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Brain Histamine Regulation Following Chronic Diazepam Treatment and Stress

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MAZURKIEWICZ-KWILECKI, I M AND P BADDOO *Brain histamine regulation following chronic diazepam treatment and stress* PHARMACOL BIOCHEM BEHAV **24**(3) 513–517, 1986 —Chronic diazepam treatment (5 mg/kg intragastrically, twice daily for 14 days) did not influence either hypothalamic, midbrain or cortical histamine (HA) levels or histidine decarboxylase (HD) activity in male Sprague-Dawley (200–220 g) rats However, a small but significant decrease in hypothalamic HA concentration and significantly increased HD activity was seen following diazepam withdrawal Air blast stress induced a significant elevation in hypothalamic HA levels and HD activity in vehicle-treated controls, diazepam-treated and diazepam-withdrawn rats, but the change in HD activity was significantly greater in the last group The latter group also displayed the greatest elevation in plasma corticosterone levels in response to stress Hence, diazepam withdrawal in rats results in some changes in the basal hypothalamic HA regulation and may influence the hypothalamic HA and corticosterone response to stress

Histamine Brain Hypothalamus Diazepam Stress Rat

THE identification of specific central H_1 and H_2 receptors in the brain of several species [1, 7, 17, 18, 35–37, 39, 40, 50] supported the suggested role of histamine (HA) as a central neurotransmitter or neuromodulator [5, 6, 15, 26, 48–51, 53, 61, 63] Ascending central histaminergic pathways possibly involved in the control of sleep and wakefulness were reported [11, 12, 47] and circadian variations in hypothalamic HA levels [34] which were inversely related to spontaneous locomotor activity and temperatures were demonstrated [29]

Histamine has been found to influence ACTH release [33,46] and changes in plasma corticosterone levels were reported to affect hypothalamic HA regulation [25] The significance of HA in hypothalamic function has been recently reviewed [43]

Hypothalamus is known to play an important role in response to stress [10] Our previous studies on rats had indicated that "platform stress" or air-blast exposure resulted in significant changes in hypothalamic HA regulation [23, 28, 30] Because of the strong emotional component of these stressors, which was reflected in a very significant plasma corticosterone elevation, we investigated the anxiolytic effects of diazepam pretreatment [24] Acute diazepam administration did not affect basal regional brain HA levels, but attenuated "platform stress" induced elevation in hypothalamic HA concentrations However, alterations in HA regulation following air blast exposure remained not affected [24] It was therefore of interest to explore in this investigation whether chronic diazepam treatment could influence the basal regional brain HA regulation and whether such treatment would affect air-blast-induced changes in hypothalamic HA levels

METHOD

Male Sprague-Dawley rats (200–220 g) were housed in plastic cages (3 rats per cage) in a temperature controlled room (22°C) with controlled light (7 a m –7 p m) The animals were treated with diazepam (5 mg/kg) intragastrically twice a day for 14 days Vehicle treated rats served as controls The vehicle consisted of lactose, corn starch and magnesium stearate, generously supplied along with diazepam by Hoffman La Roche Ltd , Montreal Vehicle or diazepam chronically-treated rats were exposed to 15 min of air blasts, 18 hr after the last treatments The animals were placed individually in a plastic cage (20 5×26 5×14 5 cm) and exposed to blasts of compressed air delivered from a nozzle placed 10 cm above the cage The blasts were of 1 second duration and were applied at different time intervals at a rate of 5/min [23,62] The last blast was always delivered at the end of the experimental period of time, i e , at 15 min Diazepam or vehicle chronically-treated rats subjected to the same handling but not exposed to air blasts served as controls

Another group of chronically diazepam-treated rats was withdrawn from treatment for 2 days and subjected to 15 min air blasts in an identical manner, as described above All

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experiments were carried out between 8 30 a m and 11 30 a m when plasma corticosterone was at a relatively low level [29]

Experimental rats were sacrificed immediately after the stressful procedures Control non-stressed animals were decapitated at the same time Following decapitation, blood was collected from the severed neck blood vessels into heparin-containing tubes for corticosterone determination 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 modified method of Glowinski and Iversen [14]

