serotonin and 5-carboxyamidotryptamine concentration-response curves to the right. Mauk et al. (1985) also observed that 5-HT_{1A} agonists depressed the amplitude of population spikes. Slices from Wistar rats were placed in a submersion chamber, superfused with a continuous flow of modified Krebs Ringer and maintained at 33-34°C. Evoked potentials following stimulation of Schaffer collaterals were recorded in the pyramidal layer. When field potentials had been stable for a least 20 min, dose-response curves were obtained by applying increasing concentrations of serotonergic agonists every 30 min. Application of the agonists buspirone, TVX-Q 7821, and DPAT produced a dose dependent reduction of the population spike. Effective concentrations were 25-100 μM.

The method of measuring spike amplitudes allows assessment of the response of a population of pyramidal cells to a variety of compounds. Beck and Goldfarb (1985) describe in detail superfusion procedures for obtaining concentration-response curves. They then applied these procedures (Beck et al., 1985) to show shifts in the concentration-response curves for a variety of ligands (serotonin alone and in the presence of 100nM spiperone or 100nM ketanserin). This procedure should prove sufficiently sensitive to detect an altered response to serotonin in animals exposed to hypergravic environments if the decrease in amplitude of the population spike is similar in magnitude to the 27% decrease in receptor number found in binding studies.

The effect of temperature, pH, and stimulus frequency on population spikes. Bath temperature has a marked effect on population spike parameters (amplitude and width) and pH a much smaller effect (Hooper et al., 1985; Thomas et al., 1986; appendix A). In experiments designed to detect changes in the physiological response to serotonin in animals exposed to a hypergravic environment, these factors must be controlled or monitored.

Experiments on hippocampal slices have been done at various bath temperatures -- some investigators maintain bath temperature between 32 and 35°C, others between 29 and 30°C. So that results can be more readily compared with other studies, one approach is to perform critical experiments over a range of temperatures.

Stimulus frequency can also modify the height of population spikes and the activation of intracellular events. Long-term potentiation (LTP) is a widely studied model of activity-dependent change in synaptic efficacy that has attracted wide interest as the basis for information storage in the mammalian brain. LTP is induced by increasing stimulus frequency above about 3 shocks/sec, and is reliably induced by frequencies greater than 10 Hz. Its onset occurs in seconds and can last for weeks in the intact animal. During LTP, the amplitude of a population spike is greatly enhanced. The role of N-methyl-D-aspartate (NMDA) receptors in inducing hippocampal LTP has been recently established by a variety of

studies in different laboratories (Collingridge and Bliss, 1987; Collingridge et al., 1983; Harris et al., 1984; Peet et al., 1986). Mg^{++} blocks NMDA-gated channels in a voltage dependent manner. When the cell is at its resting potential, many of the channels are blocked, and when the cell is depolarized Mg^{++} blockade is alleviated. Calcium then enters the cell via these NMDA channels and triggers the sequence of events that culminate in LTP.

Stimulus frequency must be carefully controlled in studies where population spike amplitude is measured because high but not low frequency stimulation induces LTP. As an added complication, Bliss et al. (1983) found reduction of LTP in the dentate gyrus of the rat following depletion of serotonin, and no effect following depletion of norepinephrine (NE). They used an in vivo preparation and it was not possible to determine whether the effect on LTP was due to depletion in the hippocampus or depletion of other brain areas. Stanton and Sarvey (1985) used the in vitro slice preparation and found that while NE reduced the occurrence of LTP in the dentate, serotonin did not prevent LTP in the hippocampus in either CA1 or the dentate. Further experiments are required to fully clarify the involvement of serotonin in LTP. On one hand, by using high frequency stimulation to evoke LTP, the involvement of serotonin on LTP can be further studied. On the other hand, by keeping the stimulus frequency less than 1 Hz, LTP is not evoked (NMDA channels are not opened) and possible effects of serotonin on LTP are avoided.

The effect of serotonin on intracellular potentials. There are many recent electrophysiological studies of the hippocampus using intracellular rather than extracellular techniques. In many cases intracellular techniques have an advantage; namely, that intermediate steps in the overall response of the system can be monitored and effects on particular cellular mechanisms can be tested. For example, transmembrane potential and membrane resistance provide information on combined receptor and channel activity. We propose to measure both potentials and resistance in rats and hamsters exposed to 2G fields. In addition, factors such as the potential role of GTP/GDP binding proteins (G proteins), intracellular messengers, and various receptor types can be investigated using intracellular techniques.

Using intracellular techniques, Andrade and Nicoll (1985) provided further electrophysiological evidence, in agreement with previous pharmacological studies, that serotonin binding appears to be predominantly of the $5\text{-}HT_1$ type. Recordings were obtained from pyramidal cells of the CA1 region. Serotonin administered either in the bath (300nM -20μM) or by microiontophoresis elicited a dose-dependent hyperpolarization (that could be as large as 20 mV) accompanied by reduced input resistance. No depolarizing responses to serotonin were ever observed. Administration of the selective $5\text{-}HT_{1A}$ agonist 8-OHDPAT (200 nM - 4μM) also hyperpolarized these cells. The classical serotonin antagonists cyproheptadine and cinanserin were relatively ineffective in antagonizing responses to iontophoretically applied serotonin, with IC50s of 50 μM and 100 μM respectively. The selective $5\text{-}HT_2$ antagonist ketanserin did not reduce serotonin responses in concentrations up to 200 μM. The ergot methysergide elicited a small hyperpolarization and

reduced the serotonin response with an IC50 of 30 μM. Similarly, the non-benzodiazepine anxiolytic, buspirone, which has been reported to be potent and selective at displacing serotonin from hippocampal membranes, also elicited a small hyperpolarization (1-4 mV) and reduced serotonin responses (IC50 = 3μM). Thus, a variety of intracellular results are consistent with the proposal that $5\text{-}HT_1$ receptors are present on pyramidal cells in the hippocampus.

