Pharmacology Biochemistry & Behavior, Vol. 21, pp. 481–485, 1984. © Ankho International Inc. Printed in the U.S.A. 0091-3057/84 $3.00 + .00

Learned Helplessness: Effects on Brain Monoamines and the Pituitary-Gonadal Axis

D. H. HELLHAMMER,* M. A. REA,† M. BELL,* L. BELKIEN† AND M. LUDWIG*

**Department of Clinical Psychology, University of Münster, D-4400 Münster, F. R. Germany*
†Max-Planck Clinical Research Unit for Reproductive Medicine, D-4400 Münster, F. R. Germany

Received 7 March 1984

HELLHAMMER, D. H., M. A. REA, M. BELL, L. BELKIEN AND M. LUDWIG. *Learned helplessness: Effects on brain monoamines and the pituitary-gonadal axis.* PHARMACOL BIOCHEM BEHAV **21**(4) 481–485, 1984.—The effect of the learned helplessness paradigm, a model of depression, on biogenic amines in eight brain regions, and on the serum levels of luteinizing hormone, corticosterone, and testosterone in male rats was determined. Rats which were exposed to uncontrollable and unpredictable shocks (HY-rats) had hormone levels similar to those in appropriate control animals. However, HY-rats had higher levels of 5-HIAA in the pons/medulla oblongata and lower levels of 5-HT in the cortex than rats which could escape the shocks (HE-rats). Furthermore, striatal levels of NE were higher in HY-rats when compared to HE-rats and non-shocked controls (HC-rats). Shock treatment *per se* resulted in lower NE levels in the hippocampus. These data implicate the serotonergic and noradrenergic systems as possible mediators of the learned helplessness phenomenon, but do not support the view that this behavior is associated with impaired pituitary-gonadal function.

Learned helplessness Brain monoamines Corticosterone Luteinizing hormone Testosterone

RECENTLY, we discussed a psychobiological concept of "learned helplessness," including two distinct behavioral and neurobiological mechanisms. We postulated that animals, after being exposed to unescapable aversive events, show deficits in the subsequent acquistion of behavioral skills due to an acetylcholine-mediated inhibition of avoidance motivation and a serotonin-mediated inhibition of behavioral activity [13].

The serotonergic mechanism may become important if aversive events are given chronic and moderate enough to allow the animal to elicit a "conservation-withdrawal" response [10]. Perhaps, this status can be characterized by a reduced functional activity of central noradrenergic systems and enhanced activity of serotonergic neurons [12,13]. It has been shown that cyproheptadine hydrochloride, a serotonin (5–HT) antagonist, reverses behavioral inactivity after such training without improving the learning ability in subsequent behavioral tests [17]. On the other hand, 5-hydroxytryptophan produces interference with the acquisition of an escape response which can be prevented by the 5-HT-antagonist methysergide [6]. Moreover, lower levels of 5-HT in the brain stem and the locus coeruleus [24] and in synaptosomal pellets of the septum and the anterior cortex [20] were reported after exposure to uncontrollable footshock. These data support a proposed serotonergic mechanism of behavioral depression [5,16], which may be related to a functional imbalance of both the serotonergic and the noradrenergic transmitter systems [12,19].

In the present study, we investigated effects of helplessness training, which was sufficient to produce behavioral inactivity, on levels of central biogenic amines and metabolites. With respect to our recent research on effects of stress on the hypophyseal-gonadal axis [15], we decided to investigate additionally the levels of luteinizing hormone ((LH) and testosterone (T), as well as corticosterone, since these hormones are considered relevant as mediators of stress effects on testicular function [7,8,9].

METHOD

EXPERIMENT 1

The first experiment was performed to investigate the effect of helplessness conditioning on subsequent escape performance.

Subjects and Apparatus

Fifteen male, adult Wistar rats were trained in the triadic yoked control paradigm [23]. Five rat triplets were placed in individual Plexiglas operant chambers, which had interior dimensions of 21×14×17 cm. Each chamber contained a movable wheel (5 cm diameter). The tails of the rats were fixed outside of the chamber and connected to needle electrodes. Triplets were weight matched and had no sensory contacts with each other during the sessions. Shocks (0.7 mA; 10 sec duration; 20 sec fixed interval) were given via tail electrodes for one hour on each of five consecutive days between 9:00 and 11:00 a.m. One rat of each triplet was capable of escaping the shock (HE-rat) by turning the wheel.