Histamine Determinations

The tissues were assayed for their histamine content according to a modification of the double isotope technique of Taylor and Snyder [60] This procedure depended on the methylation of endogenous histamine in the tissues by added histamine methyltransferase, using S-adenosyl-L- [methyl-^{14}C] methionine (56 mCi/mmole, New England Nuclear) as the methyl donor A trace 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-adenosylmethionine 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 S-adenosyl-L-[methyl-^{14}C] 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 (Econofluor) and counted in a Beckman LS 8100 liquid scintillation spectrometer

Histidine Decarboxylase Assay

The histidine decarboxylase assay was performed by a modification of the method of Bielkiewicz [27,28] The tissue samples were homogenized in 10 mM phosphate buffer (pH 7 0) and incubated for 1 5 hr at 37°C under nitrogen The composition of the incubation mixture was similar to that reported previously [32] and consisted of 0 3 ml of homogenate, histamine dihydrochloride (10^{-4} M) in 10 mM phosphate buffer (pH 7 0), pyridoxal-5'-phosphate (10^{-6} M), aminoguanidine (10^{-6} M) and 0 4 μCi of ^{14}C-histidine (55 mCi/mmole, Amersham) Blanks contained the same incubation mixture except that homogenates were substituted by phosphate buffer (pH 7 0) At the end of the incubation period, L-histidine (100 μg) was added as a carrier The incubation was stopped after 1 5 hr by adding 50 μl of 1 N perchloric acid The samples were then centrifuged for 10 min at 10,000 g Part of the supernatant was counted for total radioactivity in a Beckman LS 8100 liquid scintillation spectrometer Another part of the supernatant was subjected to high voltage electrophoresis (1500 V) in acetate formate buffer (pH 1 9) for 1 5 hr in order to separate ^{14}C-histamine from ^{14}C-L histidine Standard non-labelled histamine and L-histidine were used as markers and identified with ninhydrin Electrophoretic strips of the corresponding labelled compounds were cut off, eluted with 1 5 ml of water, and after addition of 10 ml of Aquafluor (New England Nuclear) counted for radioactivity The data are reported in terms of nmol of ^{14}C-histamine per gram of wet tissue formed within 1 5 hr of incubation period

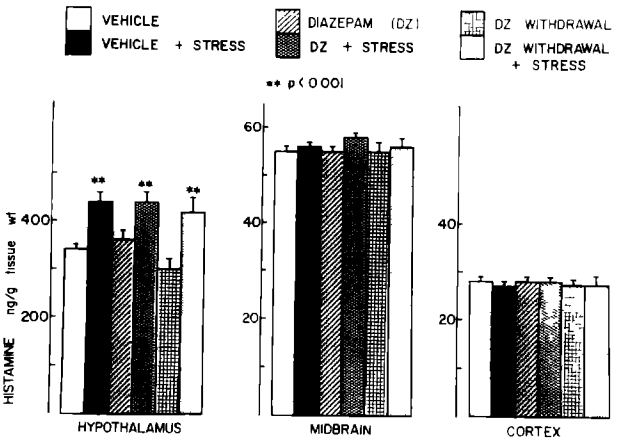

FIG 1 The effect of chronic vehicle treatment, chronic diazepam administration or diazepam withdrawal on hypothalamic, midbrain and cortical histamine concentration of rats exposed to air blasts for 15 min Non-stressed similarly treated animals served as controls The data represent the mean±S E M of 15 experiments in each group *Indicates statistical significance when tested by t-test in reference to respective non-stressed controls in each case Diazepam-withdrawn non-stressed rats had significantly lower hypothalamic HA levels (Duncan's multiple comparison among groups)

Plasma Corticosterone Assay

Plasma corticosterone concentration was determined by a modification of the method of Givner and Rochefort [13] which is based on the capability of corticosterone to fluoresce in sulfuric acid The data are reported as μg per 100 ml of plasma (μg%) All data were analysed by Student's t-test followed by Duncan's post hoc test (α=0 05) to determine statistically different groups

RESULTS

Vehicle or diazepam-treated non-stressed rats did not differ in their basal hypothalamic HA concentration, however, Duncan's multiple comparison among groups revealed that diazepam-withdrawn non-stressed animals displayed significantly lower hypothalamic HA levels as compared to vehicle or diazepam treated animals (Fig 1) Midbrain and cortical HA concentrations were unaffected by chronic diazepam treatment or diazepam withdrawal (Fig 1)

