Pharmacology Biochemistry & Behavior, Vol. 12, pp. 549–533. Printed in the U.S.A.

Brain Histamine: Plasma Corticosterone, Spontaneous Locomotor Activity and Temperature[1]

I. M. MAZURKIEWICZ-KWILECKI AND GEORGE D. PRELL[2]

Department of Pharmacology, Faculty of Health Sciences, University of Ottawa, Ottawa, Canada

Received 20 August 1979

MAZURKIEWICZ-KWILECKI, I. M., AND G. D. PRELL. *Brain histamine: Plasma corticosterone, spontaneous locomotor activity and temperature.* PHARMAC. BIOCHEM. BEHAV. 12(4) 549–553, 1980.—Hypothalamic histamine exhibited circadian fluctuations in male Sprague-Dawley rats; low values were found during the dark period when spontaneous locomotor activity (S.L.A.) and temperature were elevated. A relatively high hypothalamic histamine level was observed during the early period of the light cycle and was associated with decreased S.L.A. and temperature. Histamine concentration was high when corticosterone levels were low at the end of the dark cycle and during the morning hours (4 a.m.–1 p.m.); but histamine levels were relatively constant while corticosterone concentration dropped during afternoon and early night hours (4 p.m.–10 p.m.). Furthermore, the lowest hypothalamic histamine level (at 1 a.m.) was associated with the average plasma corticosterone value, thus no consistent relationship between histamine and corticosterone levels could be observed. Circadian fluctuations in brain histamine may support its role in brain function.

Histamine Hypothalamus Circadian rhythm Corticosterone Rat Temperature
Spontaneous locomotor activity

EXTENSIVE evidence has accumulated within recent years which has supported the role of histamine as a putative central neurotransmitter [1, 5, 9, 15, 33, 38–42, 45]. In line with these reports a role for brain histamine in several physiological processes such as temperature regulation [27,28], emesis [3], water intake [26] and avoidance behaviour [7,17] has been suggested. In addition, the possible involvement of central histamine in the regulation of antidiuretic hormone [2,10] and in the release of luteinizing hormone (LH) and prolactin was also reported [11, 12, 34, 36].

Our previous studies indicated a possible role of brain histamine in the response to stress [31]. Alterations in hypothalamic histamine concentration occurred following stressful conditions associated with a significant elevation in plasma corticosterone level, however, a causal relationship could not be established. Limited information on the brain histamine-corticosterone interaction is available and conflicting results have been reported. While hypophysectomy did not affect H^3-histamine formation from intraventricularly administered ^3H-histidine [45], decreased histamine synthesis due to decreased L-histidine decarboxylase activity was noted 5 days after adrenalectomy in mice [48]. However, stress-induced decrease in H^3-histamine turnover in mice was not affected by adrenalectomy [48].

The present studies were undertaken in order to further explore brain histamine-corticosterone interactions. The mutual influence of diurnal variations in plasma corticosterone level and hypothalamic histamine concentration was investigated.

METHOD

Male Sprague-Dawley rats (200–220 g; BBL, Ottawa) were housed in metal cages (3 per cage) in a temperature controlled (22°C) room with artificial light 7 a.m.–7 p.m. Food and water were allowed ad lib. At 3 hour intervals throughout the 24 hr cycle, six animals were decapitated. The times of sacrifice were: 10 a.m., 1 p.m., 4 p.m. and 7 p.m. of the light cycle and at 10 p.m., 1 a.m., 4 a.m. and 7 a.m. of the dark cycle.

Histamine Determination

Following decapitation the brains were rapidly removed, washed with ice cold saline, blotted and placed on glass plates kept on ice. Different brain regions were dissected according to the method of Glowinski and Iversen [19].

The tissues were assayed for their histamine content using a modified double isotope technique of Taylor and Snyder [46]. This procedure depended on the methylation of endogenous histamine in the tissues by added histamine methyltransferase, using S-adenosyl-L-methionine (methyl ^{14}C); (56 mCi/mmole, New England Nuclear) as the methyl

[1]This research was supported by the Ontario Mental Health Foundation grant no. 751; 78/80.
[2]Recipient of 1978/79 Ciba-Geigy Research Scholarship.

