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Environmental Determinants of Parachloroamphetamine Toxicity in Rats

JEFFREY A. GALLUS, ROBERT G. SEWELL, JR., NEARCHOS I. NEARCHOU AND FREDERICK P. GAULT

Department of Psychology, Western Michigan University, Kalamazoo, MI 49008

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GALLUS, J. A., R. G. SEWELL, JR., N. I. NEARCHOU AND F. P. GAULT. *Environmental determinants of parachloroamphetamine toxicity in rats*. PHARMAC. BIOCHEM. BEHAV. 17(3) 467–471, 1982.—The present investigation assessed PCA toxicity at 0.0, 5.0, and 10.0 mg/kg, in both social (4 rats per cage) and non-social (acrylic tube-restraint or tube restraint-plus-tail shock) circumstances with 16 rats per drug-environment condition. The results indicated that no dose of PCA alone yielded mortality under individual housing, and similarly no environmental circumstance by itself yielded mortality in the absence of PCA. However, various drug-environment interactions produced a dose-related enhancement of PCA toxicity. For both 5.0 mg/kg and 10 mg/kg parachloroamphetamine dose levels, restraint-plus-shock generated the highest percent mortality, followed by restraint-only, with conspecific aggregation producing a mortality incidence lower still. Further, the mortality displayed under each of these environmental conditions was greater for the 10.0 mg/kg PCA treatment than for the 5.0 mg/kg treatment. The results are discussed in terms of the relative aversiveness of the environmental setting and it is suggested that stress-related drug toxicity may be further analyzed in non-social settings. It is proposed that toxic environment-PCA interactions may result from altered cardiovascular and/or thermoregulatory processes, mediated by enhanced catecholaminergic activity.

p-Chloroamphetamine Aggregation toxicity Restraint Shock Lethality Stress Environmental determinants Catecholamines

TOXICOLOGICAL studies have indicated that housing conditions are influential determinants of the lethal properties of drugs, particularly those of the sympathomimetic amines [10, 14, 19, 24, 26, 61, 65, 66]. In investigations of this kind, mice or rats, are typically group-housed prior to drug intervention, injected, and then either housed individually or in aggregation for the duration of drug effect [26,65]. Various studies have shown *d*-amphetamine to be much more toxic in acutely grouped rodents than in acutely isolated subjects [10, 14, 26, 61]. Nielson, *et al.* [43] have demonstrated this effect for the halogenated amphetamine derivative, parachloroamphetamine (PCA). From both a pharmacological and behavioral point of view, aggregation toxicity is of interest as it demonstrates that environmental circumstance is an important determinant of drug action. However, the mechanism by which PCA and other sympathomimetic amines interact with housing population density to yield mortality remains unclear.

As in all social circumstances, the stimulation provided by group housing permits the confluence and covariation of several factors, any of which may conceivably be responsible for the aggregation toxicity effect. It is well-known for instance, that grouping of unfamilar conspecifics is stressful, yielding hormonal, neurochemical, and behavioral changes similar to those produced by a variety of aversive events (e.g., restraint or electric shock) [19, 24, 61]. In analyzing the aggregation toxicity effects of the serotonin depletor PCA, we speculated that other kinds of aversive events might also enhance the lethal properties of this drug. The present study corroborates the finding that group housing does enhance PCA's lethal properties and demonstrates that similar results are produced by aversive events of a non-social nature.

METHOD

Subjects

One hundred and ninety-two experimentally naive, male Sprague-Dawley rats, obtained from Harlan Industries (Indianapolis, IN) served. All subjects were at least six months of age and were given free access to Purina Laboratory Rodent Chow and to water. Prior to the initiation of the study all subjects were housed in groups of four rats per cage. At all points in the study the rats were colony room-housed with a twelve hour day/night cycle under constant temperature (23°C ca). At study's onset, subjects received random assignment to the various drug-environment conditions.

