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Endogenous serotonin modulates histamine release in the rat hypothalamus as measured by in vivo microdialysis

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Abstract

In vivo microdialysis was used to study the effects of serotonergic drugs on histamine release from the suprachiasmatic nuclei region of the anterior hypothalamus in anesthetized rats. Local perfusion with serotonin (5-hydroxytryptamine, 5-HT) increased histamine release significantly and dose dependently. Methysergide (10 mg/kg i.p.), a 5-$HT_{2C/2A}$ receptor antagonist, given 30 min before 5-HT perfusion, blocked the 5-HT-evoked histamine release. Methysergide (10 mg/kg i.p.), given alone, also suppressed basal histamine release by 33%. Dexfenfluramine (10 μM), a 5-HT releaser and uptake blocker, administered via the microdialysis probe, significantly enhanced hypothalamic histamine release. With the same dose of dexfenfluramine, 5-HT release increased 10-fold in the same brain area. These results show for the first time that endogenous 5-HT modulates histamine release in vivo and it has a tonic stimulatory effect on the histaminergic nerve terminals of the rat anterior hypothalamus.

Keywords: Histamine; 5-HT (5-hydroxytryptamine, serotonin); Dexfenfluramine; Methysergide; Microdialysis; Hypothalamus

1. Introduction

Histamine acts as a neurotransmitter/modulator in the mammalian brain and has been implicated in many circadian functions, including food intake, sleep/wake cycle, body temperature and hormone secretion (for review, see Schwartz et al., 1991; Wada et al., 1991; Onodera et al., 1994). In the rat brain, histaminergic cell bodies are located in the tuberomamillary nuclei of the posterior hypothalamus projecting fibers to almost all parts of the brain.

In mammals, the suprachiasmatic nuclei play a key role in the generation and synchronization of circadian rhythms (Ralph et al., 1990). The suprachiasmatic nuclei have a dense histaminergic innervation (Panula et al., 1989) and a high content of histamine (Browstein et al., 1974; Tuomisto et al., 1991). Histamine is considered to be one of the neurotransmitters modulating the circadian rhythms (Tuomisto, 1991; Nowak, 1994). Histamine had a modulatory impact on the spontaneous electrical activity of the suprachiasmatic nuclei neurons (Stehle, 1991). It also modulated the circadian phases of the spontaneous locomotor and drinking rhythms in rats and induced phase shifts, similar to those elicited by light, in suprachiasmatic nuclei neural activity (Itowi et al., 1990; Cote and Harrington, 1993). A major non-photic input to the suprachiasmatic nuclei is the serotonergic projection from the midbrain raphe nuclei (Moore et al., 1978). The function of this serotonergic input is poorly understood, but it is thought to participate in the regulation of suprachiasmatic nuclei functions (Morin et al., 1990). Hypothalamic serotonin (5-hydroxytryptamine, 5-HT) has also been implicated in feeding and sleep/wake behavior (Leibowitz et al., 1989; Imeri et al., 1994). A recent in vivo microdialysis study demonstrated that histamine release from the anterior hypothalamus exhibited a clear circadian rhythm in freely moving rats (Mochizuki et al., 1992). In addition, serotonergic transmission has been shown to have a circadian pattern with increased release during the dark period (Auerbach et al., 1989; Cagampang and Inouye, 1994).

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The release and synthesis of histamine are regulated by H_3-autoreceptors (Arrang et al., 1983; Prast et al., 1994). In the rat hypothalamus, endogenous histamine release in vivo has been shown to be modulated also by α_2-adrenergic, dopaminergic, cholinergic and glutamatergic heteroreceptors, all thought to be located on the histaminergic nerve terminals (Philippu, 1992). In spite of the dense histaminergic and serotonergic innervation of the suprachiasmatic nuclei region, surprisingly little is known about the possible interactions between 5-HT and histamine in this, or in any other brain region. In the present study, in vivo microdialysis method was used to examine the possible effects of serotonergic drugs on histamine release from the suprachiasmatic nuclei region of the anterior hypothalamus in anesthetized rats.