Vehicle diazepam treated or diazepam withdrawn animals responded to air blasts (Fig 1) with a significant elevation in hypothalamic HA levels when compared to their respective non-stressed controls Midbrain and cortical HA levels were unchanged by stress exposure (Fig 1)

Although basal hypothalamic HD activity of vehicle or diazepam-treated non-stressed rats was unaffected by chronic diazepam treatment (Fig 2), Duncan's multiple comparison between groups revealed that diazepam withdrawn rats displayed a significant increase in the hypothalamic HD activity Midbrain and cortical HD activity of non-stressed rats remained unchanged

Air blast stress induced a significant increase in hypothalamic HD activity in all groups of animals (Fig 2) Multiple comparison among groups revealed that diazepam withdrawn stressed rats had significantly higher HD activity than vehicle or diazepam-treated not withdrawn-stressed rats

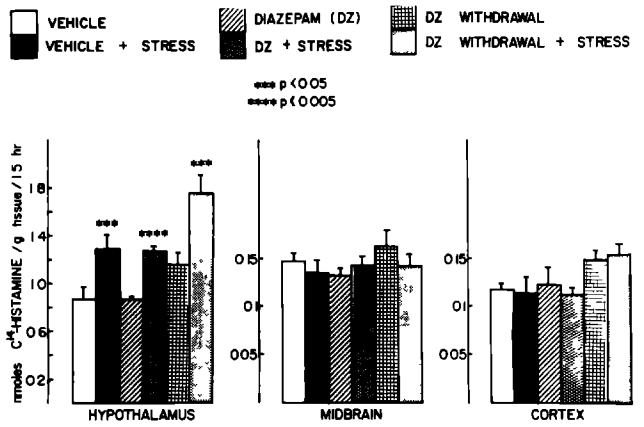

FIG 2 The effect of chronic diazepam treatment and diazepam withdrawal on hypothalamic, midbrain and cortical histidine decarboxylase activity The data represent the mean±S E M of 7 experiments in each group *Indicates statistical significance when tested by *t*-test in reference to respective non-stressed controls in each case Diazepam-withdrawn rats had significantly higher hypothalamic HD activity than vehicle or diazepam treated not withdrawn-rats Diazepam withdrawn stressed rats had significantly higher HD activity than diazepam or vehicle treated stressed rats (Duncan's multiple comparison among groups)

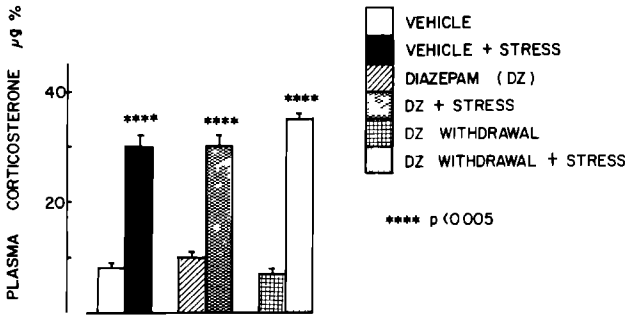

FIG 3 The effect of chronic diazepam treatment and diazepam withdrawal on plasma corticosterone concentration The data represent the mean±S E M of 15 experiments in each group *Indicates statistical significance when tested by *t*-test in reference to the respective non-stressed controls in each case Diazepam withdrawn stressed rats had significantly higher plasma corticosterone levels than chronic-vehicle or chronic diazepam-treated stressed animals (Duncan's multiple comparison amoung groups)

Basal plasma corticosterone concentration (Fig 3) was not significantly changed following chronic vehicle administration, chronic diazepam treatment or diazepam withdrawal Air blast stress induced significant elevation in plasma corticosterone levels in all groups of animals, Duncan test indicated that diazepam withdrawn stressed rats had significantly higher plasma corticosterone levels than chronic-vehicle or chronic-diazepam-treated stressed animals

DISCUSSION

Chronic diazepam treatment did not change the basal plasma corticosterone levels or the increase in plasma corticosterone concentration in response to air-blast stress This finding is in line with the reported lack of diazepam effects on pre-stress plasma corticosterone levels or on corticosterone elevation induced by 30 min footshock or 60 min immobilization stress in rats [2,20]