If the HE-animal failed to do so, it received, together with it's yoked counterpart, (HY-rat) a footshock. The HY-rats had no control over the shocks. A third rat, which served as an untreated control (HC-rat) was maintained under the same experimental conditions but did not receive shocks.

The efficiency of the conditioning procedure was tested 24 hr after the test training sessions using a shuttle-box (Campden Instruments; 49×21×23 cm) in which animals could learn a two-way escape response in order to avoid shocks (0.7 mA; 10 sec duration; 20 sec fixed interval) which were given over a 90 min period.

Behavioral Records

The behavior of HY-rats was continuously observed and recorded during intervals of five seconds. An observer recorded the dominant behavior during each interval either as "locomotor activity," "wheel-turning" activity, or "freezing" (immobility). The wheel turns of all animals were quantitatively recorded by an event recorder (Campden Instruments). Behavioral observations during shuttle-box performance included recording of successful two-way escape learning and unsuccessful one-way escape responses.

EXPERIMENT 2

Subjects and Apparatus

Another ten triplets of adult, male Wistar rats were used. They were exposed to the triadic yoked control paradigm as described above. After the last training session, these rats were killed by decapitation (between 11:00 a.m. and 11:30 a.m.); the brains were rapidly removed, placed immediately in the cold box (−10°C) and dissected into the following brain areas: pons/medulla oblongata, midbrain, hypothalamus, thalamus, striatum, hippocampus, and cortex. All brain parts were frozen in liquid nitrogen, wrapped in aluminum foil, and stored at −70°C until they were assayed.

Behavioral Records

The behavior of the triplets was recorded as described for animals of the first experiment.

HPCL-Assay of Biogenic Amines and Metabolites

Brain monoamines and metabolites were measured in formic/acid acetone extracts of brain tissue by high performance liquid chromatography with electrochemical detection as described elsewhere [14,22].

Assay Methods

For the corticosterone assay, 50–100 μl of serum were extracted with diethylether. After evaporation, the residue was dissolved in 5 ml assay buffer, and 1 ml was kept for recovery measurement. A 100 μl aliquot was used for the radioimmunoassay (RIA; antibody dilution: 1:40000). The intra- and the interassay coefficients of variation was 4.3% and 9.5%, respectively (N=5). The sensitivity of the assay was 0.42 nmol/l, and the 50% intercept was 73 pg/tube. Increasing amounts of corticosterone to steroid-free serum were estimated by this method. The correlation with the theoretical value was $r=0.9915$; $p=0.001$.

Serum luteinizing hormone was measured by radioimmunoassay. Reagents were provided by NIAMDD, Rat Pituitary Distribution Program. NIAMDD Rat LH-RP-1, Rat LH-I-4 and anti-rat-LHS-5 were used for the LH assay. The intra-assay coefficient of variation was 8.7% and the inter-assay coefficient was 11.4%. Testosterone was measured in serum extracts without chromatography by radioimmunoassay [18]. The intra- and inter-assay coefficients of variation were 3.7% and 11.9%, respectively.