Intracellular studies have also characterized the channels opened by serotonin (Segal, 1980; Jahnsen, 1980). Serotonin reduces the input resistance and hyperpolarizes the cell, results consistent with the opening of some type of potassium ion channel (Segal, 1980; Andrade et al., 1986). Intracellular measurements have also indicated that G proteins are involved in the coupling of signals from serotonergic receptors to the opening of these potassium ion channels, a major advance in understanding serotonergic mechanisms (see below).

Receptors, G proteins and potassium ion channels. Membrane receptors often signal cellular responses via a coupling system. The measurement of transmembrane potential and resistance serves to chacterize this system, from the binding of serotonin through the opening of potassium ion channels. Since we plan to make these measurements in our experiments and in this way characterize plasma membrane mechanisms for the recognition and transduction of serotonergic signals, the coupling system in pyramidal cells is described in detail.

Andrade et al. (1986) proposed that two classes of receptors in the hippocampus, 5-HT and $GABA_B$, act through a G protein to open potassium ion channels. Thus, receptors activated by a diffuse serotonergic fiber system share the same potassium channels as do receptors activated by local inhibitory interneurons that release GABA. The critical experiment pointing toward a shared population of channels was the demonstration that potassium currents evoked by the agonists are not additive. Evidence that distinct receptors for serotonin and GABA are present in the membrane includes the observation that when spiperone (a 5-HT receptor blocker) was applied in sufficient concentration to completely block the hyperpolarization evoked by serotonin, hyperpolarization could still be readily evoked by application of the $GABA_B$ agonist baclofen.

Andrade et al.(1986) tested the system to determine if G proteins were involved in the transduction of the signal from the receptor to the opening of the channels. A model involving serotonergic receptors, G proteins, and potassium channels is shown in Figure 1. This model (proposed by Andrade et al., 1986) involves the following steps in the shuttling of the G-protein between receptors (5-HT or $GABA_B$) and the ion channel (which, when open, allows potassium ions to leave the cell and the cell to hyperpolarize). When GTP is bound to the G-protein, the GTP-G-protein complex associates with the potassium ion channel, and the channel opens. When associated with the channel, the G-protein also acts as a GTPase, hydrolyzing its bound GTP to GDP. As a result, the G-protein then dissociates from the channel, and the channel