2. Materials and methods

2.1. Brain microdialysis

Male Wistar rats (300–400 g) were kept on a 12 h light-12 h dark cycle (lights on at 7 a.m.) for at least 1 week before use in experiments. All experiments were performed between 9 a.m. and 4 p.m. Animals were anesthetized with chloral hydrate (400 mg/kg ip.), with supplementary doses administered as necessery to maintain anesthesia. The body temperature was monitored by a rectal thermometer and was maintained constant throughout the experiment with a heating lamp. A microdialysis probe (membrane length 2 mm, CMA/12, Carnegie, Sweden) was stereotaxically implanted into the anterior hypothalamus, aimed at the suprachiasmatic nuclei. The coordinates were AP: −1.2, L: 0.4, V: 9.8 relative to bregma and skull surface, according to Paxinos and Watson (1986). The probe was perfused at a rate of 2 μl/min (1.5 μl/min for 5-HT analysis) with artificial cerebrospinal fluid (aCSF), composed of 138 mM NaCl, 5 mM KCl, 1 mM $MgCl_2$, 1.1 mM $CaCl_2$, pH 7.4 adjusted with 5% CO_2-95% O_2. In vitro recovery for histamine was 19 ± 1% (mean ± S.E.M., $n = 10$). The recovery for the probe was determined by perfusing standard solution of histamine (10^{-7}M) in room temperature mimicking the conditions of in vivo experiments. Brain perfusate was collected every 30 min using a refrigerated fraction collector (CMA/170, Carnegie, Sweden). Basal samples were collected for 90–120 min before drug treatment. 5-HT (10 or 100 μM) or dexfenfluramine (10 μM) were infused via the microdialysis probe for 60 min. Methysergide (10 mg/kg) or saline were injected i.p. 30 min before perfusion with 10 μM 5-HT. At the end of each experiment, the brain was removed for histological verification of the probe location.

2.2. Drugs

Serotonin creatinin sulfate (Fluka Chemika, Switzerland) and dexfenfluramine hydrochloride (kindly provided by Les Laboratoires Servier, France) were dissolved in distilled water and diluted in the aCSF just prior to infusion through the microdialysis probe. Methysergide (kindly provided by Sandoz) was dissolved in 20 μl of DMSO and diluted in 0.9% NaCl prior to i.p. injection (1 ml/kg). All reagents used in chemical assays were of HPLC analytical grade.

2.3. Histamine and 5-HT analysis

For histamine analysis, perfusate was collected in microtubes containing 10 μl of 20% perchloric acid. Samples were analyzed immediately by high pressure liquid chromatography (HPLC) using cation exchange column, postcolumn derivatization and fluorescent detection, as described by Yamatodani et al. (1985) with slight modifications (Yamatodani, 1991). The detection limit for histamine was approx. 10 fmol/injection. Under the conditions employed, the retention time for histamine was 4.8 min. 5-HT was detected in the histamine fluorometry with the retention time 10.1 min and it did not interfere with histamine analysis.

5-HT, 5-hydroxyindole-3-acetic acid (5-HIAA) and homovanillic acid (HVA) were determined by HPLC with electrochemical detection. The perfusate was collected into microtubes containing 20 μl of the mobile phase. The mobile phase (0.1 M acetic acid, 0.1 M citric acid, 25 mg/l octyl sodium sulphate and 16% methanol) was delivered at a flow rate of 1.2 ml/min by LKB 2150 pump (Bromma, Sweden) onto an RP-18 column (250 × 4.6 mm, 5 μm, Ultrasphere, Beckman). Detection was carried out with a coulometric detector (ESA Coulochem, model 5100 A) with dual electrode analytical cell. The conditioning cell was set at +0.18 V, electrode 1 at +0.3 V for 5-HT and electrode 2 at +0.4 V for 5-HIAA and HVA. The detection limit for 5-HT was approx. 5 fmol/injection. Dexfenfluramine did not interfere with histamine or 5-HT analysis.