In the present investigation, the basal regional brain HA concentration and HD activity were not altered by chronic diazepam administration However, diazepam-withdrawn rats displayed small but significant decrease in the basal hypothalamic HA levels (Fig 1), longer diazepam treatment may possibly be needed to obtain more striking changes Since changes in hypothalamic HA levels of diazepam withdrawn rats were in opposite direction to stress-induced changes, the significance of this alteration remains to be elucidated The decrease in hypothalamic HA levels of diazepam withdrawn rats was associated with a significant increase in HD activity which suggests an imbalance between HA synthesis and HA metabolism and/or release It is possible that the increased HD activity may indicate a central compensatory mechanism in response to decreased hypothalamic HA levels

The significant elevation in hypothalamic HA concentration and HD activity observed in the control rats following 15 min air blast exposure is in agreement with our previous studies [23, 28, 30] and suggests an increased HA synthesis Diazepam chronically-treated or diazepam withdrawn rats responded to air blast stress by a similar increase in brain HA levels (Fig 1) Apparently the significant increase in HD activity noted in diazepam withdrawn stressed rats (Fig 2) was not adequate to influence hypothalamic HA levels Alternatively, a certain plateau in the increase in HA concentration could have been already reached in all of the stressed groups testes The present observations are not readily comparable with those of others because, to our best knowledge, similar stress studies involving diazepam were not reported

The absence of the attenuating effects of diazepam on hypothalamic HA response to stress may suggest that either higher doses or a more prolonged treatment is needed It is also possible that diazepam, which has been found not to displace ^{3}H-mepyramine from the binding sites in the brain "in vitro" studies [50] may not interact with central H_1 receptors, the latter seemed to be involved in air-blast induced changes in hypothalamic HA regulation as suggested by our previous investigation [28]

In contrast to the extensive studies, which indicated the significant involvement of GABA in the mechanism of action of benzodiazepines [3, 9, 16, 19, 52, 56–58], the role of central histaminergic system was not extensively investigated [59]

Recent receptor binding studies in membranes prepared from several brain regions of the rat indicated that cimetidine inhibited ^{3}H-muscimol and enhanced ^{3}H-flunitrazepam binding, but in cortical membranes the effect on both GABA and benzodiazepine binding sites was specific for imidazole-derived H_2-receptor antagonists and not observed with either several H_1 receptor antagonists or histamine [21] Although cimetidine and pyrilamine, H_2 and H_1 antagonists were reported to competitively antagonize benzodiazepine binding to human cerebral receptors in "in vitro" studies, this inhibition was not specific for benzodiazepine receptor because antihistamines also antagonized the binding to GABA, opiate and muscarinic acetylcholine receptor [55]

Diazepam withdrawn rats seemed to be more sensitive to stress as indicated by small but significantly greater plasma corticosterone response than that seen in non-withdrawn

stressed rats (Fig 3) It is of interest that increased excitability and withdrawal symptoms upon sudden cessation of chronic diazepam-treatment has been reported in clinical studies [41,42]

The mechanism of the presently observed increased sensitivity and its physiological significance is not clear at the present time but it may suggest some rebound process It is possible that certain changes in HA regulation and/or diazepam receptors did occur, but were suppressed during chronic diazepam treatment and become evident only upon withdrawal of the drug Chronic administration of benzodiazepines was reported not to influence ^{3}H-diazepam receptor binding in several brain regions of the rat [32] and lack of changes in benzodiazepine receptors or apparent affinity was found in rat forebrain membranes following diazepam withdrawal after chronic treatment [4] However, others reported a significant decrease in the ^{3}H-diazepam binding in rat cortex following chronic flurazepam administration [8,45], but no change in binding affinity The discrepancy in the above reports could have occurred because of different doses, route of administration and duration of treatment The differences in the number of benzodiazepine receptors may be of physiological significance If the latter event took place in our studies, changes in sensitivity to stress could have ensued upon diazepam withdrawal It is of interest that Maudsley reactive rat, bred with high degree of fearfulness, has been found to have significantly fewer central benzodiazepine receptors when compared with Maudsley nonreactive rat selected for low fearfulness [44] In addition, depending on the type of stress, the number of benzodiazepine receptors may increase (electroconvulsive shock [31,38] or cold water swim [54]) or decrease following footshock or exposure to conflict situation [22]

In conclusion, the present data indicate that diazepam withdrawal from chronically treated rats results in small but significant alterations in the basal hypothalamic HA regulation and in an increased HD activity and slightly increased plasma corticosterone response to stress Although, under present experimental conditions, changes in the basal (prestress) HA levels of diazepam withdrawn rats were small, they suggest that chronic diazepam treatment may affect central histaminergic system in rats