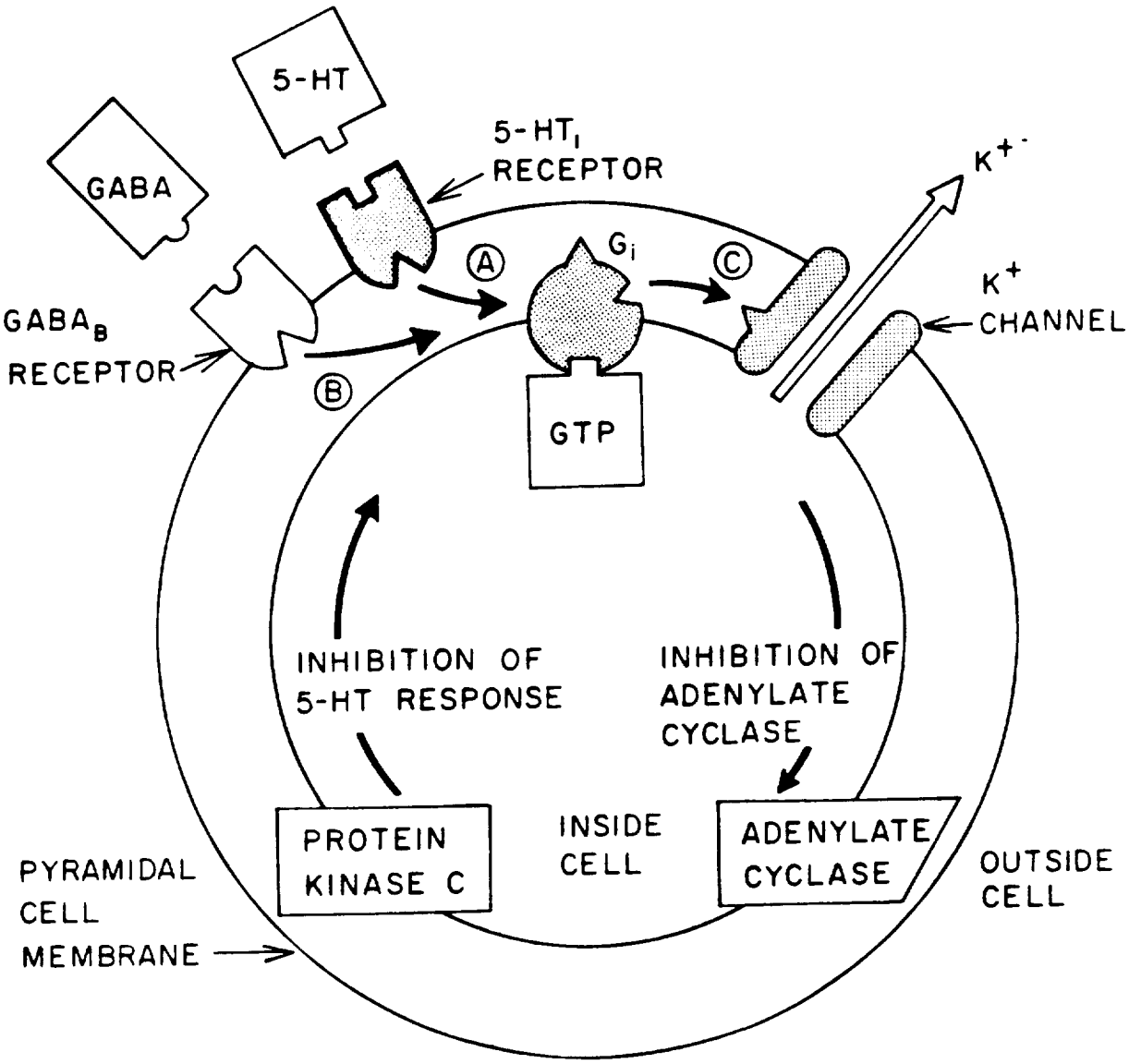

FIGURE 1. Sketch of a pyramidal cell showing a G protein coupling 5-HT receptors to potassium ion channels. serotonin binds with a 5-HT1 receptor to activate a G protein (G_i) that shuttles through the membrane (arrows A and C) to bind with a potassium channel protein, thus opening the channel. The potassium ion efflux through the open potassium channel leads to hyperpolarization and cell inhibition. The neurotransmitter GABA binds with a $GABA_B$ receptor that activates the same G protein (arrow B) and hence also opens K^+ channels. This process, the opening of potassium ion channels by either serotonin or GABA, can be inhibited by increased activity of protein kinase C as shown at lower left. Serotonin also inhibits the membrane bound enzyme adenylate cyclase as shown at lower right.

closes. The GDP-G-protein shuttles to the receptor through the membrane to combine with 5-HT-receptor or GABA-receptor complexes. When associated with these complexes, GTP displaces GDP at the nucleotide site on the coupling protein, and this GTP-G-protein shuttles back through the plasma membrane to repeat the cycle.

The experimental evidence that G proteins are involved in the coupling between the receptors and the potassium ion channel was demonstrated by experiments showing that the response to neurotransmitters is altered by treatments that modify G proteins. After intraventricular injection of pertussis toxin, a specific toxin for some G proteins, pyramidal cells from treated rats no longer showed hyperpolarization following application of either serotonin or GABA even though in other respects cellular activity was the same as controls (e.g., action potentials could be generated by depolarizing the cell). Additionally, in slices treated with GDPβS, a compound that binds with G proteins and maintains them in the inactive state, application of serotonin or $GABA_B$ did not induce pyramidal cell hyperpolarization.

These experiments show that a G protein is associated with the transduction of the signal from the membrane receptors to potassium ion channels but do not in themselves show a direct coupling of G proteins to potassium ion channels. A link that involves a second messenger within the cytoplasm could be involved, and additional experiments were carried out to determine if this was the case. By eliminating three intracellular messengers as being important in this coupling, Andrade et al. (1986) suggest that the G-proteins directly couple to potassium ion channels in the plasma membrane. Experiments excluding second messengers described below illustrate the advantage of the slice preparation in sorting out cellular mechanisms.

First, Andrade et al. (1986) considered whether cAMP served as an intracellular messenger. Madison and Nicoll (1986a,b) had previously shown that norepinephrine (NE) binds to beta receptors to increase intracellular levels of cAMP. The elevated levels of cAMP reduce or block the current through potassium ion channels opened by intracellular calcium ions. These calcium-activated potassium channels hyperpolarize the cell, leading to a waveform called an AHP (afterhyperpolarization). The experiments to rule out an intracellular link of cAMP to the effects of serotonin or baclofen (a $GABA_B$ agonist) involved bathing the tissue for at least 15 minutes in 8-bromo-cAMP, a membrane-soluble analog of cAMP. Loading the cells with 8-bromo-cAMP (to saturate calcium-activated potassium channel binding sites) had no effect on the responses of the cell to serotonin or to baclofen. These cells were loaded with sufficient 8-bromo-cAMP to completely block the effects of NE on the AHP. The fact that NE had no effect and the fact that the effects of serotonin and baclofen were unchanged negated the alternative that cytosolic cAMP was necessary for serotonin to exert its effect.

Second, Andrade et al.(1986) considered whether intracellular levels of calcium ions formed a link between serotonin or baclofen and the influx of potassium ions. Increased levels of calcium ion in hippocampal pyramidal cells affect several types of potasium ion channels. The experiments described above ruled out the possibility that serotonin

opened one type of calcium-activated potassium channel. In additional experiments, involving the use of tetraethylammonium (TEA), they ruled out the possibility that calcium opened other types of channels. Thus Andrade et al. (1986) concluded that calcium ions did not serve as a second messenger in the serotonergic response.

Third, Andrade et al. (1986) performed experiments they interpreted as ruling out a role for inositol phospholipids as a second messenger between a G protein and potassium channels. The activation of protein kinase C (with the activator phorbol-12,13-dibutyrate) showed that protein kinase C is not involved in a second messenger pathway. In addition, inositol triphosphate often acts by releasing calcium from intracellular storage sites, but changes in intracellular calcium had no effect on responses evoked by serotonin or GABA.

The lack of evidence for a second messenger involving ionositol phospholipids, together with a lack of evidence for other second messengers (cAMP and calcium), led Andrade and Nicoll (1985) to propose direct coupling between G proteins and potassium proteins. The coupling can modify and can be modified by other cellular mechanisms. The schematic diagram of a pyramidal cell (Figure 1) illustrates added interactions in the process initiated by serotonin binding on hippocampal pyramidal cells. First, De Vivo and Maayani (1986) have reviewed evidence showing that 5-HT_{1A} agonists inhibit adenylate cyclase. In addition, the serotonergic response can be inhibited by activation of protein kinase C using phorbol-12, 13-dibutyrate (Andrade et al., 1968). Figure 1 includes these added interactions to indicate mechanisms associated with events following binding in addition to the G-protein coupling between the 5-HT_{1A} receptor and K^+-channel.