2.4. Statistics

The data are expressed as percentages of the averaged basal release of two consecutive samples prior to drug treatment. The effects of the drugs were assessed by one way analysis of variance (ANOVA) followed by Dunnett's t-test.

3. Results

The mean basal release of histamine from the suprachiasmatic nuclei region of the anterior hypo-

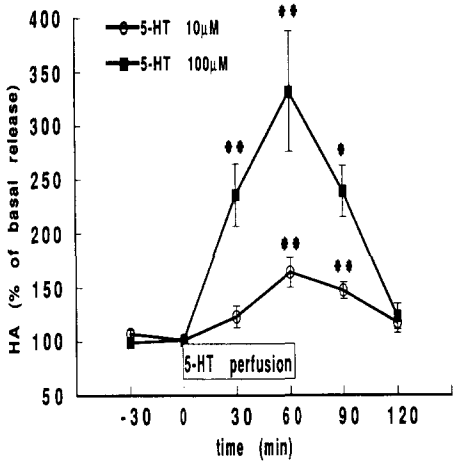

Fig. 1. Local perfusion (60 min) with 5-HT (10 and 100 μM) dose dependently enhances histamine release from the suprachiasmatic nuclei region of the rat hypothalamus. The results are expressed as percentages of the basal release (means ± S.E.M., $n = 6$). ** $P < 0.01$ and * $P < 0.05$ vs. pretreatment value.

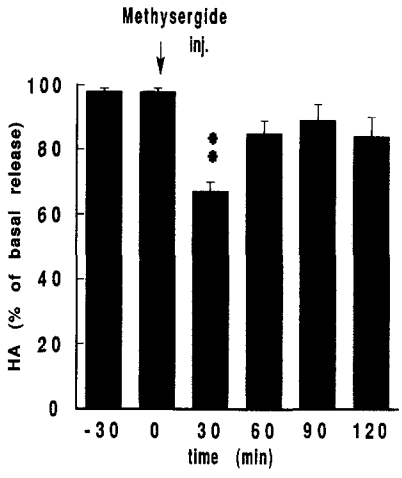

Fig. 3. Methysergide (10 mg/kg i.p.) suppresses basal histamine release from the suprachiasmatic neuclei region of the rat hypothalamus. The results are expressed as percentages of basal release (means ± S.E.M., $n = 7$). ** $P < 0.01$ vs. pretreatment value.

thalamus was 109 ± 11 fmol/30 min (mean ± S.E.M., 12 rats). Following probe implantation, histamine release in individual rats remained constant throughout the experiment.

Local perfusion with 5-HT (10 or 100 μM) increased histamine release significantly up to 164 and 332%, respectively, of the basal release, reaching maximal output 60 min after beginning of drug perfusion (Fig. 1). Methysergide (10 mg/kg, i.p.), given 30 min before perfusion with 10 μM 5-HT, completely antagonized the 5-HT-evoked histamine release (Fig. 2). Methysergide (10 mg/kg i.p.), given alone, significantly suppressed also basal histamine release by 33% 30 min after injection (Fig. 3).

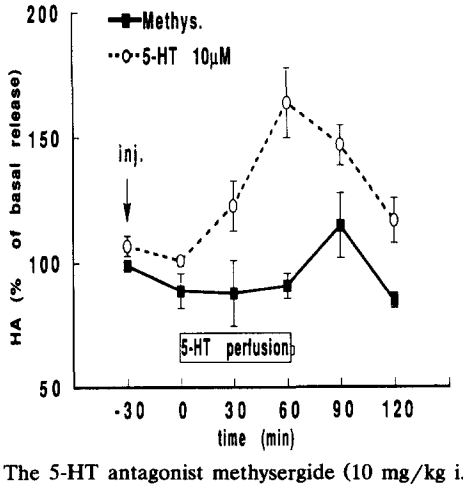

Fig. 2. The 5-HT antagonist methysergide (10 mg/kg i.p.) reverses the 5-HT-elicited (10 μM) histamine release from the suprachiasmatic nuclei region of the rat hypothalamus. Injection was given 30 min before the 5-HT perfusion (60 min), $n = 4$.

