Pharmacology Biochemistry & Behavior, Vol. 23, pp. 917–920, 1985. © Ankho International Inc. Printed in the U.S.A. 0091-3057/85 $3.00 + .00

Similarities in Feeding Behavior of Chronic Methamphetamine Treated and Withdrawn Rats to VMH Lesioned Rats

KURT KRAEUCHI, KLAUS RUDOLPH,
ANNA WIRZ-JUSTICE AND HANS FEER

Psychiatrische Universitätsklinik, 4025 Basel (Switzerland)

Received 6 August 1984

KRAEUCHI, K., K. RUDOLPH, A. WIRZ-JUSTICE AND H. FEER. *Similarities in feeding behavior of chronic methamphetamine treated and withdrawn rats to VMH lesioned rats.* PHARMACOL BIOCHEM BEHAV **23**(6) 917–920, 1985.—During chronic methamphetamine (M) administration and after drug withdrawal, total daily food intake, water consumption and body weight increase was measured. Additionally, food intake in the early light phase provided an index of normal circadian rhythmicity. A parallel development of tolerance to the anorexic effect of M and increased feeding in the early light phase occured. A further abnormal behavior of both chronic M-treated and withdrawn rats was the lack of preference reversal when given free access to concentrated vs. diluted glucose solutions. Both disturbed circadian feeding rhythmicity and inhibition of the glucose preference reversal are found in rats with ventromedial hypothalamic (VMH) lesions. Reduced food intake and diminished body weight increase is a characteristic of lateral hypothalamic lesions. By analogy, chronic M-treatment could be considered to induce a functional state similar to lesions of the medial and lateral hypothalamus, each with a different time course.

Chronic methamphetamine Withdrawal Feeding Body weight Circadian rhythmicity Tolerance
Glucose-preference-test Medial and lateral hypothalamus

IT is well-known that acute amphetamine induces anorexia and body weight loss [9,10]. With chronic administration tolerance develops to the anorexic effect, whereas body weight remains reduced [9, 10, 16]. On withdrawal, rebound feeding and increase in body weight occurs [5, 9, 16]. The acute anorexic effect of amphetamine is considered to be due to catecholamine release (e.g., noradrenaline) in the lateral hypothalamus acting through a β-adrenoceptor mechanism [7]; lateral hypothalamic lesions reduce this effect [7,16]. In contrast, the central mechanisms of anorexic tolerance are still unclear. It has been proposed that the medial hypothalamus may be involved, since lesions of the ventromedial hypothalamus (VMH) inhibit the development of tolerance to the amphetamine induced anorexia, but not the acute food suppression [16]. VMH lesions disturb circadian food intake rhythmicity so that eating in the light phase is increased [2,8]. Furthermore, rats with VMH lesions do not exhibit the usual preference reversal seen in normal rats during free access to concentrated vs. dilute glucose solution [15]. We therefore investigated both food intake in the early light phase (an index of normal circadian rhythmicity) and the glucose-preference-test (GPT) as tools to examine the functional state of the medial hypothalamus in chronic M-treated and withdrawn rats in comparison with controls.

METHOD

Male Wistar Füllinsdorf rats (n=21, body weight: 123±2 g (S.E.M.), October 1983) were kept individually at 22°C, food (NAFAG, 1 g=12.2 KJ) and water ad lib, under a light:dark (LD) cycle of 12:12 with lights on at 7:00. At the beginning of the experiment, the rats were randomly divided in three groups of 7 rats. After a baseline period of 5 days (for all groups), the controls (GROUP C) received ascorbic acid (0.02%) in the drinking water during the whole experiment. The two other groups (chronic methamphetamine, GROUP M and withdrawal, GROUP W) were treated additionally with methamphetamine chloride (Siegfried) at an initial dose of 50 mg/l for one week followed by 100 mg/l for three weeks in GROUP W, and for four weeks in GROUP M.

After three weeks treatment, the GPT was performed on GROUP C and M for 7 days. According to a previously described method [15], rats were given free access to 5% and 25% glucose-monohydrate (1 g=14.28 KJ) solutions and free chow ad lib. In this period, GROUP M continued to receive the same amount of M as before in the glucose solutions. The position of bottles was reversed each day and solutions were changed daily. In GROUP W, immediately after M was withdrawn, the GPT was applied. Throughout the entire experiment, body weight, intake of food and fluid/24 hours was measured. Additionally, prior to the GPT, food and water intake in the first four hours of the light phase was measured once a week.