Apparatus

Housing conditions apparatus. This apparatus consisted of simple stainless steel cages, each measuring 22 cm by 21 cm high by 30 cm deep (Unifab Corp., Kalamazoo, MI), located in the colony room. A food hopper and watering bottle were attached to each of these cages allowing free access to rodent chow and water.

Restraint and shock conditions apparatus. This apparatus consisted of four identical instruments, each generally similar to that described by Azrin, Rubin and Hutchinson [1]. Each instrument incorporated two principal features: (1) a restraining tube into which the rat was loosely inserted with its tail exiting through the rear of the tube toward dual electrodes; (2) two secured surface electrodes which were laid across the tail. Specifically, an acrylic baseplate (51 cm long) secured two stockades into which snapped an acrylic restraining tube (9.5 cm dia., 28 cm long) with floor, and removable cap at one end. A slit in the tube's ceiling allowed for the "threading" of the animal into the tube (this slit was subsequently covered with a snap-on acrylic strip which prevented escape). A hole (2.5 cm × 2.5 cm) in the tube's floor allowed feces and urine to exit. From the tube's rear the subject's tail protruded and was taped to an extended acrylic bar so that the tape was posterior to both electrodes. The tail restraint bar was connected to the restraint tube by two acrylic supports. To the top of each acrylic support was hinged an aluminum electrode (0.95 cm × 0.95 cm × 10.0 cm). The tail contact areas of the two electrodes were approximately 2.5 cm apart.

Each electrode and restraint-tube assembly was enclosed in a force-ventilated, and sound attenuating chamber equipped with masking noise from a running fan and "white nosie" (80 dB). Shock was produced by a Grason-Stadler Shock Generator (model #700). Duration of exposure to chamber illumination (a single GE 7.5 watt bulb), ventilation, and white noise, as well as parameters of shock (when delivered), were controlled by conventional electromechanical equipment.

Procedure

Subjects were injected with either saline, or *p*-chloroamphetamine (PCA) at a dose of either 5.0 mg/kg or 10.0 mg/kg. All injections were intraperitoneal and 0.5 cc in volume. All PCA administrations were prepared from *d,l*-para-chloroamphetamine hydrochloride (Sigma Chemical Co., St Louis, MO) and delivered in isotonic saline vehicle. Ten minutes after injection subjects were randomly selected for challenge with one of four environmental circumstances. These included either one of two "housing condition" situations, or one of two "restraint tube" situations. Those animals assigned to one of the housing conditions were placed either (a) individually into standard Unifab home cages located within the colony room, or (b) into groups of four stranger conspecifics in Unifab cages located in the colony room. These animals remained in their respective housing conditions for 24 hours. Those animals assigned to one of the restraint tube conditions were placed either (c) into a restraint tube for 0.5 hours without shock and then returned to a colony room, Unifab cage for individual housing, or (d) in a restraint tube for 0.5 hours with shock and then returned to a colony room, Unifab cage for individual housing. Thus, a total of twelve groups was generated wherein each of three drug conditions was further subdivided into four environmental conditions. These treatment conditions are summarized in Table 1. Each group consisted of 16 subjects.

For the restraint-plus-shock and the restraint-only conditions, each subject's tail was taped down to the acrylic tailstock with Zonas® 2.5 cm wide porous tape (Johnson and Johnson, New Brunswick, NJ). Subsequently, each tail was cleansed with isopropyl alcohol. Electro-Sol EKG Cream® (Lumiscope Co., New York, NY) was then firmly massaged into tail segments beneath the electrodes for approximately 10 seconds. A 0.5 hour restraint-exposure session then ensued during which masking nosie (80 dB) and house-light illumination were presented. For the restraint-plus-shock groups, there occurred concurrent fixed-time 2.0 minute tail shock such that 15 shocks were delivered during the session. Shock deliveries were 500 msec in duration, unsignalled, and 4.0 mAmp in intensity. All injections and environmental challenges were initiated between the hours of 10:00 a.m. and 5:00 p.m. Mortality was assessed at twenty-four hours post-injection, as preliminary evidence had shown that development of PCA-toxicity was unlikely after this period.

