Individual Differences in Non-Regulatory Ingestive Behavior and Catecholamine Systems

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Animals that eat and/or drink in response to electrical stimulation of the lateral hypothalamus (ESLH-pos) are more responsive to both schedule-induced polydipsia (SIP) tests and a series of amphetamine (AMPH) injections than animals that do not exhibit these behaviors (ESLH-neg). Moreover, prior exposure to the behaviorally activating SIP experience, or to AMPH, permanently transformed the ESLH-neg animals into animals that reliably ate or drank during ESLH. Prior treatment with AMPH also increases the water consumed during subsequent SIP tests. Thus, initial of induced differences in sensitivity to activating experiences can determine behavioral propensities.

INTRODUCTION

Evidence that eating and drinking can be evoked in satiated animals by such diverse conditions as electrical stimulation of the lateral hypothalamus, schedule-induced polydipsia, tail-pinch, social facilitation, and numerous non-specific stressors suggests that ingestive behavior can be influenced by factors other than nutritional needs[3,4,7,11,13,14,17,23,28,30,32,36,37,38,42]. We propose calling such eating and drinking 'non-regulatory ingestive behavior' to emphasize that different mechanisms may underlie this behavior and the eating and drinking motivated by nutritional and fluid imbalances[15,33]. What seems to be common to the diverse experimental conditions capable of evoking 'non-regulatory ingestive behavior' is that they all produce behavioral 'activation'[19,23,24]. It has also been suggested that some intermediate level of stress is often involved[1,2,6,35,39].

Of particular relevance to the present investigation is the demonstration that animals differ in their predisposition to engage in 'non-regulatory ingestive behavior'[5,18,19,32,37,40]. Recently, the present authors found that these individual differences may be consistent across experimental conditions as animals that ate and drank in response to electrical stimulation of the lateral hypothalamus (ESLH) exhibited significantly more 'displacement drinking' when tested in a schedule-induced polydipsia (SIP) paradigm[19]. SIP has been considered an example of 'displacement drinking' or 'psychogenic polydipsia' that is often evoked when a hungry animal is frustrated by giving it a small amount of food and then thwarting further eating for a period of time. Although this interpretation has been questioned[12], it has been frequently observed that animals undergoing SIP tests typically become very active and often very irritable[19].

The purpose of the present investigation was to explore the basis of the individual differences in 'non-regulatory ingestive behavior'. As catecholamines are generally recognized to be involved in behavioral activation[1,2,9,10,16,31] and dopamine (DA), in particular, has been implicated in ESLH- and SIP-induced ingestive behavior[20,21,24,25,29,39], we investigated whether some property of DA systems might underlie the differences in 'non-regulatory ingestive be-

havior'. Evidence of a difference in catecholamine systems related to the predisposition to exhibit 'non-regulatory ingestive behavior' has been found. It has also proven possible to increase the predisposition to exhibit 'non-regulatory ingestive behavior' by exposing animals to environmental or biochemical stimulation known to increase the responsiveness of catecholamine systems[41].

Specifically, it is now reported that: (1) rats that display 'non-regulatory ingestive behavior' have a significantly greater response to amphetamine than animals that do not exhibit this behavior: (2) following a regimen of amphetamine, animals display significantly more 'non-regulatory drinking'; and (3) animals that did not eat drink in response to ESLH start to display this behavior after they have been exposed to either a regimen of amphetamine or schedule-induced polydipsia testing.

MATERIALS AND METHODS

Subjects and surgical procedure

The subjects were mature (366–480 g), male Long–Evans hooded rats (Simonsen, Gilroy, CA) that were housed individually in wire-hanging cages. The vivarium was temperature regulated and lights were maintained on a 12-12 h dark-light cycle. Each rat was anesthetized with Equithesin (Jensen-Salsbery, Kansas City, MO) and twisted bipolar stainless steel electrodes (Plastic Products, Roanoke, VA, No. MS 303/1, 25 mm diameter) were bilaterally implanted into the lateral hypothalamus (coordinates: 3.5 mm posterior to bregma, 1.5 mm lateral to the sigittal suture, and 8.4 mm below the surface of the skull surface, which was level between bregma and lambda). The electrodes were fixed to the skull by stainless steel screws and cranioplastic acrylic.