The extracellular and intracellular experiments cited above provide the background for further study of serotonergic mechanisms as modified by gravitational fields. Data are consistent with the proposals that serotonin receptors in the hippocampus conform to the 5-HT_{1A} classification, and that the hippocampal slice preparation can be used to advantage to study functional effects of decreased receptor number. Coupled with the studies on altered binding of serotonin in microgravity (Miller et al., 1985) and in hypergravity (Miller et al., 1986), a basis is formed for further electrophysiological studies on the effect of hypergravic fields on serotonergic responses. The proposed study is on cellular events associated with 5-HT receptors after exposure of animals to a hypergravic environment.

We plan experiments on changes in hippocampal electrical activity and the effects of serotonin using both extracellular and intracellular procedures. Extracellular methods allow assessment of the modulatory effects of serotonin on a major hippocampal circuit, signals over Schaffer collaterals to hippocampal pyramidal cells. Modulation can be monitored by measuring the amplitude of the population spike. Intracellular methods allow a closer look at the effect of serotonin on intermediate steps in the process. Within the plasma membrane a signal is coupled from 5-HT_{1A} receptors to potassium ions channels via a G protein, and these membrane mechanisms are reflected by changes in transmembrane potentials and membrane resistance. When potassium ion

channels open in many pyramidal cells, the hyperpolarization decreases the amplitude of population spikes. The results of the proposed experiments would provide baseline data for future studies using rats exposed to microgravic environments.

3. Specific questions

(1) Does exposure to altered gravity (2G for 7 days) alter the effect of serotonin on population spike amplitude?

(2) Does exposure to altered gravity (2G for 7 days) alter the effect of serotonin on transmembrane potential of hippocampal neurons?

(3) Does exposure to altered gravity (2G for 7 days) alter the effect of serotonin on the input resistance of hippocampal pyramidal cells?

4. Rationale and experimental procedures

Experiments are designed to further characterize the response of hippocampal neurons to serotonin under differing gravitational conditions. The techniques used build on our current methods for recording extracellular activity (the population spike) in the slice preparation (Hooper et al., 1985, Appendix items A and B).

Tissue preparation. Hippocampal slices will be prepared in our laboratory following procedures we are currently using (Hooper et al, 1985; Appendices A and B). Male Sprague-Dawley rats are decapitated, and their brains quickly dissected and placed in chilled artificial cerebrospinal fluid (ACSF). The neocortex is removed to expose the bilateral hippocampi, which are removed. Slices 400-450 microns thick are cut perpendicular to the long axis of the hippocampus with a McIlwain tissue chopper. The slices are removed from the razor blade with a fine sable brush and placed in a petri dish containing chilled ACSF. The slices are then transferred with a large bore pipette to a plexiglass holding chamber where they rest at room temperature on ACSF-saturated filter paper. The holding chamber is provided with humidified 95% O_2/5% CO_2 gas. The ACSF consists of (in mmoles): 124 NaCl, 5 KCl, 1.25 NaH_2PO_4, 2 $MgSO_4$, 26 $NaHCO_3$, 2 $CaCl_2$, and 10 dextrose. At 37°C, the osmolarity is 305 $\pm$5 mOsm and the pH is 7.4.

Recording chamber. We will record from slices in a recording chamber we have recently built. The chamber is a modification of the one described by Nicoll and Alger (1981) to include thermoelectric modules for controlling bath temperature. Approximately 1-2 hours after tissue dissection, a slice is transferred from the holding chamber to the constant-perfusion slice chamber. The slice is submerged in ACSF between two nets, the top net serving to hold the slice in place. The tissue is constantly perfused with oxygen-saturated ACSF at a rate of 1.5 to 2 ml/min via a gravity-fed reservoir system. The ACSF is removed by suction from a second chamber located behind and connected to the recording chamber. The entire chamber assembly is mounted in a machined

brass plate. The temperature of the slice is controlled by heating or cooling the brass plate with thermoelectric modules situated between the plate and an aluminum heat sink. Temperature is monitored via a calibrated thermistor placed in the recording chamber next to the slice.

Extracellular recording following Schaffer collateral stimulation. The methods will follow those used in our recent studies on population spikes (Hooper et al., 1985; Apendix items A and B). Extracellular field potentials evoked by bipolar stimulation of CA1 stratum radiatum (the Schaffer collaterals) are recorded with glass microelectrodes (4-8 megohm, filled with 3M NaCl) placed in the pyramidal cell layer of CA1. Stimulus frequency is set to 0.033 Hz to avoid LTP, (except for bursts at frequencies above 10 Hz in selected experiments to induce LTP). The software for averaging extracellular fields has been developed for a Cromemco A/D converter and Zenith 100 microcomputer. The software enables us to average population spikes and determine mean spike amplitude.

Intracellular recording. While we have recorded intracellular potentials in a variety of tissues in past studies (Flaim et al., 1977; Horowitz, et al., 1969, 1971, 1980, 1982), this will be the first major study in which we will measure intracellular potentials from hippocampal pyramidal cells. (Our previous slice studies have involved extracellular recording.) Fortunately, pyramidal cells are relatively large cells, which should make them relatively easy to impale. Neurons in the pyramidal cell layer of area CA1 will be impaled with glass micropipettes driven with a Kopf hydraulic microdrive. The pipettes will be pulled on a Brown-Flaming horizontal puller and filled with 4.0M potassium acetate. Pipettes will then be connected to an oscilloscope and penwriter through a WPI high-impedance preamplifier. The preamplifier is equipped with a bridge circuit for passing a calibrated current through the micropipette. Potentials will be measured relative to a chlorided silver wire located in the suction chamber. A steady hyperpolarizing current is passed through the micropipette as cells are impaled to assist in sealing the cell and stabilizing the resting potential. Input resistance will be determined after a steady resting transmembrane potential is established by delivering 100 msec hyperpolarizing pulses. Neurons will be considered healthy if they have: (a) a resting membrane potential of at least 50 mV that is steady for 10 minutes, (b) action potentials elicited by short depolarizing pulses delivered through the pipette, (c) an input resistance of at least 30 Mohm. Data from cells meeting these criteria will be used in resolving the questions posed in this study.