Dexfenfluramine, a 5-HT releaser and uptake blocker, perfused via the probe at a concentration of 10 μM, increased histamine release significantly up to 163% (Fig. 4A). With the same dose of dexfenfluramine, 5-HT release increased up to 1088% in the same brain area (Fig. 4B). The basal extracellular 5-HT level in the suprachiasmatic nuclei region was 8.3 ± 3 fmol/30 min (mean ± S.E.M., $n = 5$).

4. Discussion

The present study clearly demonstrated that endogenous 5-HT modulated histamine release and had a tonic stimulatory effect on histaminergic nerve terminals in the suprachiasmatic nuclei region of the rat anterior hypothalamus. Local perfusion with 5-HT evoked a significant and dose-dependent histamine release. Methysergide, a $5\text{-HT}_{2C/2A}$ receptor antagonist, blocked the 5-HT-elicited effect and also suppressed basal histamine release. Moreover, dexfenfluramine, a 5-HT releaser and uptake blocker, significantly enhanced hypothalamic histamine output.

In the present study, basal histamine levels in the anterior hypothalamus were similar to those reported by other groups using anesthetized rats (Mochizuki et al., 1991; Okakura et al., 1992). Previous in vivo microdialysis studies have clearly demonstrated the neuronal origin of histamine release in the rat hypothalamus (Mochizuki et al., 1991; Itoh et al., 1991). In the rat brain, histamine exists also in the non-neuronal pool of mast cells. However, mast cells are found almost exclusively within the thalamus and are virtually absent from the hypothalamus (Hough et al., 1984).

In addition to autoreceptors, various heteroreceptors appear to participate in the regulation of hypotha-

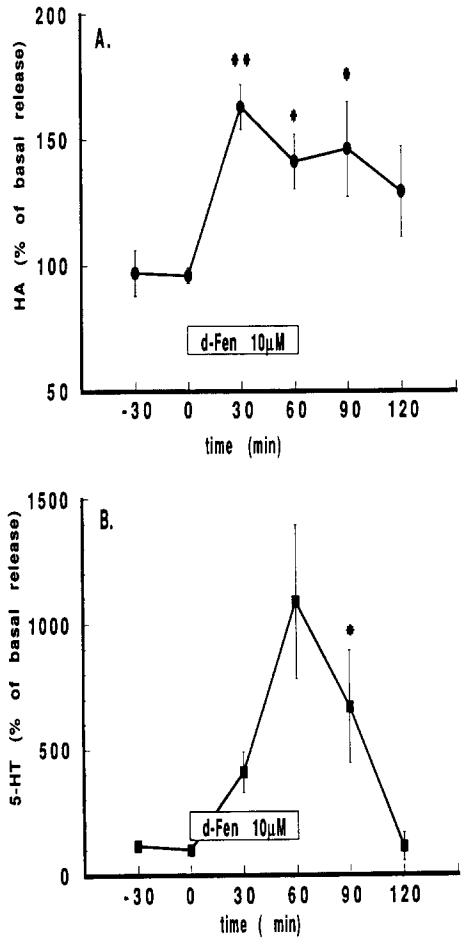

Fig. 4. Local perfusion (60 min) with dexfenfluramine (10 μM) enhances histamine (A) release and serotonin (B) release from the suprachiasmatic nuclei region of the rat hypothalamus. The results are expressed as percentages of basal release (means ± S.E.M., (A) $n = 4$, (B) $n = 3$). ** $P < 0.01$ and * $P < 0.05$ vs. pretreatment value.

lamic histamine release in vivo. These include glutamate (Okakura et al., 1992), noradrenaline, dopamine and acetylcholine receptors (Prast et al., 1991,1993, 1994). Furthermore, experiments with slice preparations revealed that opioid and galanin receptors regulate histamine release as well (Gulat-Marney et al., 1990; Arrang et al., 1991).