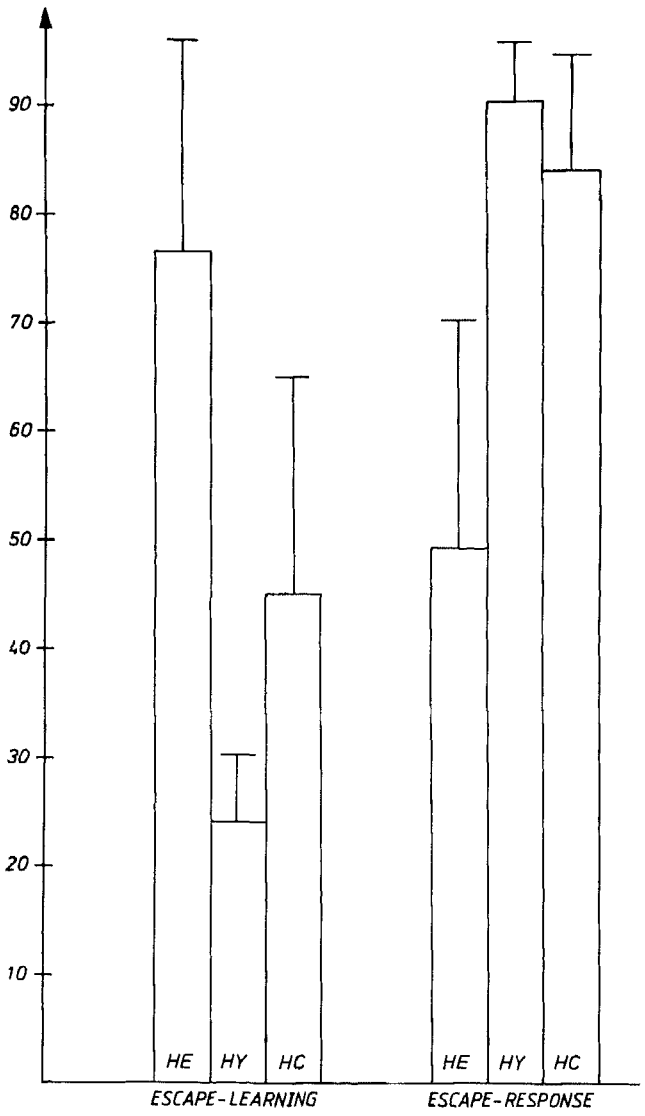

FIG. 1. After exposure to the triadic paradigm, rats with preexperience of inescapable and uncontrollable shocks (HY) showed a deficit in the acquisition of a two way escape learning task, when compared to their counterparts which could escape the shocks (HE) or received no shocks during pre-training. Rats received 180 shocks (FI 15, 0.7 mA) over a period of 90 min. Columns represent the absolute number of successful two-way escape-learning and unsuccessful one-way escape responses (Means±SD).

RESULTS

EXPERIMENT 1

During the five training sessions in the triadic paradigm, yoked rats developed a gradual increase in freezing (from 5%

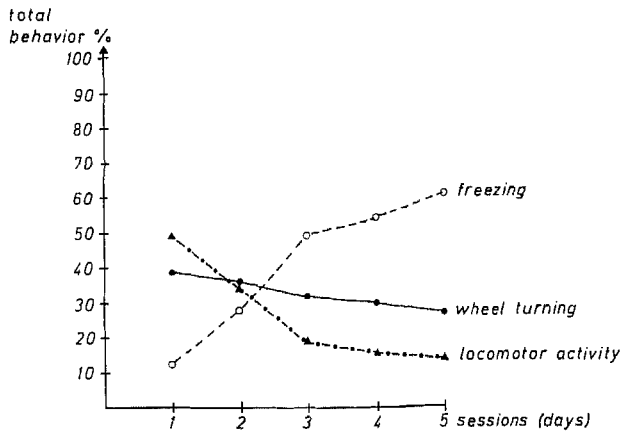

FIG. 2. Behavior of yoked rats (HY) was registered in intervals of 5 seconds as either "freezing," "wheel-turning," or "locomotor activity" over 5 session (one per day) of 1 hr each. Freezing gradually increases over the training sessions, while locomotor activity decreases.

to 54%), and reduced wheel-turning behavior (from 42% to 29%) and locomotor activity (from 53% to 27%). After having been exposed to uncontrollable and inescapable shocks, yoked rats showed a deficit in the acquisition of a two-way escape learning task in the shuttle-box (Fig. 1). On the other hand, HY-animals still showed a high rate of one-way escape responses. These data demonstrate that training was sufficient to produce interference with subsequent learning but does not result in impaired escape performance *per se*.

EXPERIMENT 2

Behavior

Similar to yoked rats from the first experiment, HY-rats of this experiment also showed increased freezing behavior and less wheel-turning and locomotor activity over the five session (Fig. 2). These data suggest that our experimental animals responded adequately to the helplessness conditioning procedure, resulting in a comparable learning deficit. The individual rating scores for freezing and locomotor activity, as well as the absolute number of wheel-turns as registered by the event recorder, were used for further correlational analysis with neurochemical and endocrine data.

Biogenic Amines

As seen from Table 1 levels of dopamine (DA) and 3,4-dihydroxyphenylacetic acid (DOPAC) showed no significant differences among groups after the last training session. However, analysis of variance (ANOVA) revealed significant differences for NE in the striatum, $F(2,16)=3.43$, $p<0.05$, and the hippocampus, $F(2,26)=4.09$, $p<0.01$.