For statistical evaluation of group-differences, Student's two-tailed *t*-test for unpaired values was used. The results of the GPT were divided into an initial period of 3 days and a

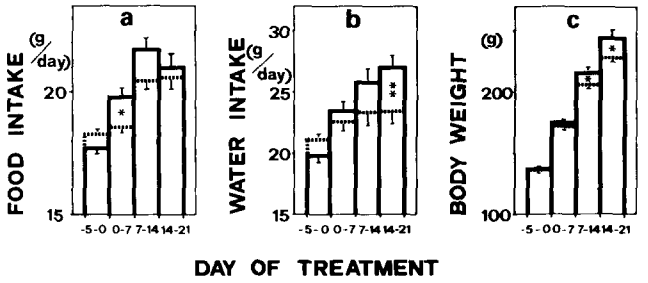

FIG. 1. Time course of food intake (1a), water consumption (1b) and body weight (1c) of controls (n=7 rats; solid columns) and methamphetamine treated rats (n=14 rats; broken columns) before glucose-preference-test. Each value represents mean±S.E.M. averaged over days indicated. *$p<0.05$; **$p<0.01$.

final period of 4 days. For statistical comparison of these two periods Student's two tailed t-test for paired values was used.

RESULTS

Pretest-Period

Figure 1 shows the development of food- (1a), water intake (1b) and body weight (1c) during the course of M-treatment. Compared with controls, daily food consumption was significantly reduced in the first week but was no longer so by the third week of M-application. In contrast, water intake and body weight progressively decreased during M-treatment compared with controls, significantly so in the second and third weeks of administration. The development of tolerance to the anorexic effect during M-treatment is shown in Fig. 2. On the third day of treatment a significant decrease in daily food intake occured without any changes in feeding during the first four hours of the light phase. Parallel to the development of tolerance to the M-induced anorexia after day 10, a significant increase of feeding during the early light phase was observed.

Glucose-Preference-Test-Period

Mean daily intakes of 5%- and 25%-glucose solution during the GPT are depicted in Fig. 3a and 3b. In the initial test period (days 1–3) no significant differences between the treatment groups could be seen. However, later (days 4–7) GROUP M and W exhibited significantly less 5%-glucose intake than controls with no significant changes in 25%-glucose intake. A comparison over time provides a further analysis. Only GROUP C showed the previously reported preference reversal, increasing 5%-glucose intake from day to day, parallel to a significant reduction in 25%-glucose consumption.

These results clearly indicate that GROUP M and W did not manifest the normal preference shift from the concentrated (25%) to the more diluted (5%) glucose solution as found in controls. Figure 4 shows the mean daily body weight increase (4a) and daily caloric intake (4b) over a period of one week before and during GPT. After three weeks of M-treatment GROUP M exhibited a reduced body weight increase ($p<0.05$) with no difference in daily caloric intake in comparison with controls. However, during the GPT, body weight increase was normalized in GROUP M and enhanced in GROUP W ($p<0.05$). All groups showed a similar elevated total caloric intake compared with the pretest values ($p<0.01$), whereas the food consumption was differentially reduced. GROUP M ate significantly ($p<0.01$) more food pellets (inversely, took less glucose) than GROUP C and W.

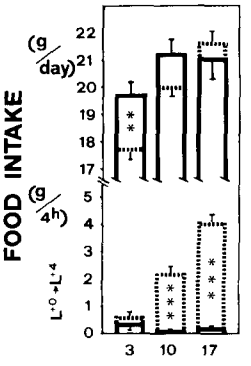

FIG. 2. Food intake during 24-hours (upper part) and the first 4 hours light phase (lower part) in the course of methamphetamine treatment. Controls (solid columns): n=7 rats; methamphetamine treated rats (broken columns): n=14 rats. Mean±S.E.M. *$p<0.01$;**$p<0.001$.

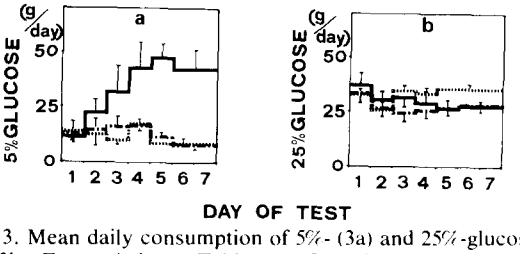

FIG. 3. Mean daily consumption of 5%- (3a) and 25%-glucose solution (3b). For statistic see Table 1; n=7 rats/group. —— GROUP C; – – GROUP M; ····· GROUP W; mean + S.E.M.