ESLH-testing procedure

One week following surgery, animals were tested in a Plexiglas chamber for the behavior evoked by ESLH. Stimulation consisted of 20 s trains of 60 Hz sine waves alternating with 15 s intertrial intervals. During testing, 75 mg food pellets (P.J. Noyes) were distributed evenly over the floor, and a standard water bottle with a metal drinking tube was attached to one wall. Stimulation intensity was increased in 1 μA steps until the animal either ate or drank, or until the

stimulation produced excessive agitation or 'forced' motor responses that precluded eating or drinking.

Animals that ate or drank were given additional stimulation at a current intensity just above threshold until they ate or drank on 5 consecutive stimulations. The number of food pellets eaten, the duration of drinking, and the current intensity threshold were recorded. Animals that did not eat or drink were given an additional 2–4 tests separated by 48–72 h. After screening with the right hypothalamic electrode, animals were tested for their response to stimulation at the left electrode. Rats that reliably displayed eating, drinking or both behaviors during stimulation at either electrode, were designated ESLH-pos; those that did not eat or drink were classified ESLH-neg.

EXPERIMENT 1

The effect of prior exposure to schedule-induced polydipsia (SIP) on sensitivity to AMPH. Comparison of ESLH-pos and ESLH-neg rats.

Following testing for ESLH-elicited ingestive behavior both ESLH-pos (n = 28) and ESLH-neg (n = 20) rats were divided into two weight matched groups. All rats were reduced to 85% of their free feeding weight. The two experimental groups were given 10 daily 30 min SIP tests in a Plexiglas cage equipped with a food dispenser and two water filled Richter tubes located 5 cm on either side of the dispenser. During the SIP test, a 75 mg food pellet was delivered every 60 s. After each test, the total amount of water consumed was recorded and animals were weighed and given sufficient food in their home cages to assure that they would be close to 85% of their body weight when tested 24 h later. The two control groups were not exposed to the SIP procedure, but received daily handling similar to the experimental animals including placement in the SIP test chambers and food deprivation.

After completion of the 10 SIP tests, all animals were given free access to food for 1 month in their home cages. The experimental (ESLH-pos-SIP, n = 11; ESLH-neg-SIP, n = 10) and control animals (ESLH-pos-CON, n = 17; ESLH-neg-CON, n = 10) were then tested for amphetamine (AMPH) stereotypy following injection of 3.25 mg/kg (i.p.) D-amphetamine sulfate dissolved in 0.9% saline. This dose of AMPH was used because it was shown in pilot

studies to produce individual differences in stereotyped behavior. Beginning 10 min after the AMPH injection each animal's behavior was videotaped for 1 min, every 10 min, for a total of 2 h (i.e. 12, 1 min samples of behavior). An observer, unaware of the animals' history, used the videotape records to rate *stereotypy* on a scale modified from MacLennan and Maier[10] in which: 1 = intermittent activity: 2 = continuous activity; 3 = intermittent stereotypy (stereotyped sniffing, rearing or repetitive head movements); 4 = continuous stereotypy over a wide area; 5 = continuous stereotypy in a restricted area; 6 = pronounced continuous stereotypy in a restricted area; 7 = intermittent stereotyped biting and licking directed at the walls and floor; and 8 = continuous stereotyped biting and licking in a restricted area. In addition, a locomotor activity score was obtained by counting the number of quarter (90°) turns in each 1 min segment.

RESULTS

As is evident in Fig. 1 (top), following the injection of AMPH, the stereotypy scores of the ESLH-pos animals exposed to SIP were significantly higher than the scores of the ESLH-neg-SIP animals (profile analysis: $F = 4.657$, df = 1,19, $P < 0.044$) and also significantly higher than all 3 other groups combined (profile analysis: $F = 5.87$, df = 3,44, $P < 0.002$). While 91% of the ESLH-pos-SIP rats showed stereotyped behavior in a restricted area of the test cage, a more intense response to AMPH than locomotion, 60% of the ESLH-neg-SIP animals and only 15% of the animals in either control group exhibited this behavior at all. This difference was statistically significant ($\chi^2 = 20.37$, df = 2, $P < 0.01$).