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REFERENCES

1 Barbin, G , J M Palacios, E Rodergas, J C Schwartz and M Garbarg Characterization of the high affinity binding sites of [^{3}H] histamine in rat brain *Mol Pharmacol* **18.** 1–10, 1980

2 Barlow, S M , A F Knight and F M Sullivan Plasma corticosterone responses to stress following chronic oral administration of diazepam in rat *J Pharm Pharmacol* **31:** 23–26, 1979

3 Braestrup, C , M Nielsen, P Krogsgaard-Larsen and E Falch Two or more conformations of benzodiazepine receptors depending on GABA receptors and other variables In *Receptors for Neurotransmitters and Peptide Hormones Advances in Biochemical Psychopharmacology*, edited by G Pepeu, M J Kuhar and S J Enna New York Raven Press, 1980, pp 301–313

4 Braestrup, C , M Nielsen and R F Squires No changes in rat benzodiazepine receptors after withdrawal from continuous treatment with lorazepam and diazepam *Life Sci* **24** 347–350, 1979

5 Cacabelos, R Histamina cerebral tema mongrafico *Jano, Med Human* **636:** 40–42, 1984

6 Calcutt, C R The role of histamine in the brain *Gen Pharmacol* **7·** 15–25, 1976

7 Chang, R S L , V T Tran and S H Snyder Heterogeneity of histamine H_1 receptors species variations in ^{3}H mepyramine binding to brain membranes *J Neurochem* **32** 1653–1663, 1979

8 Chiu, T H and H C Rosenberg Reduced diazepam binding following chronic benzodiazepine treatment *Life Sci* **23·** 1153–1158, 1978

9 Costa, E , M G Corda, B Epstein, C Forchetti and A Guidotti GABA-benzodiazepine interactions In *The Benzodiazepines From Molecular Biology to Clinical Practice*, edited by E Costa New York Raven Press, 1983, pp 117–137

10 Dunn, J and V Critchlow Pituitary-adrenal response to stress in rats with hypothalamic islands *Brain Res* **16·** 395–403, 1969

11 Garbarg, 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

12 Garbarg, M , G Barbin, C Llorens, J M Palacios, H Pollard and J C Schwartz Recent developments in brain histamine research pathways and receptors In *Neurotransmitters, Receptors and Drug Action* New York Spectrum Publications Inc , 1980, pp 179–202

13 Givner, M L and J G Rochefort An improved assay of corticosterone in rat serum and adrenal tissue *Steroids* **6** 485–489, 1965

14 Glowinski, J and L L Iversen Regional studies on catecholamine in the rat brain *J Neurochem* **13:** 655–669, 1966

15 Green, J P , C L Johnson and H Weinstein Histamine as a neurotransmitter In *Psychopharmacology A Generation of Progress*, edited by M A Lipton, A DiMascio and K F Killan New York Raven Press, 1978, pp 319–322

16 Guidotti, A Pharmacological and biochemical evidence for an interaction between the benzodiazepine and GABA receptors In *Receptors for Neurotransmitters and Peptide Hormones Advances in Biochemical Psychopharmacology*, vol 21, edited by G Pepeu, M J Kuhar and S J Enna New York Raven Press, 1980, pp 271–277

17 Hill, S J , P Daum and J M Young Affinities of histamine H_1-antagonists in guinea pig brain similarity of values determined from [^{3}H]mepyramine binding and from inhibition of a functional response *J Neurochem* **37.** 1357–1360, 1981

18 Kandel, S I , G H Steinberg, J W Wells, M Kandel and A G Gornall Separate binding sites for histaminic drugs in rat cerebral cortex *Biochem Pharmacol* **29·** 2269–2272, 1980

19 Karobath, M , P Placheta, M Lippitsch and P Krogsgaard-Larsen Characterization of GABA-stimulated benzodiazepine receptor binding In *Receptors for Neurotransmitters and Peptide Hormones Advances in Biochemical Psychopharmacology*, vol 21, edited by G Pepeu, M J Kuhar and S J Enna New York Raven Press, 1980, pp 313–321

20 Keim, K L and E B Sigg Plasma corticosterone and brain catecholamines in stress Effect of psychotropic drugs *Pharmacol Biochem Behav* **6·** 79–85, 1977

