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European Journal of Pharmacology 407 (2000) 117–122

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In vivo histamine release from brain cortex: the effects of modulating cellular and extracellular sodium and calcium channels

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Received 4 July 2000; received in revised form 30 August 2000; accepted 15 September 2000

Abstract

The in vivo mechanisms underlying the actions of modulating Na^+- and Ca^{2+}-sensitive channels and its effect on basal histamine release in the cerebral cortex of freely-moving unanesthetized rats was investigated. Basal histamine release in the cerebral cortex was determined by in vivo microdialysis coupled with high-performance liquid chromatography (HPLC) fluorometry detection. Basal levels of histamine were 0.67 ± 0.02 pmol/10 μl of dialysate. Diltiazem, a Ca^{2+} channel antagonist, produced a dose-dependent decrease in dialysate basal histamine concentration. Elevated K^+ (100 mM) in the perfusion medium increased basal histamine to a maximum of 223% of the baseline value. Similarly, diltiazem (60 mM) reduced the K^+, veratridine (100 μg/ml) and ouabain (100 μM)-evoked increase in dialysate histamine. Basal histamine decreased by 48% when the perfusate contained 3 μM of voltage dependent Na^+ antagonist tetrodotoxin. The results of these studies indicate that the release of histamine in rat cerebral cortex can be induced by modulating Na^+ and Ca^{2+} channels and that the L-type voltage-dependent sensitive Ca^{2+} channels are involved in this release process.

Keywords: Histamine; Histamine release; Microdialysis; Veratrine; Ouabain

1. Introduction

In vivo studies have demonstrated that some neurotransmitters can be released from central terminals via two discrete mechanisms (Raiteri et al., 1979; Liang and Rutledge, 1982). One mechanism is dependent on extracellular Ca^{2+} (Holz, 1975; Mulder et al., 1975; Raiteri et al., 1979; Drapeau and Blaustein, 1983; Nachshen and Sanchez-Armass, 1987) and presumably represents release via an exocytotic mechanism (Katz and Miledi, 1967; Rubin, 1970; Augustine et al., 1987). A second mechanism is insensitive to extracellular Ca^{2+} and is elicited by veratridine and ouabain, two agents known to affect transmembrane distribution of Na^+. This mechanism appears to be analogous to the exchange diffusion process of noradrenaline release described in rat atria (Paton, 1973) and hypothalamus (Raiteri et al., 1979).

Veratridine induces an influx of Na^+ into nervous tissue by opening voltage-dependent, tetrodotoxin-sensitive Na^+ channels (Ulbricht, 1969; Ohta et al., 1973; Li and White, 1977) and ouabain inhibits neuronal Na^+–K^+ ATPase, leading to an intraneuronal accumulation of Na^+ (Archibald and White, 1974; Goddard and Robinson, 1976; Vizi, 1978). An ouabain-induced release of brain transmitters has been reported both in vivo (Raiteri et al., 1979; O'Fallon et al., 1981; Liang and Rutledge, 1982; Schoffelmeer and Mulder, 1983; Vizi, 1978) and in vitro (Jacobsen et al., 1986; Arbuthnott et al., 1986; Sirinathsinghji et al., 1988; Raiteri et al., 1979; Liang and Rutledge, 1982; Fairbrother et al., 1990). The ensuing depolarization leads to an influx of Ca^{2+} (Blaustein, 1975; Adam-Vizi and Ligeti, 1986) and a release of brain transmitters (Mulder et al., 1975; Raiteri et al., 1979; Wightman et al., 1981; Jacobsen et al., 1986; Arbuthnott et al., 1986; Butcher and Hamberger, 1987). It should be noted that a similar mechanism may be involved in the release of histamine in rat cerebral cortex (Minchin, 1980; Schoffelmeer and Mulder, 1983). To date, the mechanism responsible for the release of histamine from the cerebral cortex has yet to be fully

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0014-2999/00/$ - see front matter
PII: S0014-2999(00)00733-0

elucidated. Characterization of this in vivo process should facilitate our understanding of the operation of central histaminergic neurons in the release of histamine. There are only a few reports that deal with the effects of Ca^{2+} channel antagonists on in vivo neurotransmitter release (Lazarewicz et al., 1986; Westerink et al., 1988; Pani et al., 1990).