DISCUSSION

The basic findings of this experiment are: (1) development of tolerance to the anorexic effect of M occurs parallel with increased feeding in the early light phase. (2) chronic M-treated and withdrawn rats show a lack of preference reversal when given free access to 5%- vs. 25%-glucose solutions. In addition, our results confirm previous reports of differential changes in feeding, water intake and body weight during the course of M-treatment [5, 9, 10, 16] (Fig. 1). However, it is important to be aware that induction of tolerance is dependent on the testing conditions, drug concentration and route of drug administration [9,10,16]. It could be argued that oral administration of M leads to a taste-induced reduction of water intake because of its bitterness, with consequent reduction in feeding. This argument can be refuted, first, because maximal food intake suppression by M occurred on the first day of its application, whereas water intake was gradually reduced, and second, 0.01% quinine in the drinking

TABLE 1

	Group C		Group M		Group W	
	days: 1–3	3–7	days: 1–3	3–7	days: 1–3	3–7
5% glucose (g)	17.23 ± 2.52*	43.59 ± 8.52	14.39 ± 3.29	11.95 ± 1.52‡	12.34 ± 1.69	10.81 ± 2.40‡
25% glucose (g)	33.00 ± 4.30*	27.73 ± 3.03	28.10 ± 2.20	26.86 ± 2.31	30.57 ± 1.85	35.07 ± 1.71
preference of 5% glucose (%)	37.0 ± 6.4†	58.6 ± 5.3	32.7 ± 5.7‡	31.5 ± 4.7‡	28.7 ± 3.4	22.0 ± 3.8¶

*$p<0.05$ (paired t-test) period 1–4 vs. period 4–7.
†$p<0.01$. (paired t-test) period 1–4 vs. period 4–7.
‡$p<0.01$ t-test compared with Group C.
§$p<0.05$ t-test compared with Group C.
¶$p<0.001$ t-test compared with Group C.

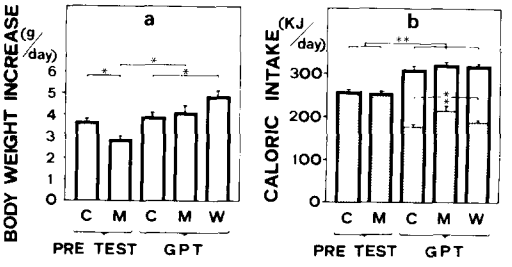

FIG. 4. Mean daily body weight increase (4a) and mean daily caloric intake (4b) averaged over one week, whereby for the glucose-preference-test period, total caloric intake was subdivided in food (dotted columns) and glucose (open columns) portion. Controls: (C), chronic methamphetamine treated rats: (M), drug withdrawn rats: (W); mean±S.E.M., n=7 rats/group.

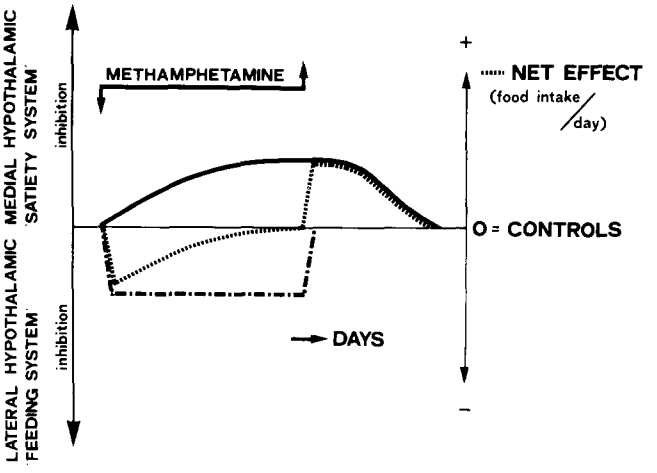

FIG. 5. Model of the behavioral effects in the course of methamphetamine treatment and withdrawal. Slow and fast processes are mediated by the medial and lateral hypothalamus, respectively (see the Discussion section).

water reduces 24-hour water intake by about 50% without significantly modifying daily food intake—only drastic reduction of water intake by very bitter drinking solutions leads to feeding suppression (unpublished results).