In spite of the dense histaminergic and serotonergic projections to the hypothalamus, very little is known of the possible effects of 5-HT on histaminergic activity. Oishi et al. (1992) found that the selective 5-HT_{1A} receptor agonist, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), inhibited histamine turnover in various brain regions. Agonists and antagonists for other 5-HT receptor subtypes were also tested. The results of the above study suggested that histaminergic activity in the brain was regulated by 5-HT_{1A} receptors. Systemic injection of 8-OH-DPAT was shown to rapidly decrease hypothalamic basal 5-HT release by 50% (Auerbach et al., 1989). Also other in vivo microdialysis studies confirmed that systemically administered 5-HT_{1A} receptor agonists reduced 5-HT release from the projection areas through autoreceptors located on the serotonergic cell bodies (Sharp et al., 1989, Adell et al., 1993). The pronounced decrease in 5-HT release following administration of 8-OH-DPAT could explain the inhibitory action of this agonist on histamine turnover in the brain. This would be in agreement with our results which for the first time directly demonstrate that endogenous 5-HT has a tonic stimulatory effect on histaminergic nerve terminals in the rat hypothalamus. In the study of Oishi et al. (1992) methysergide failed to reverse the inhibition of histamine turnover following treatment with the 5-HT_{1A} receptor agonist. In contrast, we found a significant decrease in histamine release by 30 min after methysergide injection; this was followed by a slight suppression (10–15%) that lasted till the end of the experiment. The differences between the present work and that by Oishi et al. (1992) might be due to different methodology and time schedule after methysergide administration.

The identity of the 5-HT receptor subtype mediating the histamine release remains to be clarified. Methysergide blocks both 5-HT_{2C} and 5-HT_{2A} receptors (formerly the 5-HT_{1C} and 5-HT_2, respectively) (Hoyer et al., 1994). In situ hybridization studies have revealed the presence of mRNA for 5-HT_{2C} and 5-HT_{1B} receptors within the suprachiasmatic nuclei, whereas no detectable signal was found for the 5-HT_{1A} and 5-HT_{2A} receptors (Roca et al., 1993). Binding sites for 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2C} receptors and to a lesser extent for 5-HT_{2A} receptors have been localized in the mammalian hypothalamus (Palacios et al., 1990). A novel 5-HT receptor subtype, the 5-HT_7 receptor, was recently identified in the rat hypothalamus and it has been implicated in the regulation of mammalian circadian rhythms (Lovenberg et al., 1993). The 5-HT_7 receptor has a relatively high affinity for both 5-HT_{1A} receptor agonists and 5-$HT_{2C/2A}$ receptor antagonists, including methysergide (Lovenberg et al., 1993). Various 5-HT receptor agonists and antagonists should be used to specifically reveal the 5-HT receptor subtype that acts as a heteroreceptor modulating hypothalamic histamine release.

In the present study, local perfusion with 5-HT caused a robust increase in hypothalamic histamine release. To test whether endogenously released 5-HT would have the same effect, we administered dexfenfluramine locally to enhance 5-HT content in the synaptic cleft. Indeed, local perfusion with dexfenfluramine elevated 5-HT release by more than 10-fold, histamine release also increased significantly. Large increases in the hypothalamic extracellular 5-HT levels with locally administered dexfenfluramine have also been reported by other groups (Schwartz et al., 1989; Auerbach et al., 1989). The effect of dexfenfluramine

on histamine release, however, has not been reported before.