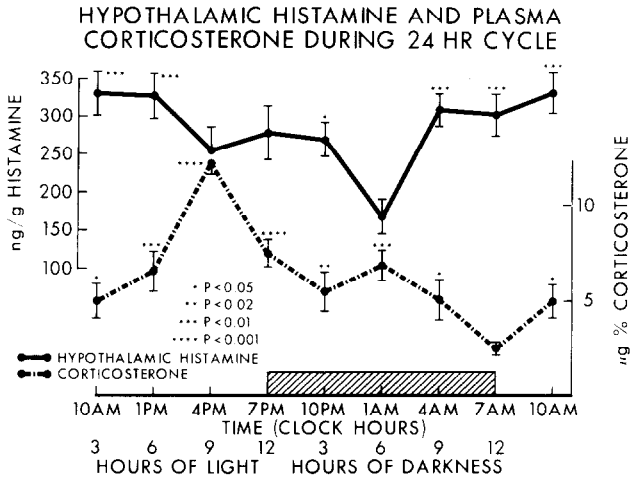

FIG. 1. Circadian fluctuations in hypothalamic histamine concentration and in plasma corticosterone level in male rat. The hours of the dark cycle are represented by the shaded area. The data represents the Means ± SEM of 4–6 rats for each point. *$p<0.05$, **$p<0.02$, ***$p<0.01$, ****$p<0.001$ compared to the lowest value observed during the 24 hour cycle.

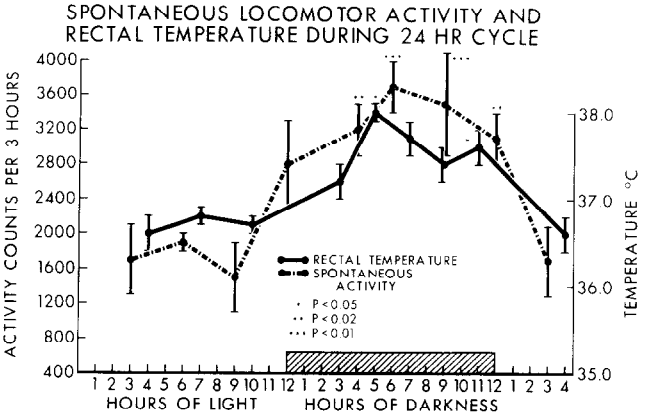

FIG. 2. Circadian fluctuations in spontaneous locomotor activity (S.L.A.) expressed in the apparatus' arbitrary units per 3 hours with the total indicated at the end of each period and in rectal temperature (°C of male rats. The data represents the Mean ± SEM of 16 rats for SLA measurement and of 6 rats for the temperature determination. *$p<0.05$, **$p<0.02$, ***$p<0.01$ as compared to the lowest value during the 24 hr cycle.

donor. A tracer amount of (^{3}H)histamine (5–10 Ci/mmole, New England Nuclear) was added to correct for the varying degree of histamine methylation in different samples. Endogenous S-adenosyl-L-methionine was destroyed by boiling the tissue, a procedure which also served to precipitate protein. The (^{14}C)-(^{3}H)methylhistamine and (^{14}C)methylhistamine were separated from (^{14}C)S-adenosyl-L-methionine and (^{3}H)histamine by extracting into chloroform from a salt-saturated alkaline solution. The chloroform was evaporated and the residue was taken up into ethanol and scintillation fluid and counted in a Beckman Model LS 8100 liquid scintillation spectrometer.

Temperature

In the environment held at 22°C the rectal temperature was measured with a telethermometer (Yellow Springs, OH).

Spontaneous Locomotor Activity (S.L.A.)

Spontaneous locomotor activity was determined with a Selective Activity Meter (Columbus Instruments, OH) and expressed in the apparatus' arbitrary units. Four cages (4 rats in each cage) were simultaneously tested during the 24 hr experimental period of time.

Plasma Corticosterone

Plasma corticosterone was determined by a modification of the method of Givner and Rochefort [18] which is based on the capability of corticosterone to fluoresce in sulfuric acid. The data is reported as μg per 100 ml of plasma (μg%).

RESULTS

Figure 1 indicates circadian variations in hypothalamic histamine level. Relatively high histamine concentrations (331 ± 31-328 ± 31 ng/g) were noted during the first 6 hr of light (up to 1 p.m.), but a decline (235 ± 28 ng/g) ensued by 9 hr of the day cycle (at 4 p.m.); a slightly higher value (275 ± 35 ng/g) was observed at the onset of the dark cycle (at 7 p.m.) and was maintained for the first 3 hr of darkness (271 ± 23 ng/g). A marked drop in hypothalamic histamine concentration to the lowest level (187 ± 28 ng/g) was noted following 6 hr of darkness (at 1 a.m.). However, hypothalamic histamine values rose again at 9 hr (317 ± 21 ng/g) and 12 hr (307 ± 27 ng/g) of darkness (4 a.m. and 7 p.m., respectively).