TABLE 1

DRUG TREATMENT AND ENVIRONMENTAL CONDITION FOR EACH GROUP

Group	Drug	Dose (mg/kg)	Environmental Condition	N
(1.)	Saline	—	(A.) Individual Housing	16
(2.)	Saline	—	(B.) Group Housing	16
(3.)	Saline	—	(C.) Restraint-Only	16
(4.)	Saline	—	(D.) Restraint-Plus-Shock	16
(5.)	PCA	5.0	(A.) Individual Housing	16
(6.)	PCA	5.0	(B.) Group Housing	16
(7.)	PCA	5.0	(C.) Restraint-Only	16
(8.)	PCA	5.0	(D.) Restraint-Plus-Shock	16
(9.)	PCA	10.0	(A.) Individual Housing	16
(10.)	PCA	10.0	(B.) Group Housing	16
(11.)	PCA	10.0	(C.) Restraint-Only	16
(12.)	PCA	10.0	(D.) Restraint-Plus-Shock	16

RESULTS

Figure 1 shows the percent mortality, observed as a function of the drug dose and the enviornmental circumstance presented. No deaths occurred in any saline group, regardless of environmental condition. In addition, no deaths occurred for individually housed animals regardless of drug presence or dose. This indicates that no single environmental challenge alone, nor any single drug treatment alone, was sufficient to produce lethal reactions. Group housing with unfamiliar conspecifics, restraint-only, and restraint-plus-shock did yield lethal reactions when subjects had been previously treated with para-chloroamphetamine. For those animals in the group-housed condition, post-mortem inspection of carcasses revealed little evidence of biting-induced tissue damage, thus suggesting death via conspecific attack as unlikely. Statistical analysis via Chi Square procedures indicated that these differences were highly significant: $\chi^2(25)=60.0$, $p<0.01$, contingency coefficient = 0.4082483. Taken together, these facts indicate that lethality was a result of a drug-environment interaction.

For each parachloroamphetamine dose level, restraint-plus-shock yielded the highest mortality incidence, followed by restraint-only with conspecific aggregation producing a percent mortality lesser still. As shown in Fig. 1, this drug-environment interaction yielded toxicity which was dose-related. Injections of 10 mg/kg produced a greater percent mortality than administration of 5 mg/kg for each enviornmental challenge in which toxicity was observed. Thus, for the group-housed condition, 10 mg/kg produced 37.5% lethality whereas 5 mg/kg yielded no deaths. For the restraint-only condition, 10 mg/kg yielded 50% lethality and 5 mg/kg yielded 31.3% lethality while for the restraint-plus-