21 Lakoski, J M , G K Aghajanian and D W Gallager Interaction of histamine H_2 receptor antagonists with GABA and benzodiazepine binding sites in the CNS *Eur J Pharmacol* **88** 641–645, 1983

22 Lippa, A S , C A Klepner, L Yunger, M C Sano, W V Smith and B Beer Relationship between benzodiazepine receptors and experimental anxiety in rats *Pharmacol Biochem Behav* **9·** 853, 1978

23 Mazurkiewicz-Kwilecki, I M Single and repeated air blast stress and brain histamine *Pharmacol Biochem Behav* **12:** 35–39, 1980
24 Mazurkiewicz-Kwilecki, I M Effect of diazepam on stress-induced changes in brain histamine *Pharmacol Biochem Behav* **14:** 333–338, 1980
25 Mazurkiewicz-Kwilecki, I M Brain histamine-plasma corticosterone interactions *Life Sci* **32.** 1099–1106, 1983
26 Mazurkiewicz-Kwilecki, I M Possible role of histamine in brain function neurochemical, physiological and pharmacological indications *Can J Physiol Pharmacol* **62·** 709–714, 1984
27 Mazurkiewicz-Kwilecki, I M and B Bielkiewicz The effects of chronic morphine treatment on histamine concentration and histidine decarboxylase activity in rat brain *Prog Neuropsychopharmacol* **2·** 92–99, 1978
28 Mazurkiewicz-Kwilecki, I M and B Bielkiewicz Effect of diphenhydramine on-stress-induced changes in brain histidine decarboxylase activity, histamine and plasma corticosterone levels *Pharmacol Biochem Behav* **16:** 591–597, 1982
29 Mazurkiewicz-Kwilecki, I M and G D Prell Brain histamine Plasma corticosterone, spontaneous locomotor activity and temperature *Pharmacol Biochem Behav* **12:** 549–553, 1980
30 Mazurkiewicz-Kwilecki, I M and H Taub Effect of stress on brain histamine *Pharmacol Biochem Behav* **9.** 465–468, 1979
31 McNamara, J O , A M Peper and V Patrone Repeated seizures induce long-term increase in hippocampal benzodiazepine receptors *Proc Natl Acad Sci USA* **77:** 3029–3032, 1980
32 Mohler, H , T Okada and S J Enna Benzodiazepine and neurotransmitter receptor binding in rat brain after chronic administration of diazepam or phenobarbital *Brain Res* **156:** 391–395, 1978
33 Morita, Y and K Koyama Histamine-induced ACTH secretion and inhibitory effect of antihistaminic drugs *Jpn J Pharmacol* **29:** 59–65, 1979
34 Orr, E and W B Quay Hypothalamic 24 hour rhythms in histamine, histidine decarboxylase and histamine-N-methyltransferase *Endocrinology* **96:** 941–945, 1975
35 Palacios, J M , M Garbarg, G Barbin and J C Schwartz Pharmacological characterization of histamine receptors mediating stimulation of cyclic AMP accumulation in slices from guinea pig hippocampus *Mol Pharmacol* **14:** 971–982, 1978
36 Palacios, J M , J C Schwartz and M Garbarg High affinity binding of ^{3}H-histamine in rat brain *Eur J Pharmacol* **50.** 443–444, 1978
37 Palacios, J M , W S Young, III and M J Kuhar Autoradiographic localization of H_1-histamine receptors in brain using ^{3}H-mepyramine preliminary studies *Eur J Pharmacol* **58·** 295–304, 1979
38 Paul, S M and P Skolnick Rapid changes in brain benzodiazepine receptors after experimental seizures *Science* **202** 892–893, 1978
39 Phillis, J W , G K Kostopoulos and A Odutola On the specificity of histamine H_2 receptors antagonists in the rat cerebral cortex *Can J Physiol Pharmacol* **53:** 1205–1209, 1975
40 Portaleone, P , G Paganini, A Crispino and E Genazzi Histamine-sensitive adenylate cyclase in hypothalamus of rat brain H_1 and H_2 receptors *J Neurochem* **31:** 1371–1374, 1978
41 Prescott, L F Safety of the benzodiazepines In *The Benzodiazepines From Molecular Biology to Clinical Practice,* edited by E Costa New York Raven Press, 1983, pp 253–267
42 Rickels, K Benzodiazepines in the treatment of anxiety North American Experiences In *The Benzodiazepines From Molecular Biology to Clinical Practice,* edited by E Costa New York Raven Press, 1983, pp 295–311