Dexfenfluramine possesses an anorectic activity and it is assumed to cause hypophagia by enhancing the availability of hypothalamic 5-HT (Mennini et al., 1985). On the other hand, activation of hypothalamic histaminergic neurons also suppressed food intake (Lecklin and Tuomisto, 1990; Sakata et al., 1990) and regulated the circadian rhythm of feeding (Doi et al., 1994). It is therefore tempting to suggest that serotonergic modulation of histamine release may well participate in the anorectic effect of dexfenfluramine. According to our hypothesis, the increased levels of extracellular 5-HT stimulate hypothalamic histamine release, thus potentiating the suppression of food intake. Whether the stimulatory effect of dexfenfluramine on histamine release is due to increased levels of 5-HT or direct stimulation of serotonergic heteroreceptors located on the histaminergic nerve terminals, remains to be evaluated.

In conclusion, the results of the present study clearly demonstrate that endogenous 5-HT modulates histamine release in vivo in the rat anterior hypothalamus. Furthermore, our studies suggest that histamine may partly mediate the anorectic effect of dexfenfluramine.

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References

Adell, A., A. Carceller and F. Artigas, 1993, In vivo brain dialysis study of the somatodendritic release of serotonin in the raphe nuclei of the rat: effects of 8-hydroxy-2-(di-*n*-propylamino)tetralin, J. Neurochem. 60, 1673.

Arrang, J.M., M. Garbarg and J.C. Schwarz, 1983, Autoinhibition of brain histamine release mediated by a novel class (H_3) of histamine receptor, Nature 302, 832.

Arrang, J.M., C. Gulat-Marnay, N. Defontaine and J.C. Schwartz, 1991, Regulation of histamine release in rat hypothalamus and hippocampus by presynaptic galanin receptors, Peptides 12, 1113.

Auerbach, S.B., M.J. Minzenberg and L.O. Wilkinson, 1989, Extracellular serotonin and 5-hydroxyindoleacetic acid in hypothalamus of the unanesthetized rat measured by in vivo dialysis coupled to high-performance liguid chromatography with electrochemical detection: dialysate serotonin reflects neuronal release, Brain Res. 499, 281.

Browstein, M.J., J.M. Saavedra, M. Palkowits and J. Axelrod, 1974, Histamine content of hypothalamic nuclei of the rat, Brain Res. 77, 151.

Cagampang, F.R.A. and S.-I.T. Inouye, 1994, Diurnal and circadian changes of serotonin in the suprachiasmatic nuclei: regulation by light and an endogenous pacemaker, Brain Res. 639, 175.

Cote, N.K. and M.E. Harrington, 1993, Histamine phase shifts the circadian clock in manner similar to light, Brain Res. 613, 149.

Doi, T., T. Sakata, H. Yoshimatsu, H. Machidori, M. Kurokawa, L.A.L.W. Jayasekara and N. Niki, 1994, Hypothalamic neuronal histamine regulates feeding circadian rhythm in rats, Brain Res. 641, 311.

Gulat-Marney, C., A. Lafitte, J.M. Arrang and J.C. Schwartz, 1990, Modulation of histamine release in the rat brain by κ-opioid receptors, J. Neurochem. 55, 47.

Hough, L.B., R.C. Goldschmidt, S.D. Glick and J. Padawer, 1984, Mast cells in the rat brain: characterization, localization, and histamine content, in: Frontiers in Histamine Research, eds. C.R. Ganellin and J.-C. Schwartz (Pergamon Press, Oxford) p. 131.

Hoyer, D., D.E. Clarke, J.R. Fozard, P.R. Hartig, G.R. Martin, E.J. Mylecharane, P.R. Saxena and P.P.H. Humprey, 1994, International union of pharmacology classification of receptors for 5-hydoxytryptamine (serotonin), Pharmacol. Rev. 46, 157.