Drug Application. Agonists will be applied to hippocampal neurons by microinjection, microiontophoresis, or superfusion. Antagonists will be applied by adding them to the perfusion line of the recording chamber. Thus the agonists serotonin or 8-OHDPAT will be injected directly into the recording chamber at concentrations of 300 nM-20 μM and 200 nM-4 μM, respectively, via a calibrated microsyringe (Hamilton). The drugs will be introduced into the recording chamber through a small hole near the ACSF inlet to assure consistent application. For microiontophoretic application (Horowitz et al., 1980), glass micropipettes will be filled with serotonin or 8-OHDPAT. In some cases, double-barreled pipettes will be used, one barrel filled with serotonin and the other with 8-

OHDPAT. Pipettes will be placed next to the intracellular recording electrode in area CA1 via a micromanipulator. A Dagan Model 6400 multichannel current generator is used to control drug microiontophoresis. The antagonist methylsergide or buspirone will be mixed with ACSF to concentrations of 30 μM and 3 μM, respectively. Switching between media reservoirs (with and without antagonist) will be accomplished through the use of electric solenoid-actuated valves to minimize pressure pulses to the impaled neuron. Rapid changeover time will be achieved with a small recording chamber volume and minimal dead space in the media tubing (2/3 turnover time is approximately 1.5 minutes at 1 ml/min medium flow rate).

Protocols. EXPERIMENT 1. EXTRACELLULAR RECORDING (see Figure 2) is devoted to the development of extracellular techniques for measuring the response of hippocampal pyramidal cells to serotonin at 1G and will be performed in the first year of the grant. We will focus on experiments to characterize variables (e.g., concentration of serotonin) that modify cellular activity in order to select an operating range for reproducible, stable population spikes. The pyramidal cell response is dependent on Schaffer collateral stimulus variables (pulse amplitude, duration and repetition rate) and these will be varied to determine appropriate ranges for obtaining stable recording. We have already completed several studies characterizing the effects of temperature and pH on the system (Hooper et al., 1985, Appendix items A and B). All studies will be performed in the same time period to avoid any circadian variation in sensitivity to serotonin. Slices from each animal will be prepared as described above and placed in a holding chamber. Slices will then be transferred individually to the recording chamber and experiments performed such that all cells are characterized between 1000 and 1700 hours.

EXPERIMENT 2. INTRACELLULAR RECORDING (Figure 2) is a study also scheduled for the first year of the grant. This study will develop intracellular techniques. Hippocampal pyramidal cells in area CA1 will be impaled and transmembrane potential and resistance measured as described above. After the membrane potential and input resistance have stabilized (thus establishing baseline values), agonists will be applied via microsyringe to the bath or via a micropipette situated next to the intracellular electrode. The following response variables will be recorded: (a) maximum change in potential, (b) time to maximum potential, (c) time to return to baseline resting potential, (d) maximum change in input resistance, and (e) time course of resistance change. Responses will not be used unless the membrane potential returns to within 10% of baseline resting potential. After the neuron has returned to baseline conditions, the agonist will be applied again with an antagonist present in the bathing medium. Responses in the presence of antagonist will be compared with those obtained without antagonist present.

EXPERIMENT 3. EXTRACELLULAR RECORDING IN RATS EXPOSED TO 2G will be done in years 2 and 3. Population spike amplitudes will be measured (Methods, Appendix items A and B) for control rats and rats exposed to 2G fields. This will be a major experimental series because spike amplitudes reflect the overall activity of the system (the output for a