Analysis of the locomotor activity scores shown in Fig. 1 (bottom) indicated that ESLH-pos rats that had undergone SIP testing were significantly less active than all other rats (profile analysis: $F = 4.16$, df = 1.33 $P < 0.05$). Rats in this group exhibited an initial increase in locomotion, but within 10 min after the amphetamine injection, stereotypy increased and locomotion declined sharply and remained low throughout the 2 h test (Fig. 1, bottom). This was true only of the ESLH-pos-SIP animals, as the rats in the other 3 groups typically exhibited an increase in locomotor activity following AMPH administration
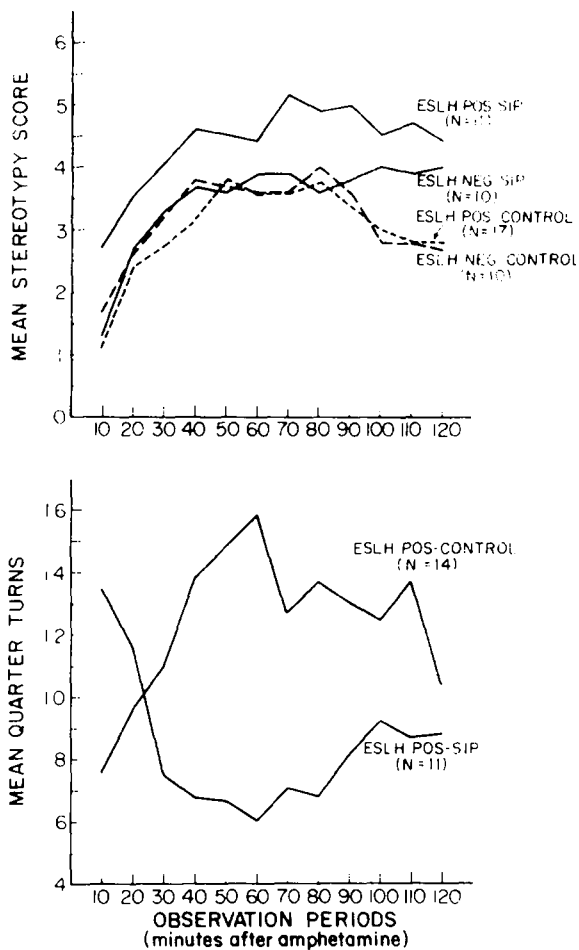

Fig. 1. Top: the average stereotypy score for each 1 min observation period during the 2 h following amphetamine injections. Bottom: the average number of quarter turns in each 1 min observation period.

that was sustained throughout the 2 h test.

EXPERIMENT 2

The effect of AMPH sensitization on ingestive behavior elicited by SIP and ESLH.

Naive rats were implanted with lateral hypothalamic electrodes and tested for ESLH-induced eating and drinking as described in Expt. 1. Only the ESLH-neg rats were used and these were divided into the following 4 groups. Group 1 (AMPH-SIP; n = 7) was given twice daily i.p. injections (8 h apart) of 5 mg/kg AMPH in their home cages for 5 days. This regimen has been shown to increase the responsivity of catecholamine systems and to elevate striatal dopamine

release[26,27]. Group 2 (saline-SIP; n = 6) were given twice daily injections of 0.9% saline on the same schedule. One week following the last injection, when Groups 1 and 2 were at comparable weight, the rats were food deprived to 85% of their free feeding weight and given 10 SIP tests, as described in Expt. 1. Group 3 (AMPH; n = 7) and Group 4 (saline; n = 5) animals were injected with AMPH or saline, respectively, as described above, but were not given SIP tests. Rats in Groups 2 and 4 that received saline injections were partially food deprived during the injection period to control for the weight loss of the AMPH rats (mean weight loss: AMPH −9.29; saline −9.33). Six weeks following completion of the injection schedule all animals were retested with ESLH. At the time of the ESLH testing, animals had been on ad libitum feeding for at least 3 weeks.