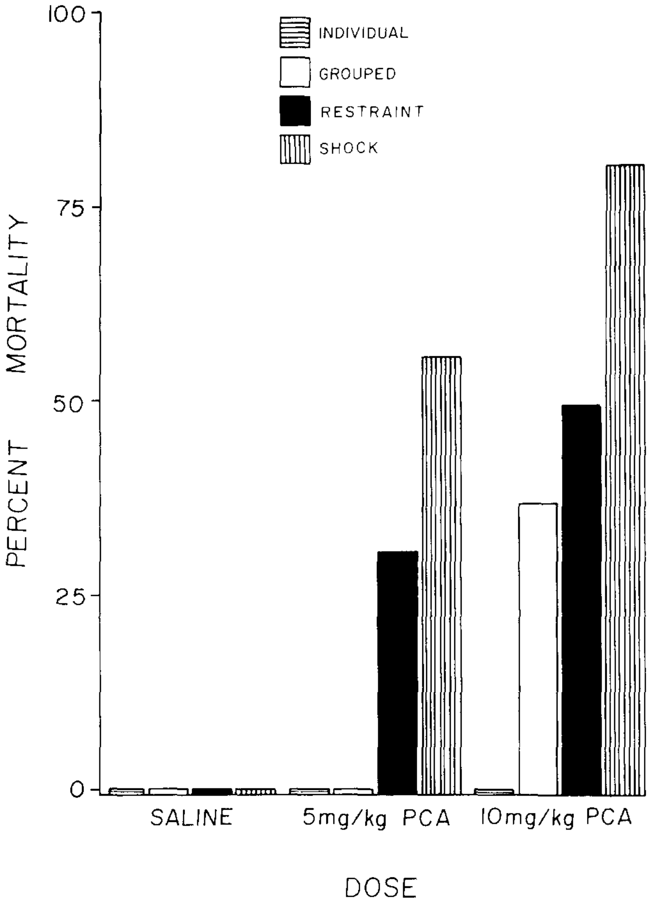

FIG. 1. Percent mortality 24-hours post-injection for groups of 16 subjects which were exposed to one of four environmental conditions (individual housing, group housing, restraint-only, or restraint-plus-shock) and one of three drug treatments (saline, 5.0 mg/kg PCA, or 10.0 mg/kg PCA).

shock condition, 10 mg/kg produced a percent mortality of 81.2% and 5 mg/kg effected a 56.3% death rate.

DISCUSSION

This experiment demonstrated toxic drug-environment interactions for para-chloroamphetamine which occurred in both social and non-social circumstances. Neither environmental circumstance nor drug treatment was lethally toxic when presented alone. However, when drug and various environmental challenges were presented in concert, toxic interactions appeared and were dose-related. Under PCA treatment, restraint-plus-shock produced the greatest percent morality followed by simple restraint while crowding of unfamiliar conspecifics produced a lesser percent mortality. These findings thus corroborate several previous reports of toxic drug-environment interactions. The toxicity of *d*-amphetamine has been related to the stress of aggregation and electric shock [24,65]; morphine aggregation toxicity related to the stress of aggregation and tactile stimulation [18,40]; and digitalis toxicity related to restraint stress [42].

Taken collectively, these data show that drug-environment interactions occur in both social and non-social settings, and indicate that determinants of stress-related drug toxicity may be evaluated in situations simpler than those afforded by the social environment. In addition, these data emphasize that a drug's lethal dose-50 characteristics (LD_{50}) (e.g., the dose of drug at which 50% of subjects die) should not be considered as immutable properties of the drug. Rather, the LD_{50} index appears to be highly specific to environmental context.

It has been repeatedly shown that animals will escape and avoid environments which are crowded [8,9], yield physical restraint [2], or involve electric shock [5,28]. Although in the present study no attempt was made to index the degree of aversiveness associated with each enviornmental condition, it seems likely that restraint-plus-shock was more aversive than restraint-alone, which was in turn more aversive than individual housing. On a speculative level, the present findings have suggested that the greater the aversiveness associated with a given environment, the greater will be the toxic interaction with the sympathomimetic amines.

Acute exposure to various aversive stimuli enhances both central and peripheral sympathetic functions via mediating hypothalamic events [3, 23, 36, 41]. Increased catecholamine synthesis and release occur, as well as increased biosynthesis of related enzymes (e.g., tyrosine hydroxylase) in brain and adrenal medulla [4, 30, 37, 62]. Aversive stimuli yield altered cardiovascular function including tachycardia [6,17], increased arterial blood pressure [7,27], and increased release of norepinephrine from heart [64]. Noxious circumstances also produce emotional behaviors [29], locomotion [48], changes in body temperature [11, 14, 48, 60, 67], and various peripheral manifestations of sympatho-medullary action such as piloerection, mydriasis, and proptosis [31].