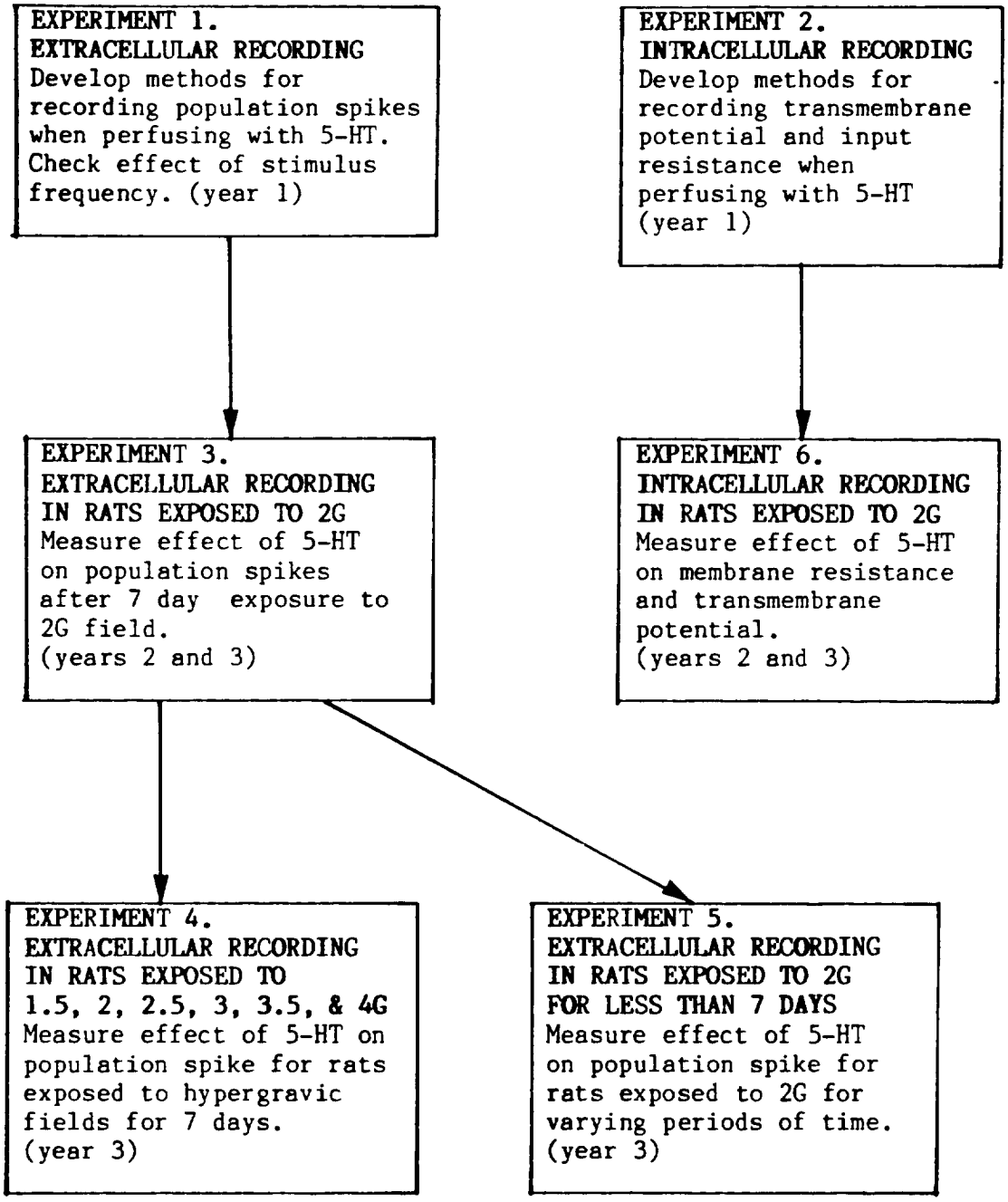

FIGURE 2 -- Outline of experiments.

volley of action potentials over the Schaffer collaterals). There is a 27% decrease in receptor number in rats exposed to 7 days to a 2G field. We will be using rats similarly exposed on the small animal centrifuge at the Chronic Accleration Laboratory).

Experiments will be performed on two groups of animals. . An experimental group, consisting of 10 male Sprague-Dawley rats, will be exposed to a 2G hypergravic field for 7 days and and a control group of 10 rats will be housed at 1G. Experiments will be performed at 1G within 5 hours after transferring rats from 2G to 1G. All animals will be fed Purina rat chow and water ad libitum and housed at 23-25°C. Animals from both groups will be identified by a code number unknown to the investigator making the measurements.

EXPERIMENT 4. EXTRACELLULAR RECORDING IN RATS EXPOSED TO 1.5, 2, 2.5, 3, 3.5 & 4G will be carried out in year 3 provided results obtained in EXPERIMENT 3 show changes in the amplitude of population spikes. Once data are obtained for rats exposed to a gravitational field of 2G for 7 days (for direct comparison with data on receptor number), the gravitational field and the exposure time will be varied. The gravitational field will be varied in 0.5G steps from 1 to 3G for 7 day exposure periods. The intent of this experiment is to determine if the modulatory effect of serotonin on electrical activity is a function of the gravitational field amplitude.

EXPERIMENT 5. EXTRACELLULAR RECORDING IN RATS EXPOSED TO 2G FOR LESS LESS THAN 7 DAYS will be carried out in year 3 provided results obtained in EXPERIMENT 3 show changes in electrical activity. Holding the field at 2G, the period of exposure will be shortened to determine the minimum time required to detect effects on acclimation.

EXPERIMENT 6. INTRACELLULAR RECORDING IN RATS EXPOSED TO 2G will be done in years 2 and 3. This is a major experimental series comparing resistance and transmembrane potential changes in rats exposed to 2G and 1G.

(In developing techniques for the six experiments both hamsters and rats will be used.)

5. Data interpretation

Changes in the amplitude of population spikes will first be compared between animals exposed to 1G and to 2G for 7 days. A significant decrease in mean spike amplitude in rats exposed to 2G vs 1G controls would demonstrate that <u>functional</u> neuronal changes accompany the observed reduction in receptor number. The extent of these changes would be then determined as the gravitational field is increased and as the period of exposure is decreased.

Changes in transmembrane potential in response to serotonin or a 5-HT_1 agonist will be compared in hippocampal slices from rats exposed to a 2 G hypergravic field and control rats kept at 1 G. A significant change in rats exposed to hypergravity would lend support to the hypothesis that there is a direct affect of the gravitational field on hippocampal serotonin responsiveness. No significant change in serotonin

responsiveness in rats exposed to hypergravity would indicate that membrane (receptor) changes induced by gravity are not reflected in changes of electrical activity.

Changes in input resistance in response to serotonin or 5-HT_1 agonist will be compared in hippocampal slices from rats exposed to a 2 G hypergravic field and control rats kept at 1 G. Changes in input resistance will be compared with changes in transmembrane potential to determine if resistance and transmembrane potentials are correlated with gravitational fields. A decreased resistance (or an increased conductance) would indicate an increase in the number of open channels.

C. SIGNIFICANCE

This proposal outlines neurobiological experiments on rats at earth gravity and in hypergravic fields. The series of experiments deal with serotonin receptors in the hippocampus. Receptor binding has been shown to be modified by microgravity and hypergravic environments. This study will focus on electrical activity mechanisms at the membrane level as a link to functional changes.