Imeri, L., M.G. De Simoni, R. Giglio, A. Clavenna and M. Mancia, 1994, Changes in the seroronergic system during the sleep-wake cycle: simultaneous polygraphic and voltammetric recordings in hypothalamus using a telemetry system, Neuroscience 58, 353.

Itoh, Y., R. Oishi, M. Nishibori and K. Saeki, 1991, Characterization if histamine release from the rat hypothalamus as measured by in vivo microdialysis, J. Neurochem. 56, 769.

Itowi, N., A. Yamatodani, K. Nagai, H. Nakagawa and H. Wada, 1990, Effects of histamine and α-fluoromethylhistidine injections on circadian phase of free-running rhythms, Physiol. Behav. 47, 549.

Lecklin, A. and L. Tuomisto, 1990, Feed intake after inhibition of histamine catabolism, Agent Actions 30, 216, 549.

Leibowitz, S.F., G.F. Weiss, U.A. Walsh and D. Viswanath, 1989, Medial hypothalamic serotonin: role in circadian patterns of feeding and macronutrient selection, Brain Res. 503, 132.

Lovenberg, T.W., B.M. Baron, L. De Lecea, J.D. Miller, R.A. Prosser, M.A. Rea, P.E. Foye, M. Racke, A.M. Slone, B.W. Siegal, P.E. Danielson, J.G. Sutcliffe and M.G. Erlander, 1993, A novel adenylyl cyclase-activating serotonin receptor ($5\text{-}HT_7$) implicated in the regulation of mammalian circadian rhythms, Neuron 11, 449.

Mennini, T., S. Garattini and S. Caccia, 1985, Anorectic effect of fenfluramine isomers and metabolites: relationship between brain levels and in vitro potencies on serotonergic mechanisms, Psychopharmacology 85, 111.

Mochizuki, T., A. Yamatodani, K. Okakura, M. Takemura, N. Inagaki and H. Wada, 1991, In vivo release of neuronal histamine in the hypothalamus of rats measured by microdialysis, Naunyn-Schmied. Arch. Pharmacol, 343, 190.

Mochizuki, T., A. Yamatodani, K. Okakura, A. Horii, N. Inagaki and H. Wada, 1992, Circadian rhythm of histamine release from the hypothalamus of freely moving rats, Physiol. Behav. 51, 391.

Moore, R.Y., A.E. Halaris and B.E. Jones, 1978, Serotonin neurons of the midbrain raphe: ascending projections, J. Comp. Neurol. 180, 417.

Morin, L.P., K.M. Michels, L. Smale and R.Y. Moore, Serotonin regulation of circadian rhythmicity, 1990, in: The Neuropharmacology of Serotonin, eds. P.A. Whitaker-Azmitia and S.J. Peroutka, Ann. NY Acad. Sci. p. 418.

Nowak, J.Z., 1994, Histamine in the central nervous system: its role in circadian rhythmicity, Acta Neurobiol. Exp. 54, 65.

Oishi, R., Y. Itoh and K. Saeki, 1992, Inhibition of histamine turnover by 8-OH-DPAT, busbirone and 5-hydroxytryptophan in the mouse and rat brain, Naunyn-Schmied. Arch. Pharmacol. 345, 495.

Okakura, K., A. Yamatodani, T. Mochizuki, A. Horii and H. Wada, 1992, Glutamatergic regulation of histamine release from rat hypothalamus, Eur. J. Phamacol. 213, 189.

Onodera, K., A. Yamatodani, T. Watanabe and H. Wada, 1994, Neuropharmacology of the histaminergic neuron system in the brain and its relationship with behavioral disorders, Prog. Neurobiol. 42, 685.

Palacios, J.M., C. Waeber, D. Hoyer and G. Mengod, 1990, Distribution of serotonin receptors, in: The Neuropharmacology of Serotonin, eds. P.M. Whitaker-Azmitia and S.J. Peroutka, NY Acad. Sci., p. 36.