The plasma corticosterone level was lowest (2.5 ± 0.3 μg%) at the start of the light cycle (7 a.m.); a gradual steady increase was noted until the peak (12.2 ± 0.06 μg%) was reached following 9 hr of light (at 4 p.m.). A sharp decline (7.5 ± 0.7 μg%) had occurred by the start of the dark cycle (at 7 p.m.) and continued during the next 3 hr of darkness (5.5 ± 1.0 μg%). Plasma corticosterone slightly increased (6.8 ± 0.8 μg%) at 6 hr of darkness but declined again (5.1 ± 1.0 μg%) 3 hr before the start of the light cycle.

Relatively high hypothalamic histamine levels were seen between 4 a.m.–1 p.m. (112, 109, 119 and 118% of the average 24 hour value) when plasma corticosterone concentration was low (80, 40, 79%) or average (102% of the average 24 hour value). A decrease in hypothalamic histamine concentration (83% of the average 24 hour value) occurred when plasma corticosterone level reached a peak (191% of the average 24 hour value) at 4 p.m. However, histamine levels remained relatively constant (83, 99 and 96% of the average 24 hour value) when corticosterone levels dropped from 191% to 86% of the average 24 hour value (4 p.m.–10 p.m.). Furthermore, when histamine concentration dropped to its lowest level (66% of the average 24 hour period) at 1 a.m., plasma corticosterone was 106% of the average 24 hour value.

Spontaneous Locomotor Activity (S.L.A.)

S.L.A. (Fig. 2) was low during the first 3, 6 and 9 hr of light (1668 ± 400, 1903 ± 553, 1528 ± 400 units, respectively) but increased before the start of the darkness (2796 ± 500 units) and reached a maximum (3745 ± 300 units) in the middle of the dark cycle (i.e., following 6 hr of darkness); S.L.A. remained elevated until the end of the

dark cycle (3096 ± 600 units). The decreased S.L.A. observed during the early hr of the light cycle was associated with relativepy high levels of hypothalamic histamine (Fig. 1) while the increased S.L.A. noted during the dark cycle especially between 6–8 hr of darkness was associated with a low hypothalamic histamine concentration (Fig. 1).

Temperature

Fluctuations in rectal temperature resembled those in S.L.A. Rectal temperature was low during the light cycle (36.6 ± 0.2, 36.8 ± 0.1 and 36.7 ± 0.1°C) at 4, 7 and 10 hr of light, respectively, but increased gradually during the first 3 hr of darkness (37.4 ± 0.2°C) until the maximum (38.0 ± 0.1°C) following 5 hr of darkness. This was followed by a gradual decline at 7 hr (37.7 ± 0.1°C), 9 hr (37.4 ± 0.2°C) and 11 hr (37.6 ± 0.2) of the dark cycle.

DISCUSSION

Present results are in line with earlier reports which indicated diurnal variations in the endogenous hypothalamic histamine concentration [32,41]. These alterations did not seem to be influenced by the level of endogenous hypothalamic L-histidine [41], and no significant correlation was found between hypothalamic histamine concentration and the activity of L-histidine decarboxylase or histamine methyltransferase [32]. Under our experimental conditions high hypothalmic histamine values (176–177% of minimum value) were found during the first 6 hr of the light and coincided with low S.L.A.

On the other hand the low hypothalamic histamine level observed during the dark phase was associated with high S.L.A. A similar inverse relationship between hypothalamic histamine concentration and S.L.A. was observed by others [41] and supported the suggested role of central histaminergic pathways in the regulation of sleep and wakefulness [1,41].

In agreement with our present observations others using a different strain of rats (Holtzman) [32] also reported a minimum hypothalamic histamine level during the dark phase. However, in the latter studies this maximum decline was noted earlier (1 hour after the start of the night cycle) than in our investigation. A peak in the hypothalamic histamine level was observed by previous investigators [32] 1 hour after the start of the light phase while under our experimental conditions hypothalamic histamine levels started to increase already 3 hr before light and remained elevated for the first 6 hr of the light cycle. This discrepancy could have been due to different times of sampling and the different strain of rats used in our investigation. It is of interest that no diurnal variations were reported [25] in Sprague-Dawley rats supplied by Hormone Assay Laboratories, but the same strain of animals obtained from Zinc Miller Labs exhibited an 18% rise in hypothalamic histamine level at the end of the daily dark period.