Core experiments will use animals exposed to 2 G fields for 7 days. The period of 7 days is chosen so that data obtained at 1 G and 2 G can be compared with recent Spacelab 3 experiments and with hypergravic experiments on serotonin receptors. Moreover, there is a great deal of data available on rats exposed 2 G fields.

The results of the proposed experiments serve as baseline data for future studies in hypogravic fields, including experiments on a space station. The studies involving the neurotransmitter serotonin will provide data on the effects of hypergravic fields and determine whether the number of binding sites is accompanied by changes in physiological function. If so, further experiments involving this transmitter could be performed on neural tissue after prescribed periods of exposure to a microgravity environment, with analysis of tissue samples performed shortly upon return of the animals to earth.

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E. PROGRESS REPORT (1985-1987)

Description of research. Over the past year we have shifted our experimental work almost completely to the hippocampus and away from studies on thermoregulation and the vestibular and auditory system. Our hippocampal experiments are related to a striking experimental finding from Spacelab-3, namely that there is an elevation in serotonin binding in rats exposed to microgravity for 7 days. This observation led us to focus primarily on developing techniques to study the hippocampus where the changes in receptor number have been reported. The goal of the experiments was to lay the basis for determining if there are functional changes in hippocampal neurons after exposure to hypergravic fields.

In addition to hippocampal studies, we completed experiments on vestibular, auditory and thermoregulatory systems that concluded a series of NASA supported projects on sensory mechanisms and regulatory systems.

Thus we finished one series of experiments and started another one on hippocampal slices. All focused on central neural function as modified by altered accleration fields.

Hippocampal studies. Our major emphasis in recent experimental studies was centered on mastering the hippocampal slice preparation. A primary goal was to gain command of the techniques for recording electrical activity in the hippocampal slice preparation. We focused on thermal and pH effects on hippocampal electrical activity. With our shift in emphasis to the effects of neurotransmitters on cellular activity, a simulation study was completed on the effects of temperature on ion channel activity in hippocampal cells (Appendix C).

Experimental methods The hippocampus was sliced and placed in chilled artificial cerebrospinal fluid (ACSF). Slices 400-450 microns thick were cut perpendicular to the long axis of the hippocampus with a McIlwain tissue chopper and placed in a holding chamber. The chamber was provided with humidified 95% O_2 / 5% CO_2 gas. The ACSF consisted of (in mmoles): 124 NaCl, 5 KCl, 1.25 NaH_2PO_4, 2 $MgSO_4$, 26 $NaHCO_3$, 2 $CaCl_2$, and 10 dextrose. At 37°C, the osmolarity was 305 $\pm$5 mOsm and the pH was 7.4.

Approximately 1-2 hours after tissue dissection, a slice was transferred from the holding chamber to the submerged, constant-perfusion slice chamber. The slice was submerged in ACSF between two nets, the top net serving to hold the slice in place. The tissue was constantly perfused with oxygen-saturated ACSF at a rate of 1.5 to 2 ml/min via a gravity-fed reservoir system. The ACSF was removed by suction from a second chamber located behind and connected to the recording chamber. Temperature was monitored via a calibrated thermistor placed in the recording chamber next to the slice. Action potentials from a population of hippocampal pyramidal neurons were evoked by stimuating an afferent fiber tract, the Schaffer collaterals. The temperature and the pH of the ACSF bathing the slice were varied by controlling the temperature of a water chamber jacketing the recording chamber.

Experimental results. The effects of pH and temperature on hippocampal slices were studied in detail (references 5A, 1, 3, 4 and 6). Thresholds for evoked activity were significantly different in noncold-acclimated, cold-acclimated and hibernating hamsters, and may reflect acclimation of hippocampal neurons to cold. Plots of population spike amplitude (action potentials from a group of pyramidal cells) versus temperature have bell-shaped curves. The population spikes increased in amplitude as temperature was lowered from 35°C, reached a peak amplitude between 25 and 20°C, and then decreased until a response could not be evoked when temperature was further lowered. Techniques were thus developed for studying population spikes in the slice over a range of bath temperatures. Pilot studies on the effect of serotonin on population spikes were initiated. These techniques will be used in the experiments proposed in this grant renewal.

Simulation of the effect of temperature on ion channels in nerve membranes. We have developed a model to predict the effect of temperature on the electrical activity of a hippocampal pyramidal cell (5). With the development of brain slice techniques for voltage-clamping single cells, several types of ion channels in membranes of mammalian nerve cells have been identified and characterized in sufficient detail to allow a simulation of channel currents. Four populations of membrane channels in the pyramidal cell were simulated. Equations for current through these ion channels are similar to those first developed by Hodgkin and Huxley for sodium and potassium channels in the squid axon and more recently extended by Traub to include not only these channel types but, in addition, calcium and calcium-mediated potassium channels in hippocampal cells. Voltage and/or concentration dependent rate functions were used to describe the kinetic behavior of each population of channels. A temperature dependent term was included for each rate function to simulate the effect of changing temperature on neural activity. Model simulations correspond to experimental data over a range of temperature from 40°C to 35°C.

Vestibular and auditory system. Pulse angular acceleration evokes short latency far-field responses that can be attributed in large measure to the activation of the vestibular periphery and brain stem nuclei. The frequency spectrum of bone conducted vibrations coupled to the skull of rats during impulse angular acceleration stimulation was estimated to have greatest power at 2-3 kHz. The intensity of these vibrations was approximately 5 dB lower than the vibrations evoked by bone-conducted auditory clicks, which had their greatest power between 9 and 11 kHz. Moreover, the amplitudes of the first two major components of the response evoked by angular acceleration were greater than the first two major components of the response evoked by bone-conducted clicks. These results indicate that in rats, one can evoke far-field responses due to activity over the vestibular system and that this activity can be distinguished from auditory evoked responses (2, 9, 10).