In the striatum NE levels were higher in HY-rats than in both HE-animals ($t=2.29$, $p<0.035$) and HC-controls ($t=2.27$, $p<0.037$). In the hippocampus, NE levels were lower in HE-rats ($t=2.69$, $p<0.012$) and HY-rats ($t=2.70$, $p<0.012$) when compared to HC-animals. No differences were found for the NE metabolite, 4-hydroxy-3-methoxyphenylglycol (MHPG), in any of the brain parts. As seen from Table 1, changes for 5-HT were found in the cortex, $F(2,24)=3.67$, $p<0.04$, and for its metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the pons/medulla oblongata. Cortical 5-HT levels were lower in HY-rats when compared to HE-animals ($t=2.69$, $p<0.013$), and 5-HIAA levels were higher in HY-rats than in HE-rats ($t=2.40$, $p<0.023$).

Hormones

Levels for corticosterone, LH, and testosterone did not differ significantly between the groups (Table 2).

Relationships Among Behavior, Biogenic Amines and Hormones

To investigate the relationship between the behavioral and biological data, behavioral records from the last training session were analysed for correlations with levels of biogenic amines and hormones (Pearson and Student's two tailed t-test).

In HY-animals, freezing was negatively correlated with cerebellar levels of DOPAC ($r=-0.92$, $p<0.01$). Locomotor activity was positively associated with levels of corticosterone ($r=0.84$, p 0.01), and the number of received shocks was negatively correlated with cerebellar levels of 5-HT ($r=-0.94$, $p<0.001$) and DA ($r=-0.81$, $p<0.01$).

In the HE-rats, however, wheel turning activity was positively correlated with levels of cortical DA ($r=0.90$, $p<0.001$) and DOPAC ($r=0.82$, $p<0.01$). The number of obtained shocks was negatively correlated with wheel turning activity, thus resulting in negative correlations with DA ($r=-0.90$, $p<0.001$) and DOPAC ($r=-0.88$, $p<0.01$) in the cortex, but was also associated with low levels of 5-HT in this brain region ($r=-0.86$, $p<0.01$).

GENERAL DISCUSSION

The helplessness conditioning procedure used in this study produces behavioral depression after a minimal chronic exposure to aversive events. Our first experiment has shown that the training was sufficient to produce interference with a subsequent learning task, which is unlikely to be caused by motor impairment.

Recent research on inescapable and uncontrollable shocks primarily focused on the noradrenergic system and provided evidence that acute stress results in a transient NE depletion, while prolonged chronic stress results in unchanged NE levels in the brain [1, 3, 24]. With respect to studies in mice [2], we would expect lower levels of NE in yoked animals which were killed after the last exposure to stress. In our study, however, this was only true for the hippocampus. Since the same effect has been observed in HE-animals, lower hippocampal NE levels may be better attributed to the stressful treatment than to shock controllability. If hippocampal NE depletion reflects an unspecific stress response, these data agree with our findings in activity-stressed animals which show the same effect after exposure to this paradigm [21]. On the other hand, yoked animals showed elevated levels of NE in the striatum, a brain region which plays an important role in regulating both behavioral and mental activity [11]. With respect to our theory [12], hypoactivity of noradrenergic striatal nerve terminals may underlie conservation-withdrawal behavior.

In this study, we did not find significantly different levels for DA and DOPAC among the experimental groups. How-

TABLE 1

CONTENTS OF BIOGENIC AMINES AND METABOLITES IN EIGHT BRAIN REGIONS (pmol/mg) OF MALE RATS WHICH RECEIVED ESCAPABLE (HE; N=10), NON-ESCAPABLE (HY; N=10), OR NO SHOCKS (HC; N=10) IN AN OPERANT CHAMBER