Nevertheless, the route of drug administration is not a trivial point with regard to effect of M on circadian feeding rhythms. We have recently shown that continuous, tonic M delivery via an osmotic minipump, that largely bypass the liver, induces rapid tolerance without a change in circadian rhythmicity [6].

In an earlier study measuring the entire 24-hour patterns of different physiological parameters, M given chronically in the drinking water not only shifted feeding into the light phase but also water intake, body temperature and plasma corticosterone [13]. The rhythm of plasma and brain M levels showed a main peak at dawn with high concentrations of the drug in the early light phase [13]. This precludes any simple interpretation of disturbed feeding rhythmicity being related to the anorexic properties of M.

In the medial hypothalamus, especially in the paraventricular nucleus, noradrenaline can stimulate food intake and inhibit postprandial drinking via an α_2- adrenoceptor mechanism [7,11]. Moreover, lesions in the VMH increase food intake and disrupt the circadian rhythm of feeding [2,8], as well as inhibiting the development of tolerance to amphetamine-induced anorexia [16]. We found a parallel change in food intake rhythmicity and α_2-adrenoceptor rhythmicity in the medial hypothalamus after chronic M treatment [5]. This supports the conjecture that the tolerance phenomenon occuring when M is given in the drinking water and the disturbance in circadian organization of food intake is mediated by noradrenergic mechanisms in the medial hypothalamus. Thus chronic M-treatment could be considered as suppressing medial hypothalamic functions so that its effect is equivalent to lesions of the medial hypothalamus.

The GPT provides further evidence to support this interpretation. Normal rats show a greater preference for the more concentrated glucose solution initially, with a gradual reversal in preference over several days [3,15]. This preference reversal has been considered to result from the metabolic consequence of consuming a calorically dense glucose solution [3,15]. Since the VMH is concerned with long-term metabolic adjustments in feeding behavior based on the depletion/repletion of nutrient stores, it seems plausible that VMH lesions can lead to a prevention of the preference reversal [15]. In this respect, chronic M-treated rats

resemble VMH lesioned rats. Further, prevention of the preference reversal seems to be independent of body weight, since VMH-lesioned rats have increased, M-treated rats decreased body weight.

The prevention of preference reversal by M is still maintained one week after drug withdrawal. Thus functional impairment of the medial hypothalamus by M, that takes time to develop, also takes time to disappear after drug withdrawal.

During the GPT, total caloric intake in all three groups is elevated. It is interesting to note that during this period of glucose consumption, chronic M-treated rats can normalise their daily body weight increase, and rats undergoing withdrawal show a rebound daily body weight increase greater than in both other groups. However, GROUP C did not translate this increase in energy intake into an additional weight gain (as also found in a recent study that shows an age dependency for this effect [4]). Thus chronic M-treated rats exhibit a reduced metabolic efficiency on normal lab chow, that can be counteracted by long-term glucose consumption—at least in younger rats. Therefore, M may interfere not only with central sites, e.g., catecholamine sensitive neurons in the LH and medial hypothalamus, regions which are known to stimulate and inhibit food intake, respectively, but also with peripheral mechanisms, e.g., glucose related afferent signals through visceral nerve fibres, which may interact with hypothalamic mechanisms controlling centrifugal influences upon hepatic carbohydrate metabolism [1, 7, 12, 14, 15, 17, 18].

Nevertheless, it is possible to model these complex mechanisms—at a first step—by slow and fast processes in the medial and lateral hypothalamus, respectively (Fig. 5). According to this model, the acute anorexic effect of M and consequently the reduced body weight increase is mediated by a rapid and persisting inhibition of the lateral hypothalamic "feeding system." In the course of M treatment, inhibition of the medial hypothalamic "satiety system" slowly develops, parallel to increased feeding in the early light phase and preference shift inhibition during GPT. Conversely, in the withdrawal period, the inhibition of the lateral hypothalamus disappears rapidly and that of the medial hypothalamus slowly, again parallel to the behaviors mediated by each region. Tolerance to the M-induced anorexia can be considered to be a net result of both medial and lateral hypothalamic inhibition. This model is in agreement with earlier reports showing that short-term regulatory mechanisms (e.g., prandial rhythmicity) seem to be monitored by the lateral hypothalamus while long-term (e.g., circadian rhythmicity) mechanisms of food intake behavior appear to be controlled by the medial hypothalamus [8]. Furthermore, a strikingly similar two-component feeding model has been recently developed from independent studies of amphetamine-induced anorexia following pretreatment with antidepressants [19].