Presently observed diurnal variations in hypothalamic histamine differ from the reported [13,14] circadian rhythm of histamine concentration (determined by a fluorimetric method) in the caudate nucleus and in the midbrain of Sprague-Dawley rats. In these brain regions a relatively high histamine level was seen during the dark phase of the cycle (with a peak occurring at 10 hr of darkness) while a low concentration was noted during the light phase. Also in the pineal gland the circadian rhythm of histamine has a different pattern [16] with the highest level being at the beginning of the dark cycle followed by a fall to low values in the middle of this period and low values maintained during the light cycle. It is of interest that other central neurotransmitters were reported to have different diurnal rhythms in different brain regions [35].

Hypothalamic histamine fluctuations observed in this investigation differ from the reported diurnal variations in hypothalamic norepinephrine [29] and 5-hydroxytryptamine level [35]. The maximum norepinephrine concentration was noted during the middle of the dark period while the peak values for 5-hydroxytryptamine were seen at the end of the light cycle and a low concentration during the night and during early hours of the light phase.

The 24 hour plasma corticosterone fluctuations noted in this investigation resembled that reported by others [8,43]. Although the histamine level was high when corticosterone concentration was low (4 a.m.–1 p.m.) and the histamine concentration dropped to 83% of the average 24 hour value at the peak of corticosterone level, a consistent relationship could not be observed. The lowest hypothalamic histamine level at 1 a.m. corresponded to the average corticosterone value and a drop in corticosterone levels (7 p.m.–10 p.m.) was associated with the average histamine concentration. In our previous studies [31] a significant increase in plasma corticosterone following a short exposure to stress was associated with a significant elevation of hypothalamic histamine levels. However, in spite of a significant rise in plasma corticosterone following stress of longer duration, hypothalamic histamine was not significantly altered. Thus a strict relationship between these 2 events could not be observed possibly because of stress induced rapid activation of homeostatic mechanisms involved in central histamine regulation. Interestingly enough, a decreased histamine level in the brain of mice following histidine decarboxylase inhibition by α-hydrazino-histidine was reported [48] to be associated with a strong elevation of plasma corticosterone level. However, the administration of the histamine precursor, L-histidine, which significantly increased brain histamine levels did not affect plasma corticosterone concentration [48]. Thus, no conclusion on brain histamine-corticosterone interactions could be reached.

An earlier report has indicated that corticosteroids may alter the rate of histamine formation in the peripheral tissues [37]. It is known that chronic treatment with corticosteriods causes a fall in histamine levels of many peripheral tissues [6, 23, 47]. On the other hand adrenalectomy results in an increased histamine level [24,30]. These data suggest an effect of steroids on histamine concentration of peripheral tissues.

The steep increase in rectal temperature noted in this study at the onset of darkness and the peak ensuing during the night cycle coincided with a similar increase in S.L.A. A similar diurnal fluctuation in temperature was reported by others [14]. The presently observed elevation of rectal temperature during the dark phase was associated with a decrease in hypothalamic histamine level. This supports the suggested role of hypothalamic histamine in thermoregulation [21, 22, 27, 28]. Direct injection of histamine into preoptic/anterior hypothalamic nuclei of the rat [4] or intraventricular administration in mice [44] was reported to cause a fall in body temperature which in rats was prevented by the H_1 antagonist, chlorcyclizine [20]. It was suggested that the central thermoregulatory effects of histamine are elicited by its effects on H_1 receptors in the rostral hypothalamic thermoregulatory centers and by activation of

H_2 receptors on neurones lying close to the wall of the third ventricle [28].

The present investigation which demonstrated diurnal fluctuations in hypothalamic histamine associated with changes in S.L.A. and temperature gives additional support for the role of histamine in brain function.

ACKNOWLEDGEMENT

The technical assistance of Mr. F. Huang is greatly appreciated.