		DA	DOPAC	NE	MHPG	5-HT	5-HIAA
pons/medulla	HE	0.27 ± 0.08	0.08 ± 0.02	3.80 ± 0.54	0.44 ± 0.15	4.94 ± 0.60	3.10 ± 0.79
	HY	0.27 ± 0.04	0.08 ± 0.01	3.90 ± 0.35	0.40 ± 0.19	5.37 ± 0.49	4.14 ± 1.36‡
	HC	0.32 ± 0.05	0.09 ± 0.04	4.05 ± 0.17	0.50 ± 0.18	5.34 ± 0.43	3.30 ± 0.50
midbrain	HE	0.70 ± 0.18	0.16 ± 0.04	2.69 ± 0.41	0.34 ± 0.09	6.13 ± 0.64	4.47 ± 1.03
	HY	0.65 ± 0.22	0.12 ± 0.04	2.69 ± 0.48	0.37 ± 0.05	6.21 ± 0.75	4.67 ± 0.89
	HC	0.76 ± 0.21	0.13 ± 0.05	2.97 ± 0.52	0.40 ± 0.14	6.53 ± 0.48	4.53 ± 0.66
thalamus	HE	1.18 ± 0.40	0.13 ± 0.05	3.34 ± 0.58	0.52 ± 0.15	5.62 ± 0.81	3.60 ± 0.87
	HY	1.44 ± 1.11	0.16 ± 0.09	3.80 ± 0.92	0.56 ± 0.09	5.77 ± 1.24	3.66 ± 1.02
	HC	1.07 ± 0.39	0.12 ± 0.06	3.68 ± 0.49	0.68 ± 0.37	5.77 ± 0.74	3.54 ± 0.54
hypothalamus	HE	2.09 ± 0.57	n.d.	13.55 ± 2.96	0.23 ± 0.07	7.01 ± 1.30	2.87 ± 0.62
	HY	2.02 ± 0.22	n.d.	12.98 ± 1.84	0.24 ± 0.05	7.07 ± 0.59	2.81 ± 0.49
	HC	2.45 ± 0.48	n.d.	14.68 ± 2.90	0.25 ± 0.10	7.71 ± 1.45	3.18 ± 0.93
striatum	HE	77.03 ± 11.54	4.73 ± 1.47	1.37 ± 0.58	0.55 ± 0.16	4.20 ± 0.91	4.12 ± 1.09
	HY	73.80 ± 10.74	4.77 ± 0.54	2.18 ± 0.85*	0.57 ± 0.10	4.39 ± 0.70	4.25 ± 0.94
	HC	81.77 ± 9.78	5.18 ± 0.79	1.35 ± 0.38	0.62 ± 0.16	4.31 ± 0.71	4.09 ± 0.63
hippocampus	HE	0.69 ± 0.34	n.d.	1.67 ± 0.25†	0.18 ± 0.08	2.84 ± 0.55	3.15 ± 0.82
	HY	0.69 ± 0.18	n.d.	1.65 ± 0.26†	0.22 ± 0.04	2.63 ± 0.33	3.16 ± 0.79
	HC	0.75 ± 0.24	n.d.	2.16 ± 0.58	0.22 ± 0.09	2.98 ± 0.35	3.26 ± 0.51
cortex	HE	7.02 ± 1.97	0.63 ± 0.13	1.67 ± 0.66	0.23 ± 0.26	4.62 ± 0.78	2.16 ± 0.24
	HY	6.11 ± 2.01	0.48 ± 0.17	1.75 ± 0.65	0.23 ± 0.24	3.82 ± 0.50‡	1.83 ± 0.53
	HC	6.06 ± 1.19	0.52 ± 0.11	1.92 ± 0.69	0.46 ± 0.30	4.17 ± 0.49	1.90 ± 0.28
cerebellum	HE	0.47 ± 0.14	0.03 ± 0.03	0.99 ± 0.24	0.83 ± 0.25	1.06 ± 0.45	0.71 ± 0.39
	HY	0.66 ± 0.25	0.10 ± 0.03	0.81 ± 0.23	1.25 ± 0.69	1.21 ± 0.82	0.97 ± 0.55
	HC	0.51 ± 0.17	0.05 ± 0.03	0.95 ± 0.21	0.99 ± 0.31	0.94 ± 0.21	0.80 ± 0.30

*Significant ($p<0.05$) when compared to HE and HC animals.
†Significant ($p<0.01$) when compared to HC animals.
‡Significant ($p<0.01$) when compared to HE animals.
n.d.=Non detectable.
Means ± SD.