Within minutes after parenteral parachloroamphetamine administration serotonin is released from CNS neurons [15, 44, 45, 50] yielding a serotonin-mediated abnormal motor syndrome [15, 25, 53, 63]. There then occurs a well-documented, steady decline in serotonin and 5-hydroxyindoleacetic acid levels which persists for some months [34, 39, 44, 52]. Besides serotonergic changes, however, PCA also induces marked alterations in CNS catecholaminergic activity, for short durations (24 hours, maximum). PCA yields pronounced release of catecholamines [15, 34, 56, 59] with concurrent enhancement of tyrosine hydroxylase activity [51] and catecholamine turnover [13]. Catecholamine reuptake into CNS neurons is simultaneously diminished [34,49]. These catecholaminergic changes have been demonstrated *in vivo*, in hypothalamus [59] and other brain structures [58]. Catecholaminergic shifts are temporally-related to PCA-induced hyperthermia [20, 35, 46, 47], accelerated cardiovascular function [43] and enhancement of locomotor [13, 21, 32, 33, 38, 43, 53, 58] and aversively motivated behaviors [16, 55, 57]. Thus, PCA and aversive environmental events can each yield enhanced sympatho-medullary functions, accompanied by hypothalamic activation, increased arterial blood pressure, tachycardia, and hyperthermia. Cardiovascular and/or thermoregulatory functions, mediated by catecholaminergic activity, are therefore suggested as potential mechanisms involved in toxic PCA-environment synergisms.