ACKNOWLEDGEMENTS

K.R. was a fellow of the German Academic Exchange Service (DAAD).

REFERENCES

1. Benzo, C. A. The hypothalamus and blood glucose regulation. *Life Sci* **32:** 2509–2515, 1983.
2. Bernardis, L. L. Disruption of diurnal feeding and weight gain cycles in weanling rats by ventromedial and dorsomedial hypothalamic lesions. *Physiol Behav* **10:** 855–861, 1973.
3. Booth, D. A., D. Lovett and G. M. McSherry. Postingestive modulation of the sweetness preference gradient in the rat. *J Comp Physiol Psychol* **78:** 485–512, 1972.
4. Kanarek, R. and E. Hirsch. Dietary-induced overeating in experimental animals. *Fed Proc* **36:** 154–158, 1977.
5. Kräuchi, K., A. Wirz-Justice, T. Morimasa, R. Willener and H. Feer. Hypothalamic α_2- and β-adrenoceptor rhythms are correlated with circadian feeding: Evidence from chronic methamphetamine treatment and withdrawal. *Brain Res* **321:** 83–90, 1984.
6. Kräuchi, K., A. Wirz-Justice, R. Sütterlin-Willener and H. Feer. Circadian food intake rhythm disturbance after chronic methamphetamine treatment depends on route of application. *Experientia* **4:** 822, 1985.
7. Leibowitz, S. F. Neurochemical systems of the hypothalamus in control of feeding and drinking behavior and water-electrolyte excretion. In: *Handbook of the Hypothalamus*, vol 3A, edited by P. J. Morgane and J. Panksepp. New York: Marcel Dekker, 1980, pp. 299–437.
8. LeMagnen, J. The metabolic basis of dual periodicity of feeding in rats. *Behav Brain Sci* **4:** 561–607, 1981.
9. Levitsky, D. A., B. J. Strupp and J. Lupoli. Tolerance to anorectic drugs: Pharmacological or artifactual? *Pharmacol Biochem Behav* **14:** 661–667, 1981.
10. Magour, S., H. Coper and E. Fähndrich. The effects of chronic treatment with d-amphetamine on food intake, body weight, locomotor activity and subcellular distribution of the drug in rat brain. *Psychopharmacologia* **34:** 45–54, 1974.
11. Marino, L. A., M. D. DeBellis and S. F. Leibowitz. α_2-adrenergic receptors in the paraventricular nucleus mediate feeding induced by noradrenaline and clonidine. *Soc Neurosci Abstr* **9:** 467, 1983.
12. Marshall, J. F., M. I. Friedman and T. G. Heffner. Reduced anorexic and locomotor-stimulant action of d-amphetamine in alloxan-diabetic rats. *Brain Res* **111:** 428–432, 1976.
13. Morimasa, T., A. Wirz-Justice, K. Kräuchi, H. Feer, J. Arendt, J. Baumann and P. Degen. Chronic methamphetamine and its withdrawal: differential effects on behavioral and neuroendocrine circadian rhythms. Submitted manuscript.
14. Novin, D., J. Sanderson and M. Gonzalez. Feeding after nutrient infusions: Effects of hypothalamic lesions and vagotomy. *Physiol Behav* **22:** 107–113, 1979.
15. Panksepp, J. The ventromedial hypothalamus and metabolic adjustments of feeding. *Behav Biol* **9:** 65–75, 1973.
16. Panksepp, J. and D. A. Booth. Tolerance in the depression of intake when amphetamine is added to the rat's food. *Psychopharmacologia* **29:** 45–54, 1973.
17. Russek, M. and J. A. F. Stevenson. Correlation between the effects of several substances on food intake and on the hepatic concentration of reducing sugars. *Physiol Behav* **8:** 245–249, 1972.
18. Tordoff, M. G., J. Hopfenbeck, L. L. Butcher and D. Novin. A peripheral locus for amphetamine anorexia. *Nature* **297:** 148–150, 1982.
19. Willner, P., A. Towell and T. Montgomery. Changes in amphetamine-induced anorexia and stereotypy during chronic treatment with antidepressant drugs. *Eur J Pharmacol* **98:** 397–406, 1984.