TABLE 2

LEVELS OF CORTICOSTERONE, LUTEINIZING HORMONE AND TESTOSTERONE AS DETERMINED IN TRUNK BLOOD (MEAN ± SD) AFTER THE LAST FIVE TRAINING SESSIONS IN RATS WHICH RECEIVED ESCAPABLE (HE; N=10), INESCAPABLE (HY; N=10) AND NO SHOCKS (HC; N=10)

Corticosterone (ng/ml)	164.30 ± 147.80	200.50 ± 114.50	184.60 ± 94.30
Luteinizing Hormone (ng/ml)	7.59 ± 3.27	8.00 ± 3.44	5.61 ± 3.79
Testosterone (ng/ml)	3.60 ± 1.63	5.12 ± 3.10	3.50 ± 2.31

ever, in yoked helpless rats, cerebellar levels of DOPAC were negatively correlated with freezing behavior in the last training session. This may suggest that freezing is related to cerebellar DA turnover. Furthermore, wheel turning activity was positively correlated with levels of cortical DOPAC and DA in HE-animals, supporting the view that the metabolism of DA in this brain region is associated with behavioral activity. Lower levels of DA in the anterior cortex were also found in yoked rats when compared to their avoidance-escape counterparts [24]. Pharmacological studies [1, 2, 3] and neurochemical data have recently suggested (see [4]) that the dopaminergic system may also play a role in stress controlability.

The levels of serotonin were lower in the cortex of yoked rats when compared to HE-animals. With respect to the proposed functional imbalance of serotonergic and noradrenergic mechanisms during conservation-withdrawal behavior, one may interpret this, as well as the enhanced levels of 5-HIAA in the pons/medulla, in terms of an increased serotonin turnover in the brain. If so, our data agree with the recently reported depletion of 5-HT in the locus coeruleus and brain stem of yoked rats 90 min after exposure to uncontrollable stress [24]. Since levels of cerebellar 5-HT were negatively correlated with the number of unpredictable and uncontrollable shocks, one may also speculate that the serotonergic Raphé systems responds to the amount of this

type of stress. In HE animals, we found a positive correlation between cortical 5-HT levels and the number of shocks received. This supports the idea of a relationship between successful control of shocks and 5-HT metabolism.

The stress conditions used in this study were not sufficient to produce any observable changes on the hypophyseal-gonadal axis. However, in yoked rats, there was a positive correlation between the levels of corticosterone and locomotor activity in the last session, suggesting that rats which have not yet fully developed behavioral depression have a higher release of this stress hormone.

With respect to recent research on different types of chronic stress, we would expect that levels of LH would return to normal under chronic stress conditions, but not testosterone [9]. Other investigators have speculated that the reduction in serum T levels under stress is not due to decreased serum LH levels but occurs either as a consequence of sympathetic nervous arousal or increased corticosterone levels [7]. Data from this study showed no correlations between T and corticosterone; this does not support the hypothetical relationship between these two hormones under such treatment conditions. On the other hand, we recently provided evidence that male infertility is associated with an ergotropic stress response and sympathetic arousal [15]. Yoked animals in our study, which emit gradually more freezing behavior, seem to develop a conservation-withdrawal response which is likely to be associated with a trophotropic status of the organism. The tendency towards higher levels of T in these animals is consistent with the view that such a psychobiological status may, rather, improve gonadal functions [15].

ACKNOWLEDGEMENTS

This study was supported by the Deutsche Forschungsgemeinschaft (He 1013/2-1). We thank Ms. H. Lehmann and A. Over for excellent technical assistance, and Ms. A. Jung-Dieckheuer for secretarial help. We appreciate the help of Prof. M. Schöneshöfer, Berlin, who provided the corticosterone antibodies.