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REFERENCES

1. Azrin, N. H., H. B. Rubin and R. R. Hutchinson. Biting attack by rats in response to aversive shock. *J. exp. Analysis Behav.* **11:** 633–640, 1968.
2. Barchas, J. D. and D. Freedman. Response to psychological stress. *Biochem. Pharmac.* **12:** 1232–1235, 1957.
3. Barrows, S., E. Luschei, M. Nathan and C. A. Saslow. A training technique for the daily chairing of monkeys. *J. exp. Analyses Behav.* **9:** 680, 1966.
4. Bliss, E. L., J. Ailion and J. Zwanziger. Metabolism of norepinephrine, serotonin, and dopamine in rat brain with stress. *J. Pharmac. exp. Ther.* **164:** 122–134, 1968.
5. Boren, J. J., M. Sidman and R. J. Hernstein. Avoidance, escape, and extinction as functions of shock intensity. *J. comp. physiol. Psychol.* **52:** 420–425, 1959.
6. Boshes, B. Emotions, hypothalamus, and the cardiovascular system. *A. J. Cardiol.* **1:** 212–223, 1958.
7. Brady, J. and A. Harris, The experimental production of altered physiological states: Concurrent and contingent behavioral models. In: *Handbook of Operant Behavior*, edited by W. K. Hönig and J. E. R. Staddon. Englewood Cliffs, NJ: Prentice-Hall, 1977, pp. 596–618.
8. Brown, J. L. *The Evolution of Behavior.* New York: Norton, 1975, p. 676.
9. Calhoun, J. B. Population density and social pathology. *Scient. Am.* **206:** 139–148, 1962.
10. Chance, M. R. A. Aggregation as a factor in influencing the toxicity of sympathetic amines in mice. *J. Pharmac. exp. Ther.* **87:** 214–219, 1946.
11. Clark, W. C., H. J. Blackman and J. E. Preston. Certain factors in aggregated mice d-amphetamine toxicity. *Archs int. Pharmacodyn. Thér.* **170:** 350–363, 1967.
12. Costa, E. Parachloroamphetamine effects on turnover. *Psychopharmac. Bull.* **12:** 51–52, 1976.
13. Costa, E., K. Naimzada and A. Revuelta. Effects of phenmetrazine, aminorex, and parachloroamphetamine on the motor activity and turnover rate of brain catecholamines. *Br. J. Pharmac.* **43:** 570–579, 1971.
14. Craig, A. L. and H. J. Kupferberg. Hyperthermia in d-amphetamine toxicity in aggregated mice of different strains. *J. Pharmac. exp. Ther.* **180:** 616–624, 1972.
15. Curzon, G., J. C. Fernando and A. J. Less. Backward walking and circling: responses induced by drug treatments which cause simultaneous release of catecholamines and 5-hydroxytryptamine. *Br. J. Pharmac.* **66:** 573–579, 1979.
16. Davis, M. and M. H. Sheard. p-Chloroamphetamine: acute and chronic effects on habituation and sensitization of the acoustic startle response in rats. *Eur. J. Pharmac.* **35:** 261–273, 1976.
17. Davis, R. C., A. M. Buchwald and R. W. Frankmann. Autonomic and muscular responses and their relation to simple stimuli. *Psychol. Monogr.* **69:** 1–71, 1955.
18. Davis, W. M. and C. C. Brister. Increased toxicity of morphine-like analgesic in aggregated mice. *J. Pharm. Pharmac.* **23:** 882–884, 1971.
19. DeFeudis, F. V. Cerebral, biochemical, and pharmacological changes in differentially housed mice. In: *Current Developments in Psychopharmacology*, vol. 1, edited by W. B. Essman. New York: Spectrum Publications, 1975, pp. 143–202.
20. Frey, H. Hyperthermia induced by amphetamine, p-chloroamphetamine, and fenfluramine in the rat. *Pharmacology* **13:** 163–176, 1975.
21. Frey, H. and M. P. Magnussen. Different control mediation of the stimulant effects of amphetamine and its p-chloro analogue. *Biochem. Pharmac.* **17:** 1299–1307, 1968.