REFERENCES

1. Barbin, G., M. Garbarg, J. C. Schwartz and J. Storm-Mathisen. Histamine synthesizing afferents to the hippocampal region. *J. Neurochem.* **26:** 259–263, 1976.
2. Bhargava, K. P., V. K. Kulshrestha, G. Santhakumari and Y. P. Srivastava. Mechanism of histamine-induced antidiuretic response. *Br. J. Pharmac.* **47:** 700–706, 1973.
3. Bhargava, K. P., K. S. Dixit and G. Palit. Nature of histamine receptors in the emetic chemoreceptor trigger zone. *Br. J. Pharmac.* **57:** 211–213, 1976.
4. Brezenoff, H. E. and P. Lomax. Temperature changes following microinjection of histamine into the thermoregulatory centers of the rat. *Experientia* **26:** 51–52, 1970.
5. Calcutt, C. R. The role of histamine in the brain. *Gen. Pharmac.* **7:** 15–25, 1976.
6. Cass, R. and P. B. Marshall. Effect of adrenocortical hormones on tissue histamine and 5-hydroxytryptamine in rat. *Archs int. Pharmacodyn.* **136:** No. 3–4, 311–332, 1962.
7. Cohn, C. K., G. G. Gall and J. Hirsch. Histamine: Effect on self-stimulation. *Science* **180:** 757–758, 1973.
8. Critchlow, V., R. A. Liebelt, M. Bar-Sela, W. Mountcastle and H. S. Lipscomb. Sex difference in resting pituitary-adrenal function in the rat. *Am. J. Physiol.* **205:** 807–815, 1963.
9. Dismukes, K. and S. H. Snyder. Dynamics of brain histamine. *Adv. Neurol.* **5:** 101–109, 1974.
10. Dogterom, J., T. B. van Wimersma Greidanus and D. De Wied. Histamine as an extremely potent releaser of vasopressin in the rat. *Experientia* **32:** 659–660, 1976.
11. Donoso, A. O. and A. M. Banzan. Acute effects of histamine on plasma prolactin and luteinizing hormone levels in male rats. *J. Neural Trans.* **39:** 95–101, 1976.
12. Donoso, A. O., A. M. Banzan and M. I. Borzino. Prolactin and luteinizing hormone release after intraventricular injection of histamine in rats. *J. Endocr.* **68:** 171–172, 1976.
13. Friedman, A. H. and C. A. Walker. Rat brain amines, blood histamine and glucose levels in relationship to circadian changes in sleep induced by pentobarbitone sodium. *J. Physiol.* **202:** 133–146, 1969.
14. Friedman, A. H. and C. A. Walker. Circadian rhythms in rat midbrain and caudate nucleus biogenic amine levels. *J. Physiol.* **197:** 77–85, 1968.
15. Barbarg, M., G. Barbin, J. Figer and J.-C. Schwartz. Histaminergic pathway in rat brain evidenced by lesions of the medial forebrain bundle. *Science* **186:** 833–835, 1974.
16. Garbarg, M., C. H. Julien and J.-C. Schwartz. Circadian rhythm of histamine in the pineal gland. *Life Sci.* **14:** 539–543, 1974.
17. Gerald, M. C. and R. O. Maickel. Studies on the possible role of brain histamine in behaviour. *Br. J. Pharmac.* **44:** 462–471, 1972.
18. Givner, M. I. and J. G. Rochefort. An improved assay of corticosterone in rat serum and adrenal tissue. *Steroids* **6:** 485–489, 1965.
19. Glowinski, J. and I. I. Iversen. Regional studies on catecholamines in the rat brain. *J. Neurochem.* **13:** 655–669, 1966.
20. Green, M. D., B. Cox and P. Lomax. Histamine H_1 and H_2 receptors in the central thermoregulatory pathways of the rat. *J. Neurosci. Res.* **1:** 353–359, 1975.
21. Green, J. P., C. J. Johnson and H. Weinstein. Histamine as a neurotransmitter. In: *Psychopharmacology: A Generation of Progress*, edited by M. A. Lipton, A. Di Mascio and K. F. Killam. New York: Raven Press, 1978, pp. 319–332.
22. Green, M. D., B. Cox and P. Lomax. Sites and mechanisms of action of histamine in the central thermoregulatory pathways of the rat. *Neuropharmacology* **15:** 321–324, 1976.
23. Hicks, R. and G. B. West. Adrenal cortical hormones and the formation of histamine and 5-hydroxytryptamine. *Nature* **181:** 1342–1343, 1958.
24. Hicks, R. and G. B. West. Adrenalectomy and tissue amines. *Nature* **182:** 401–402, 1958.
25. Kobayashi, R. M. and K. J. Kopin. The effects of stress and environmental lighting on histamine in the rat brain. *Brain Res.* **74:** 356–359, 1974.
26. Leibowitz, S. F. Histamine: A stimulatory effect on drinking behaviour in the rat. *Brain Res.* **63:** 440–444, 1973.
27. Lomax, P. and M. D. Green. Histamine and temperature regulation. In: *Temperature Regulation and Drug Action*, edited by P. Lomax, E. Schönbaum and J. Jacob. Basel: Karger, 1975, pp. 85–94.
28. Lomax, P. and M. D. Green. Histamine. In: *Body Temperature: Regulation, Drug Effects and Therapeutic Implications*, edited by P. Lomax and E. Schönbaum. New York: Marcel Dekker, 1979, pp. 289–304.
29. Manshardt, J. and R. J. Wurtman. Daily rhythm in the noradrenaline content of rat hypothalamus. *Nature* **217:** 574–575, 1968.
30. Marshall, B. P. The influence of adrenal cortical deficiency on the histamine content of rat tissue. *J. Physiol.* **102:** 180–190, 1943.
31. Mazurkiewicz-Kwilecki, I. M. and H. Taub. Effect of stress on brain histamine. *Pharmac. Biochem. Behav.* **9:** 465–468, 1978.
32. Orr, E. and W. B. Quay. Hypothalamic 24 hour rhythms in histamine, histidine decarboxylase and histamine-N-methyltransferase. *Endocrinology* **96:** 941–945, 1975.
33. Pollard, H., S. Bischoff, C. Llorens-Cortes and J. C. Schwartz. Histidine decarboxylase and histamine in discrete nuclei of rat hypothalamus and the evidence for mast-cells in the median eminence. *Brain Res.* **118:** 509–513, 1976.
34. Pontiroli, A. E. and G. Pozza. Histamine stimulates prolactin release in normal man. *Acta Endocr.* **88:** 23–28, 1978.
35. Quay, W. B. Differences in circadian rhythms in 5-hydroxytryptamine according to brain region. *Am. J. Physiol.* **215:** 1448–1452, 1968.
36. Rivier, C. and W. Vale. Effects of α-aminobutaric acid and histamine on prolactin secretion in the rat. *Encocrinology* **101:** 506–511, 1977.