REFERENCES

1. Anisman, H., J. Irwin and L. S. Sklar. Deficits of escape performance following catecholamine depletion: Implications for behavioral deficits induced by uncontrollable stress. *Psychopharmacology (Berlin)* **64:** 163–170, 1979.
2. Anisman, H. and L. S. Sklar. Catecholamine depletion in mice upon reexposure to stress: Mediation of the escape deficits produced by inescapable shock. *J Comp Physiol Psychol* **93:** 610–625, 1979.
3. Anisman, H., A. Suissa and L. S. Sklar. Escape deficits produced by uncontrollable stress: Antagonism by dopamine and norepinephrine agonists. *Behav Neurol Biol* **28:** 34–47, 1980.
4. Anisman, H. and R. M. Zacharko. Depression: The predisposing influence of stress. *Behav Brain Sci* **5:** 89–137, 1982.
5. Aprison, M. H., R. Takahashi and K. Tachiki. Hypersensitive serotonergic receptors involved in clinical depression—A theory. In: *Neuropharmacology and Behavior*, edited by B. Haber and M. H. Aprison. New York: Plenum Press, 1978, pp. 23–53.
6. Brown, L., R. A. Rosellini, O. B. Samuels and E. P. Riley. Evidence for a serotonergic mechanism of the learned helplessness phenomenon. *Pharmacol Biochem Behav* **17:** 877–883, 1982.
7. Collu, R., W. Gibb and J. R. Ducharme. Role of catecholamines in the inhibitory effect of immobilization stress on testosterone secretion in rats. *Biol Reprod* **30:** 416–422, 1984.
8. Collu, R., Y. Taché and J. R. Ducharme. Hormonal modifications induced by chronic stress in rats. *J Steroid Biochem* **11:** 989–1000, 1979.
9. Ducharme, J. R., Y. Taché, G. Charpenet and R. Collu. Effects of stress on the hypothalamic-pituitary-testicular function in rats. In: *Brain Peptides and Hormones*, edited by R. Collu *et al.* New York: Raven Press, 1982, pp. 305–318.
10. Engel, G. L. and A. H. Schmale. Conservation-withdrawal: A primary regulatory process for organismic homeostasis. In: *Physiology, Emotion & Psychosomatic Illness*, vol 8, edited by Ciba Foundation Symposium. New York: Elsevier, 1972, pp. 57–75.
11. Hassler, R. Striatal control of locomotion, intentional actions and integrating perceptive activity. *J Neurol Sci* **36:** 187–224, 1978.
12. Hellhammer, D. H. *Gehirn und Verhalten.* Münster: Aschendorff, 1983.
13. Hellhammer, D. H. Learned Helplessness—An animal model revisited. In: *The Origins of Depression*, edited by J. Angst. Berlin: Springer, 1983, pp. 147–161.
14. Hellhammer, D. H., J. Hingtgen, S. E. Wade, P. A. Shea and M. H. Aprison. Serotonergic changes in specific areas of rat brain associated with activity-stress gastric lesions. *Psychosom Med* **45:** 115–122, 1983.
15. Hellhammer, D. H., W. Hubert, C. W. Freischem and E. Nieschlag. Male infertility: Relationship among gonadotropins, sex steroids, seminal parameters and personality attitudes. *Psychosom Med*, in press, 1984.
16. Hingtgen, J. N. and M. H. Aprison. Hypersensitive serotonergic receptors and depression, *Behav Brain Sci* **5:** 108–109, 1982.
17. Ludwig, L. and D. H. Hellhammer. Die Wirkung von Cyproheptadin Hydrochlorid auf Gelernte Hilflosigkeit und Vermeidungsverhalten bei Ratten. In: *Bericht über den 31.Kongreß der Deutschen Gesellschaft für Psychologie*, edited by L. Eckensberger. Göttingen: Hofgrefe, 1979, pp. 171–174.
18. Nieschlag, E. and D. L. Loriaux. Radioimmunoassay for plasma testosterone. *J Clin Chem Clin Biochem* **10:** 164–168, 1972.
19. Olpe, H. and A. Schellenberg. Reduced sensitivity of neurons to noradrenaline after chronic treatment with antidepressant drugs. *Eur J Pharmacol* **63:** 7–13, 1980.
20. Petty, F. and A. Sherman. A neurochemical differentiation between exposure to stress and the development of learned helplessness. *Drug Develop Res* **2:** 43–45, 1982.
21. Rea, M. A. and D. H. Hellhammer. Activity-wheel stress: Changes of norepinephrine turnover and the occurrence of gastric lesions. *Psychother Psychosom* Supplement, in press.
22. Shea, P. A. and R. K. Jackson. Liquid chromatography and electrochemical determination of biogenic amines. *Trans Am Soc Neurochem* **10:** 183, 1979.
23. Weiss, J. M. Psychological and behavioral influences on gastrointestinal lesions in animal models. In: *Psychopathology: Experimental Models*, edited by J. Maser and M. Seligman. San Francisco: Freeman, 1977, pp. 232–269.
24. Weiss, J. M., P. A. Goodman, P. G. Losito, S. Corrigan, J. M. Charry and W. H. Bailey: Behavioral depression produced by an uncontrollable stressor: Relationship to norepinephrine, dopamine and serotonin levels in various region of rat brain. *Brain Res Rev* **3:** 167–205, 1981.
25. Zeman, W. and J. R. M. Innes. *Craigie's Neuroanatomy of the Rat.* New York: Academic Press, 1963.