22. Fuller, R. W. Structure-activity relationships among the halogenated amphetamines. *Ann. N.Y. Acad. Sci.* **305:** 147–159, 1978.
23. Glowinski, J. Effects of amphetamine on various aspects of catecholamine metabolism in the central nervous system of the rat. In: *International Symposium on Amphetamines and Related Compounds*, edited by E. Costa and S. Garattini. New York: Raven Press, 1970, pp. 301–316.
24. Goldberg, M. E. and A. I. Salama. Amphetamine toxicity and brain monoamines in three models of stress. *Toxic. appl. Pharmac.* **14:** 447–456, 1969.
25. Growdon, J. H. Postural changes, tremor, and myoclonus in the rat immediately following injections of p-chloroamphetamine. *Neurology* **27:** 1074–1077, 1977.
26. Gunn, J. A. and M. R. Gurd. The action of some amines related to adrenaline cyclohexylalkylamines. *J. Physiol.* **97:** 453–470, 1940.
27. Hilton, S. M. Hypothalamic regulation of the cardiovascular system. *Br. med. Bull.* **22:** 243–248, 1966.
28. Hineline, P. N. Negative reinforcement and avoidance. In: *Handbook of Operant Behavior*, edited by W. K. Hönig and J. E. R. Staddon. Englewood Cliffs, NJ: Prentice-Hall, 1977, pp. 364–414.
29. Hutchinson, R. R. By-products of aversive control. In: *Handbook of Operant Behavior*, edited by W. K. Hönig and J. E. R. Staddon. Englewood Cliffs, NJ: Prentice-Hall, 1977, pp. 415–431.
30. Kenessey, A. and S. Huszti. The effect of monoamine oxidase inhibitors on the synthesis and degradation of catecholamines in immobilized rats. In: *Catecholamines and Stress*, edited by E. Usdin, R. Kventnansky and I. Kopin. New York: Pergamon Press, 1976, pp. 331–341.
31. Koizumi, K. and C. M. Brooks. The integration of autonomic system actions: A discussion of autonomic reflexes, their control and their association with somatic reactions. *Ergebn. Physiol.* **67:** 1–68, 1972.
32. Lassen, J. B. The effect of p-chloroamphetamine on motility in rats after inhibition of monoamine synthesis, storage, uptake, and receptor interaction. *Psychopharmacology* **34:** 243–254, 1974.
33. Lassen, J. B. Influence of the new 5-HT uptake inhibitor paroxetine on hypermotility in rats produced by p-chloroamphetamine (PCA) and 4,alpha-dimethyl-7-tyramine (H 77/77). *Psychopharmacology* **57:** 151–153, 1978.
34. Leonard, B. E. Acute and chronic effects of 4-chloroamphetamine on monoamine metabolism in the rat brain. *Psychopharmacologia* **46:** 11–18, 1976.
35. Mantegazza, P., E. E. Muller, M. K. Naimzada and M. Riva. Studies on the lack of correlation between hyperthermia, hyperactivity and anorexia induced by amphetamine. In: *International Symposium on Amphetamines and Related Compounds*, edited by E. Costa and S. Garattini. New York: Raven Press, 1970, pp. 559–575.
36. Matlina, E. Sh. Main phases of catecholamine metabolism under stress. In: *Catecholamines and Stress*, edited by E. Usdin, R. Kventnansky and I. Kopin. New York: Pergamon Press, 1975, pp. 353–366.
37. Maynert, E. W. and R. Lewi. Stress-induced release of brain norepinephrine and its inhibition by drugs. *J. Pharmac. exp. Ther.* **143:** 90–95, 1964.
38. Messing, R. B., L. Phebus, L. A. Fisher and L. D. Lytle. Effects of p-chloroamphetamine on locomotor activity and brain 5-hydroxyindoles. *Neuropharmacology* **15:** 157–163, 1976.
39. Miller, K. E., E. Sanders-Bush and J. V. Dingell. p-Chloroamphetamine: species differences in the rate of metabolism and the lowering of cerebral serotonin. *Biochem. Pharmac.* **20:** 500–503, 1971.