Panula, P., U. Pirvola, S. Auvinen and M.S. Airaksinen, 1989, Histamine-immunoreactive nerve fibers in the rat brain, Neuroscience 28, 585.

Paxinos, G. and C. Watson, 1986, The Rat Brain in Stereotaxic Coordinates, 2nd edn. (Academic Press, New York).

Philippu, A., 1992, Modulation by heteroreceptors of histamine release in the brain, Ann. Psychiatr./An. Psiquiatr. 3, 79.

Prast, H., M. Heistrachter and A. Philippu, 1991, In vivo modulation of the histamine release in the hypothalamus by adrenoceptor agonist and antagonist, Naunyn-Schmied. Arch. Pharmacol. 344, 183.

Prast, H., M. Heistracher and A. Philippu, 1993, Modulation by dopamine receptors of the histamine release in the rat hypothalamus, Naunyn-Schmied. Arch. Pharmacol. 347, 301.

Prast, H., H.-P. Fisher, M. Prast and A. Philippu, 1994, In vivo modulation of histamine release by autoreceptors and muscarinic acetylcholin receptors in the rat anterior hypothalamus, Naunyn-Schmied. Arch. Pharmacol. 350. 599.

Ralph, M.R., G.F. Foster, F.C. Davis and M. Menaker, 1990, Transplanted suprachiasmatic nucleus determines circadian period, Science 247, 975.

Roca, L.A., D.R. Weaver and S. Reppert, 1993, Serotonin receptor gene expression in the rat suprachiasmatic nuclei, Brain Res. 608, 159.

Sakata, T., K. Fukagawa, K. Ookuma, K. Fujimoto, H. Yoshimatsu, A. Yamatodani and H. Wada, 1990, Hypothalamic neuronal histamine modulates ad libitum feeding by rats, Brain Res. 537, 303.

Schwartz, D., L. Herdandez and B.G. Hoebel, 1989, Fenfluramine administered systemically or locally increases extracellular serotonin in the lateral hypothalamus as measured by microdialysis, Brain Res. 482, 261.

Schwartz, J.-C., J.-M. Arrang, M. Garbarg, H. Pollard and M. Ruat, 1991, Histaminergic transmission in the mammalian brain, Physiol. Rev. 71, 1.

Sharp, T., S.R. Bramwell, D. Clark and D.G. Grahame-Smith, 1989, In vivo measurements of extracellular 5-hydroxytryptamine in hippocampus of the anaesthetized rat using microdialysis: changes in relation to 5-hydroxytryptaminergic neuronal activity, J. Neurochem. 53, 234.

Stehle, J., 1991, Effects of histamine on spontaneuos electrical activity of neurons in rat suprachiasmatic nucleus, Neurosci. Lett. 130, 127.

Tuomisto, J.T., M. Unkila, R. Pohjanvirta, M. Koulu and L. Tuomisto, 1991, Effect of a single dose of TCDD on the level of histamine in discrete nuclei in rat brain, Agents Actions, 33, 154.

Tuomisto, L., 1991, Involvement of histamine in circadian and other rhythms, in: Histaminergic neurons: morphology and function, eds. T. Watanabe and H. Wada (CRC Press, Boca Raton) p. 283.

Yamatodani, A., 1991, Assay of histamine and its metabolites in the brain, in: Histaminergic Neurons: Morphology and Functions, eds. T. Watanabe and H. Wada (CRC Press, Boca Raton) p. 35.

Yamatodani, A., H. Fukuda, H. Wada, T. Iwaeda and T. Watanabe, 1985, High-performance liquid chromatographic determination of plasma and brain histamine without previous purification of biological samples: cation-exchange chromatography coupled with post-column derivatization fluorometry, J. Chromatogr. 344, 115.

Wada, H., N. Inagi, A. Yamatodani and T. Watanabe, 1991, Is the histaminergic neuron system a regulatory center for whole-brain activity, Trends Neurosci. 14, 415.