37. Schayer, R. W. Inhibition by corticosterone of the binding of new histamine in rat tissues. *Proc. Soc. exp. Med. Biol.* **87:** 590–592, 1954.
38. Schayer, R. W. Evidence for a specific function of histamine in brain. *Adv. Neurol.* **5:** 111–114, 1974.
39. Schwartz, J. C. Minireview: Histamine as a transmitter in brain. *Life Sci.* **17:** 503–518, 1976.
40. Schwartz, J. C. Histaminergic mechanisms in the brain. *A. Rev. Pharmac. Tox.* **17:** 325–329, 1977.
41. Schwartz, J. C., G. Barbin, M. Garbarg, H. Pollard, C. Rose and M. Verdiere. Neurochemical evidence for histamine acting as a transmitter in mammalian brain. *Adv. Biochem. Psychopharmac.* **15:** 111–126, 1976.
42. Schwartz, J. C., M. Baudry, S. Bischoff, M.-P. Martres, H. Pollard, C. Rose and M. Verdiere. Pharmacological studies of histamine as a central neurotransmitter. In: *Drugs and Central Synaptic Transmission,* edited by P. B. Bradley and B. N. Dhawan. Baltimore: University Park Press, 1976, pp. 371–382.
43. Seggie, J., B. Shaw, I. Uhlir and G. M. Brown. Baseline 24-hour plasma corticosterone rhythm in normal, sham-operated and septally-lesioned rats. *Neuroendocrinology* **15:** 51–61, 1974.
44. Shaw, G. G. Hypothermia in mice by histamine acting on the central nervous system. *Br. J. Pharmac.* **42:** 205–214, 1971.
45. Snyder, S. H. and K. M. Taylor. Histamine in the brain: A neurotransmitter? In: *Perspectives in Neuropharmacology–A Tribute to Julius Axelrod,* edited by S. H. Snyder. New York: Oxford University Press, 1972, pp. 43–73.
46. Taylor, K. M. and S. H. Snyder. Isotopic microassay of histamine, histidine, histidine decarboxylase and histamine methyltransferase in brain tissue. *J. Neurochem.* **19:** 1343–1358, 1972.
47. Telford, J. M. and G. B. West. The effects of corticosteroids and related compounds on the histamine and 5-hydroxytryptamine content of rat tissues. *Br. J. Pharmac.* **15:** 532–539, 1960.
48. Verdiere, M., C. Rose and J. C. Schwartz. Turnover of central histamine in a stressful situation. *Brain Res.* **129:** 107–119, 1977.