RESULTS

The results clearly show that pretreatment with AMPH increased the amount of schedule-induced drinking displayed (Fig. 3). During the SIP testing, ESLH-neg rats that were sensitized with AMPH displayed significantly more drinking than saline-injected animals (ANOVA: $F = 7.33$, df = 1.11, $P < 0.02$). As previously reported, untreated ESLH-neg animals drank very little water during SIP tests[19]. As is evident in Fig. 2, the significant increase in amount of water consumption of the AMPH animals over the 10 test days was particularly striking. This increase over days was statistically significant (ANOVA: $F = 5.502$, df = 9.99, $P < 0.001$). The ESLH-neg rats that received saline injection did not increase their sched-
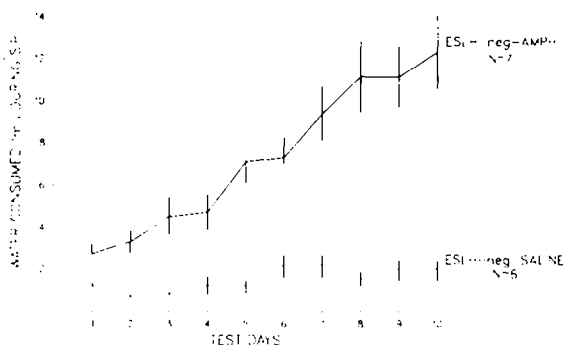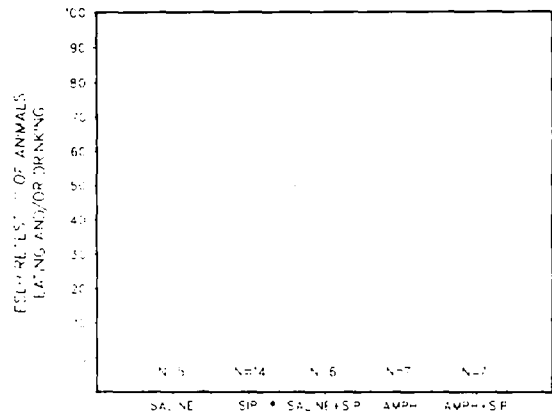

Fig. 3. The percentage of originally ESLH-neg rats that ate or drank when retested for ESLH-elicited behavior after different experiences (see text). (* from Mittleman and Valenstein, 1984) On retest, significantly fewer ESLH-neg rats that recieved saline pretreatment drank than any other group (χ^2 ranged from 4.1 to 6.1, df = 1, $P < 0.05$).

ule-induced drinking during the SIP tests. In addition, whereas 100% of the AMPH animals were drinking by test day 8, only 57% of the saline animals drank even on day 10 and the amount consumed was relatively low.

Exposure to SIP or AMPH significantly changed the response of many animals when they were retested for ESLH-elicited ingestive behavior (Fig. 3). Following AMPH treatment, 57% of the previously ESLH-neg rats in the non-SIP group ate and/or drank during ESLH in contrast to 0% of the saline-non-SIP group. After the SIP experience, 50% of the saline-injected rats became ESLH-pos, while 71% of the rats that were given both AMPH injections and the SIP tests exhibited ESLH-elicited eating and drinking when retested. The animals that became ESLH-pos ate and drank as reliably as the animals initially classified as positive, and they consumed as much. The current threshold for evoking this behavior was also comparable. As the animals continued to eat and drink in response to ESLH when tested repeatedly during a one month period, the change appeared to be permanent.

Fig. 2. The average (± S.E.M) amount of water consumed in each SIP test of rats pretreated with amphetamine or saline.

DISCUSSION

The results lend considerable support to the hypothesis that predisposition to display 'non-regulatory eating and drinking' is related to some property of

catecholamine systems. Expt. 1 demonstrated that the ESLH-pos animals exhibited significantly more stereotypy in response to amphetamine after exposure to a series of behaviorally activating SIP tests. To be noted, however, is the finding that ESLH-pos and ESLH-neg animals did not differ in their response to AMPH unless they had been exposed to the SIP testing schedule (Fig. 1). Apparently, the differences between the ESLH-pos and -neg animals is not evident in their response to AMPH until the neural systems stimulated by this drug have been 'sensitized' by the SIP experience. This 'sensitization' appears to be long-lasting as it was evident when the animals were tested one month after the SIP tests. As the more intense stereotyped responses to AMPH are thought to be dependent on DA mechanisms[8,22], these results suggest that differences in predisposi-

tion to eat and drink in response to ESLH are related to some property of neuronal circuits that utilize this transmitter.

Expt. 2 demonstrated that the majority of ESLH-neg animals, that are 'sensitized' by a regimen of amphetamine injections, become ESLH-pos. Such animals also tend to drink atypically high amounts of water during SIP tests. The percentage of ESLH-neg that became ESLH-pos was greatest in animals that underwent both the amphetamine-sensitization and the SIP testing. These results provide a striking example of how repeated exposure to either environmental or pharmacological experiences that modify catecholamine systems may influence subsequent behavior. We believe the present results have applicability to behaviors other than 'non-regulatory ingestive behaviors'.