40. Mohrland, J. S. and A. L. Craigmill. Possible mechanism for the enhanced lethality of morphine in aggregated mice. *Pharmac. Biochem. Behav.* **13:** 475–477, 1980.
41. Moore, K. E. and E. W. Lariviere. Effects of stress and d-amphetamine on rat brain catecholamines. *Biochem. Pharmac.* **13:** 1098–1100, 1964.
42. Natelson, B. H., S. L. Hoffman and N. A. Cagin. A role for environmental factors in the production of digitalis toxicity. *Pharmac. Biochem. Behav.* **12:** 235–237, 1980.
43. Nielson, C. K., M. P. Magnussen, E. Kampmann and H.-H. Frey. Pharmacological properties of racemic and optically active p-chloroamphetamine. *Archs int. Pharmacodyn. Thér.* **170:** 428–443, 1967.
44. Pletscher, A., M. DaPrada, W. Burkard, G. Barthalini, F. Steiner, H. Bruderer and F. Bigler. Arylalkylamines with different effects on the metabolism of aromatic monoamines. *J. Pharmac. exp. Ther.* **154:** 64–72, 1966.
45. Pletscher, A., M. DaPrada and W. Burkard. The effects of substituted phenylethylamines on the metabolism of biogenic amines. In: *International Symposium on Amphetamines and Related Compounds*, edited by E. Costa and S. Garattini. New York: Raven Press, 1970, pp. 331–341.
46. Quock, R. M. and B. G. Weick. p-Chloroamphetamine-induced hyperthermia pharmacologically distinct from fenfluramine-induced hyperthermia. *J. Pharm. Pharmac.* **31:** 27–32, 1979.
47. Quock, R. M., B. G. Weick and G. A. Beal. Comparison of the effects of hyperthermic serotonergic agents in the rabbit. *Proc. west. Pharmac. Soc.* **19:** 100–101, 1976.
48. Saito, H., A. Morita, I. Niyazaki and K. Takagi. Comparison of the effects of various stresses on biogenic amines in the central nervous system and animal symptoms. In: *Catecholamines and Stress*, edited by E. Usdin, R. Kventnansky and I. Kopin. New York: Pergamon Press, 1976, pp. 95–103.
49. Sanders-Bush, E., J. Bushing and F. Sulser. Long-term effects of p-chloroampetamine and related drugs on central serotonergic mechanisms. *J. Pharmac. exp. Ther.* **192:** 33–41, 1975.
50. Sanders-Bush, E., D. A. Gallager and F. Sulser. On the mechanism of brain 5-hydroxytryptamine depletion by p-chloroamphetamine and related drugs and the specificity of their action. In: *Advances in Biochemical Psychopharmacology*, vol. 10, edited by E. Costa, G. L. Gessa and M. Sandler. New York: Raven Press, 1974, pp. 185–194.
51. Sanders-Bush, E. and L. R. Steranka. Immediate and long-term effects of p-chloroamphetamine on brain amines. *Ann. N.Y. Acad. Sci.* **305:** 208–221, 1978.
52. Sanders-Bush, E. and F. Sulser. p-Chloroamphetamine: in-vivo investigations on the mechanism of action of the selective depletion of cerebral serotonin. *J. Pharmac. exp. Ther.* **175:** 419–426, 1970.
53. Scheel-Kruger, J. Behavioral and biochemical comparisons of amphetamine derivatives, cocaine, benztropine, and tricyclic antidepressant drugs. *Eur. J. Pharmac.* **18:** 63–73, 1972.
54. Scheffe, H. *The Analysis of Variance.* New York: John Wiley, 1959, p. 369.
55. Steranka, L. R., R. J. Barrett and E. Sanders-Bush. Facilitation of Sidman avoidance performance by p-chloroamphetamine: role of biogenic amines. *Neuropharmacology* **16:** 751–759, 1977.
56. Steranka, L. and E. Sanders-Bush. Temporal effects of p-chloroamphetamine on catecholamine synthesis. *Eur. J. Pharmac.* **45:** 83–86, 1977.
57. Steranka, L. R., E. Sanders-Bush and R. J. Barrett. Tolerance to p-chloroamphetamine effects on Sidman avoidance performance and catecholamine metabolism. *Neuropharmacology* **16:** 761–769, 1977.
58. Strada, S. J., E. Sanders-Bush and F. Sulser. Parachloroamphetamine: temporal relationship between psychomotor stimulation and metabolism of brain norepinephrine. *Biochem. Pharmac.* **19:** 2621–2630, 1970.
59. Strada, S. J. and F. Sulser. Comparative effects of parachloroamphetamine and amphetamine on metabolism and in-vivo release of 3-H-norepinephrine in the hypothalamus. *Eur. J. Pharmac.* **15:** 45–51, 1971.
60. Swan, H. *Thermoregulation and Bioenergetics: Patterns of Vertebrate Survival.* New York: American Elsevier, 1974, p. 317.
61. Swinyard, E. A., L. D. Clark, J. T. Miuyara and H. H. Wolf. Studies on the mechanisms of amphetamine toxicity in aggregated mice. *J. Pharmac. exp. Ther.* **132:** 97–102, 1961.
62. Thierry, A. M., F. Javoy, J. Glowinski and S. S. Kety. Effects of stress on the metabolism of norepinephrine, dopamine, and serotonin in the central nervous system of the rat. I. modifications of norepinephrine turnover. *J. Pharm. exp. Ther.* **163:** 163–171, 1968.
63. Trulson, M. E. and B. L. Jacobs. Behavioral evidence for the rapid release of CNS serotonin by parachloroamphetamine and fenfluramine. *Eur. J. Pharmac.* **36:** 149–154, 1976.
64. Weil-Fugazza, J. and F. Godefroy. Effect of acute stress on norepinephrine and 5-hydroxytryptamine in rats. In: *Catecholamines and Stress*, edited by E. Usdin, R. Kventnansky and I. Kopin. New York: Pergamon Press, 1976, pp. 469–474.
65. Weiss, B., V. G. Laties and F. L. Blanton. Amphetamine toxicity in rats and mice subjected to stress. *J. Pharmac. exp. Ther.* **132:** 366–371, 1961.
66. Welch, B. L. and A. S. Welch. Graded effect of social stimulation on d-amphetamine toxicity, aggressiveness and heart and adrenal weight. *J. Pharmac. exp. Ther.* **151:** 331–338, 1966.
67. Welch, B. L. and A. S. Welch. Chronic social stimulation and tolerance to amphetamine: interaction effects of amphetamine and natural nervous stimulation upon brain amines and behavior. In: *Current Concepts in Amphetamine Abuse*, edited by E. H. Ellinwood, Jr. and S. Cohen. Washington, DC: United States Gov't Printing Office, 1973, pp. 107–136.