43 Roberts, F and C R Calcutt Histamine and the hypothalamus *Neuroscience* **9:** 721–739, 1983
44 Robertson, H A , I L Martin and J M Candy Difference in benzodiazepine receptor binding in Maudsley reactive and Maudsley non-reactive rats *Eur J Pharmacol* **50:** 455–457, 1978
45 Rosenberg, H C and T H Chiu Decreased ^{3}H-diazepam binding is a specific response to chronic benzodiazepine treatment *Life Sci* **24:** 803–808, 1979
46 Rudolph, C , G E Richards, S Kaplan and W F Ganong Effect of intraventricular histamine on hormone secretion in dogs *Neuroendocrinology* **29** 169–177, 1979
47 Sastry, B S R and J W Phillis Evidence for ascending inhibitory histaminergic pathway to the cerebral cortex *Can J Physiol Pharmacol* **54·** 782–786, 1976
48 Schwartz, J C Histaminergic mechanisms in the brain *Annu Rev Pharmacol Toxicol* **17.** 325–329, 1977
49 Schwartz, J C , G Barbin, M Baudry, M Garbarg, M P Martres, H Pollard and M Verdiere Metabolism and functions of histamine in the brain *Current Dev Psychopharmacol* **5** 173–261, 1979
50 Schwartz, J C , G Barbin, A M Duchemin, M Garbarg, J M Palacios, T T Quach and C Rose Histamine receptors in the brain characterization by binding studies and biochemical effects In *Receptors for Neurotransmitters and Peptide Hormones,* edited by G Pepeu, M J Kuhar and S J Enna New York Raven Press, 1980, pp 169–182
51 Schwartz, J C , M Pollard and T T Quach Histamine as a neurotransmitter in mammalian brain neurochemical evidence *J Neurochem* **35.** 26–33, 1980
52 Skolnik, P and S M Paul The mechanism of action of benzodiazepines *Med Res Rev* **1/3·** 1–22, 1981
53 Snyder, S J 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
54 Soubrie, P , M H Thiebot, A Jobert, J L Montastruc, F Hery and M Hamon Decreased convulsant potency of picrotoxin and pentetrazol and enhanced [^{3}H] flunitrazepam cortical binding following stressful manipulations in rats *Brain Res* **189·** 505–517, 1980
55 Speeg, K V , Jr , S Wang, G R Avant, R Parker and S Schenker In vitro antagonism of benzodiazepine binding to cerebral receptors by H_1 and H_2 antihistamines *J Lab Clin Med* **97** 112–122, 1981
56 Squires, R F , C A Klepner and D I Benson Multiple benzodiazepine receptor complexes some benzodiazepine recognition sites are coupled to GABA receptors and ionophores In *Receptors for Neurotransmitters and Peptide Hormones Advances in Biochemical Psychopharmacology,* edited by G Pepeu, M J Kuhar and S J Enna New York Raven Press, 1980, pp 285–295
57 Tallman, J F , D W Gallager, P Mallorga, J W Thomas, W Strittmatter, F Hirata and J Axelrod Studies on benzodiazepine receptors In *Receptors for Neurotransmitters and Peptide Hormones Advances in Biochemical Psychopharmacology,* vol 21, edited by G Pepeu, M J Kuhar and S J Enna New York Raven Press, 1980, pp 277–285
58 Tallman, J F , S M Paul, P Skolnick and D W Gallager Receptor for the age of anxiety Pharmacology of the benzodiazepines *Science* **207** 274–281, 1980
59 Taylor, K M and R Laverty The interaction of chlordiazepoxide, diazepam and nitrazepam with catecholamines and histamine in regions of the rat brain In *The Benzodiazepines* New York Raven Press, 1973, pp 191–202
60 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
61 Tohyama, M , T Watanabe and H Wada Vias histaminergicos centrales *Jano, Med Human* **636:** 67–79, 1984
62 Usher, D R , P Kasper and M K Birmingham Comparison of pituitary-adrenal function in rats lesioned in different areas of limbic system and hypothalamus *Neuroendocrinology* **2** 157–174, 1976
63 Wada, H and R Cacabelos Introduccion a la histamina cerebral *Jano, Med Human* **636:** 43–56, 1984