Our data confirms a previous report that noninvasive procedures can be used to record brainstem vestibular evoked responses in rats. Particular attention was devoted to ruling out the possibility that what had been

called a vestibular response was in reality an auditory response. Stimulus characteristics were precisely determined. Using this type of stimulation, the amplitudes of the first two major components of the response evoked by angular acceleration were greater than the first two major components of the response evoked by bone-conducted clicks.

Thus, two independent laboratories have reported brainstem vestibular responses. These far-field potentials provide a means to record overall brainstem activity using noninvasive techniques. We have concluded experiments in this area and have manuscripts in preparation. (While we have turned our attention to the hippocampus, one of our former collaborators, Dr. T. Jones, is carrying on an indepedent series of studies on brainstem-evoked responses based, in part, on these studies.)

Thermoregulatory studies Previous studies in a variety of laboratories showed that the rat, dog, and monkey have an impaired ability to regulate their body temperature when exposed to hypergravic fields. One set of experiments using the rat was directed toward clarifying mechanisms underlying this impairment. The rat was chosen as an experimental animal because of studies at earth gravity, 1 G, that provided basic background for further studies both at zero-G and in hypergravic fields from 1.5 to 4 G.

One series of completed experiments (7) showed that rats acclimated to a gravitational field of 2.1 G are able to regulate their core temperature better when cold stressed at 2.1 G than are rats acclimated at earth gravity (1 G). Rats acclimated to 2.1 G also increased tail temperature (T_t) and decreased core temperature during exposure to 5.8 G. Thus, rats acclimated to 2.1 G were not able to regulate their temperature when exposed to higher gravitational fields. Acclimation did not result in a change in thermoregulatory ability at 1 G. It appears that rats acclimated to 1 G conditions continue to regulate their core temperature, albeit at a lower core temperature, when placed in a hypergravic field of 2.1 G.

Another series of completed experiments (2, 8) compared groups of rats acclimated to gravitational fields of 1 or 2.1 G. That is, one group was born and raised at 2.1 G and belonged to the 12th generation of rats living continuously on a centrifuge in a 2.1 G field, except for brief periods of routine care at 1 G. The finding that rats acclimated at 2.1 G could thermoregulate better than rats raised at 1 G when cold stressed at 2.1 G shows that acclimation to a hypergravic environment can modify the activity of a neural control system in mammals. However, rats acclimated to 2.1 G were not able to regulate their core temperature when first exposed to 5.8 G indicating that acclimation at one level of a hypergravic field does not improve the ability of the animal to thermoregulate at higher field levels.

(While we have concluded the experimental series on temperature regulation in rats exposed to hypergravic fields, one of our early collaborators, Dr. C. Fuller, is carrying on related hypergravic studies on temperature regulation and circadian rhythms.)

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F. BIOGRAPHICAL SKETCH OF PIs

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1978-present	Professor of Physiology and Research Physiologist in the Experiment Station (UC Davis)
1973-1978	Associate Professor of Physiology and Research Physiologist in the Experiment Station (UC Davis)
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University of Florida, Gainesville	M.S.	1962	Biology
Emory University, Atlanta, Georgia	Ph.D.	1966	Physiology
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THESIS WORK:

Master of Science
"Temperature Effects on Oxygen Uptake of Liver and Kidney Tissues of a Hibernating and a Non-hibernating Mammal"

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HONORS AND MEMBERSHIP IN PROFESSIONAL SOCIETIES:

Phi Beta Kappa
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Outstanding undergraduate in Biological Sciences
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MAJOR RESEARCH INTERESTS:

Regulation of Cellular Metabolism
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RESEARCH AND/OR PROFESSIONAL EXPERIENCE

1978-present	Professor of Physiology (UC Davis)
1975-1978	Associate Professor of Physiology (UC Davis)
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G. BUDGET

Grant No.: **NASA NAG 2-341**
Period covered by budget: **March 1, 1988 - February 28, 1991**

	1988-89	1989-90	1990-91
SALARIES			
Staff Res. Assoc.	16,000	17,000	20,000
Employee Benefits	4,640	5,100	6,200
Total Salaries	20,640	22,100	26,200
SUPPLIES Animal procurement & care, misc. lab supplies, publication costs, equipment maintenance.	3,000	4,000	5,000
EQUIPMENT Electronics & micromanipulators for intracellular recording and signal processing.	4,500	3,000	1,000
TRAVEL P.I. to present papers at FASEB and at ASGSB annual meetings.	2,000	2,100	2,300
TOTAL DIRECT COSTS	30,140	31,200	34,500
TOTAL INDIRECT COSTS (39.2%)	10,051	11,055	13,132
TOTAL	$40,191	$42,255	$47,632

H. BUDGET JUSTIFICATION

We have the equipment required for the proposed experiments on hippocammpal slices except for two micromanipulators to hold additionalelectrodes for stimulating fiber tracts and/or to hold pipettes for iontophoretic injection of compounds and for measuring electrical potentials.

I. AVAILABLE FACILITIES

We have the standard hippocampal slice equipment required to stimulate a fiber track (in our experiments Schaffer collaterals) and record extracellular and intracellular activity in hippocampal pyramidal cells. Thus we have an air table, Brown-Flaming microelectrode puller, WPI amplifier, Zenith computer, XY plotters, WPI stimulators, and associated electronic equipment.

The PI has a laboratory of over 800 sq ft. In addition, the facilities at the Chronic Acceleration Research Unit on the Davis Campus, including animal centrifuges in the Unit, will be used to expose rats to a hypergravic environment.