REFERENCES

1 Antelman, S.M. and Chiodo, L.A., Amphetamine as a stressor. In I. Creese (Ed.), *Stimulants: Neurochemical, Behavioral, and Clinical Perspectives*, Raven, New York, 1983, pp. 269–290.
2 Antelman, S.M. and Chiodo, L.A., Stress: its effect on interactions among biogenic amines and role in the induction and treatment of disease. In L.L. Iversen, S.D. Iversen and S.H. Snyder (Eds.), *Handbook of Psychopharmacology*, Plenum, New York, 1984, pp. 279–341.
3 Antelman, S.E., Rowland, N.E. and Fisher, A.E., Stimulation-bound ingestive behavior: a view from the tail, *Physiol. Behav.*, 17 (1976) 743–748.
4 Antelman, S.M. and Szechtman, H., Tail-pinch induces eating in sated rats which appears to depend on nigrostriatal dopamine, *Science*, 189 (1975) 731–733.
5 Bachus, S.E. and Valenstein, E.S., Individual behavioral responses to hypothalamic stimulation persist despite destruction of tissue surrounding electrode tip, *Physiol. Behav.*, 23 (1979) 421–426.
6 Brett, L.P. and Levine, S., Schedule-induced polydipsia suppresses pituitary-adrenal activity in rats, *JCPP*, 5 (1979) 946–956.
7 Cantor, M.B., Bad habits: models of induced ingestion in satiated rats and people. In S.A. Miller (Ed.), *Behavior and Nutrition*, Franklin Inst. Press, Philadelphia, 1981, pp. 31–49.
8 Creese, I. and Iversen, S.D., The pharmacological and anatomical substrates of amphetamine response in the rat, *Brain Research*, 83 (1975) 242–248.
9 Curzon, G., Hutson, P.H. and Knot, P.J., Voltammetry in vivo: effect of stressful manipulations and drugs on the caudate nucleus of the rat, *Br. J. Pharmacol.*, 66 (1979) 127P–128P.
10 Dunn, A.J. and Kramarcy, N.R., Neurochemical responses in stress: relationships between the hypothalamic-pituitary-adrenal and catecholamine systems. In L.L. Iver-

sen, S.D. Iversen and S.H. Snyder, (Eds.), *Handbook of Psychopharmacology*, Plenum, New York, 1984, pp. 455–514.
11 Falk, J.L., Production of polydipsia in normal rats by an intermittent food schedule, *Science*, 133 (1961) 195–196.
12 Falk, J.L., Conditions producing psychogenic polydipsia in animals, *Ann. New York Acad. Sci.*, 157 (1969) 569–593.
13 Falk, J.L., The nature and determinants of adjunctive behavior, *Physiol. Behav.*, 6 (1971) 577–588.
14 Katz, D., *Animals and Man*, Penguin, Hammondworth, 1953, pp. 117–118.
15 Kissileff, H.R., Nonhomeostatic controls of drinking. In A.N. Epstein, H.R. Kissileff and E. Stellar (Eds.), *The Neuropsychology of Thirst: New Findings and Advances in Concepts*, V.H. Winston, Washington DC, 1973, pp. 163–198.
16 MacLennan, A.J. and Maier, S.F., Coping and the stress-induced potentiation of stimulant stereotypy in the rat, *Science*, 219 (1983) 1091–1093.
17 Mayer, J.E. and Pudel, V.E., Experimental studies on food-intake in obese and normal-weight subjects, *J. Psychosom. Res.*, 16 (1972) 305–308.
18 Mittleman, G. and Valenstein, E.S., Strain differences in eating and drinking evoked by electrical stimulation of the lateral hypothalamus, *Physiol. Behav.*, 26 (1981) 371–378.
19 Mittleman, G. and Valenstein, E.S., Ingestive behavior evoked by hypothalamic stimulation and schedule-induced polydipsia are related, *Science*, 224 (1984) 415–417.
20 Phillips, A.G. and Fibiger, H.C., The multivariate nature of motivated behavior elicited by electrical stimulation of the lateral hypothalamus. In W.L. Veale and K. Lederis (Eds.), *Current Studies of Hypothalamic Function, Vol. 2*, Karger, Basel, 1978, pp. 195–205.
21 Phillips, A.G. and Nikaido, R.S., Disruption of brain stimulation-induced feeding by dopamine receptor blockade, *Nature (London)*, 258 (1975) 750–751.
22 Randrup, A. and Munkvad, I., Stereotyped activities produced by amphetamine in several animal species *Psycho-*

pharmacologia, 1 (1967) 300–310.

23 Robbins, T.W. and Fray, P.J., Stress-induced eating: fact, fiction or misunderstanding? *Appetite*, 1 (1980) 103–133.

24 Robbins, T.W. and Koob, G.F., Selective disruption of displacement behaviour by lesions of the mesolimbic dopamine system, *Nature (London)*, 285 (1980) 409–412.

25 Robbins, T.W., Roberts, D.C.S. and Koob, G.F., Effects of d-amphetamine and apomorphine upon operant behavior and schedule-induced licking in rats with 6-hydroxydopamine-induced lesions of the nucleus accumbens, *J. Pharmacol. Exp. Ther.*, 224 (1983) 662–673.

26 Robinson, T.E. and Becker, J.B., Behavioral sensitization is accompanied by an enhancement in amphetamine-stimulated dopamine release from striatal tissue in vitro, *Eur. J. Pharmacol.*, 85 (1982) 253–254.

27 Robinson, T.E., Becker, J.B. and Presty, S.K., Long term facilitation of amphetamine-induced rotational behavior and striatal dopamine release produced by a single exposure to amphetamine: sex differences, *Brain Research*, 253 (1982) 231–241.

28 Rowland, N.E. and Antelman, S.M., Stress-induced hyperphagia and obesity in rats: a possible model for understanding human obesity, *Science*, 191 (1976) 310–312.

29 Rowland, N., Marques, D.M. and Fisher, A.E., Comparison of the effects of brain dopamine-depleting lesions upon oral behaviors elicited by tail pinch and electrical brain stimulation, *Physiol. Behav.*, 24 (1980) 273–281.

30 Slowchower, J., Emotional labeling and over-eating in obese and normal weight individuals, *Psychosomatic Med.*, 38 (1976) 131–139.

31 Thierry, A.M., Tassin, J.P., Blanc, G. and Glowinski J., Selective activation of the mesocortical DA system by stress, *Nature (London)*, 263 (1976) 242–244.

32 Valenstein, E.S., Behavior elicited by hypothalamic stimulation: a prepotency hypothesis, *Brain Behav. Evol.*, 2 (1969) 295–316.

33 Valenstein, E.S. Electrical stimulation and hypothalamic function: historical perspective. In A.N. Epstein, H.R. Kissileff and E. Stellar (Eds.), *The Neuropsychology of Thirst: New Findings and Advances in Concepts*, V.H. Winston, Washington, DC, 1973, pp. 155–161.

34 Valenstein, E.S. The interpretation of behavior evoked by electrical stimulation. In A. Wauquier and E.T. Rolls (Eds.), *Brain-Stimulation Reward*, North-Holland, Amsterdam, 1976, pp. 557–575.

35 Valenstein, E.S., Stereotypy and sensory-motor changes evoked by hypothalamic stimulation: possible relation to schizophrenic behavior patterns. In A. Routtenberg (Ed.), *Biology of Reinforcement*, Academic Press, New York, 1980, pp. 39–52.

36 Valenstein, E.S., Cox, V.C. and Kakolewski, J.W., Modification of motivated behavior elicited by electrical stimulation of the hypothalamus, *Science* 159 (1968) 1119–1121.

37 Valenstein, E.S., Cox, V.C. and Kakolewski, J.W., A re-examination of the role of the hypothalamus in motivation, *Psychol. Rev.*, 77 (1970) 16–31.

38 Wayner, M.J., Barone, F.C. and Loullis, C.C., The lateral hypothalamus and adjunctive behavior. In P.J. Morgane and J. Panksepp (Eds.), *Handbook of the Hypothalamus, Vol. 3-Part B. Behavioral Studies of the Hypothalamus*, Marcel Dekker, New York, 1981, pp. 107–145.

39 Wallace, M., Singer, G., Finlay, J. and Gibson, S., The effect of 6-OHDA lesions of the nucleus accumbens septum on schedule-induced drinking, wheelrunning and corticosterone levels in the rat, *Pharmcol. Biochem. Behav.*, 18 (1983) 129–136.

40 Wise, R.A., Individual differences in the effects of hypothalamic stimulation: the role of stimulation locus, *Physiol. Behav.*, 6 (1971) 569–572.

41 Yuwiler, A., Stress. In A. Lajtha (Ed.), *Handbook of Neurochemistry, Vol. 6*, Plenum, New York, 1971, pp. 103–171.

42 Zajonc, R.B., Social facilitation, *Science*, 149 (1965) 269–274.