Brain microdialysis has proven to be a useful technique in studying in vivo mechanisms of neurotransmitter release in the central nervous system (Ungerstedt et al., 1982; Westerink et al., 1987; Kato et al., 1992; Cumming et al., 1991; Chikai et al., 1993; Itoh et al., 1991). In the present study, the in vivo action of modulating cellular and extracellular Na^+ and Ca^{2+} channels on extracellular histamine release in the cerebral cortex of freely moving, unanesthetized rats using microdialysis was examined. The cerebral cortex was selected as the principal target because of its relatively dense innervation with histaminergic neurons extending from the hypothalamus (Wada et al., 1991).

2. Material and methods

2.1. Animals

Male Sprague–Dawley rats (weighing 200–220 g) were maintained in a normal 12-h light–dark cycle with food and water given ad libitum. All procedures were conducted under the guidelines approved by the Animal Care and Use Committee and were in direct accordance with the NIH Guide for the Care Use of Laboratory Animals.

2.2. Brain microdialysis

Animals were anesthetized with pentobarbital (35 mg/kg, i.p.) and the dura was exposed through a 0.6-mm burr hole in the skull. A cannula, for insertion of microdialysis probes was permanently implanted into the cerebral cortex. The stereotaxic coordinates from bregma were: AP = +2.0, L = −2.5, V = −2.0, according to the atlas of Paxinos and Watson (1986). All experiments were performed 48 h after cannula implantation. On the day of the experiment, the rat was placed in a hemispheric bowl and the microdialysis probe inserted (outer diameter 0.5 mm with a 3-mm dialyzing membrane at the tip, CMA 12, from Carnegie Medicin, Stockholm, Sweden). The probe was connected via a liquid swivel to a microinfusion pump (CMA 120 system 4, Carnegie Medicin). Artificial cerebrospinal fluid (NaCl, 147 mM; KCl, 4 mM; $CaCl_2$, 1.3 mM; $MgCl_2$; and 1 mM sodium phosphate, pH 7.4), freshly prepared from sterilized double distilled water immediately before use, was perfused at a rate of 0.9 μl/min. When perfusion was with a high-K^+ medium, the KCl concentration was raised to 100 mM and the NaCl concentration was reduced to maintain isomolarity. Similarly, Ca^{2+}-free medium was prepared by replacing $CaCl_2$ with isomolar NaCl and adding 0.1 mM EGTA. To obtain a stable level of histamine in the dialysate samples, the probe was inserted into the cerebral cortex and perfused for 2 h before sample collection. Basal brain dialysate levels of histamine were determined by sampling dialysate at 20-min intervals for 80 min. At the end of the experiments, the rats were euthanized and the placement of the canal were verified by microscopic examination.

2.3. Determination of histamine

The histamine concentration of the dialysate was determined by a sensitive high-performance liquid chromatography (HPLC) fluorometric method (Egger et al., 1994). The samples were injected into a Bioanalytical System and separated by a reversed-phase ODS column, 100 × 3.2 mm I.D., 3 μm (McMod) with a mobile phase of methanol–0.02 M sodium acetate (1:1, v/v) supplemented with 1.25 mM 1-heptanesulfonic acid (flow rate: 0.5 ml/min) after precolumn derivatization with *o*-phthalaldehyde. A 100-μl volume of *o*-phthalaldehyde reagent consisting of 50% methanol, 19 mM *o*-phthalaldehyde, 45 mM sodium tetraborate pH 9.5 and 2 mM 2-mercaptoethanol were added to samples (5–25 μl) and stirred vigorously for 60 s at room temperature and injected into the HPLC system (BioAnalytical System) exactly 1.5 min after the reaction was started. The amine-*o*-phthalaldehyde adducts were detected fluorimetrically (excitation 360 nm, emission 456 nm) with a fluorimetric detector (BioAnalytical System).

2.4. Chemical and drug

Histamine dihydrochloride, diltiazem, tetrodotoxin, veratridine, and ouabain were purchased from Sigma (St. Louis, MO, USA) and were of the highest analytical grade. Thioperamide was purchased from Tocris Cookson (Baldwin, MO, USA). All drugs were dissolved in artificial cerebrospinal fluid solution.

2.5. Data analysis

In experiments in which the composition of the cerebrospinal fluid was altered, two syringes were connected to a four-way switching valve. In these experiments, the syringe that was not connected to the microdialysis probes was connected through the valve to another probe that was not used, thus maintaining the appropriate back pressure on both syringes. Thus, the first baseline sample was not included in calculations of baseline. Samples collected before beginning drug treatment were averaged and used as baseline values. Microdialysis data are reported as percent change from baseline and expressed as mean ± S.E.M. values. The data were analyzed by one-way analysis of variance (ANOVA) and the Dunnett's test between

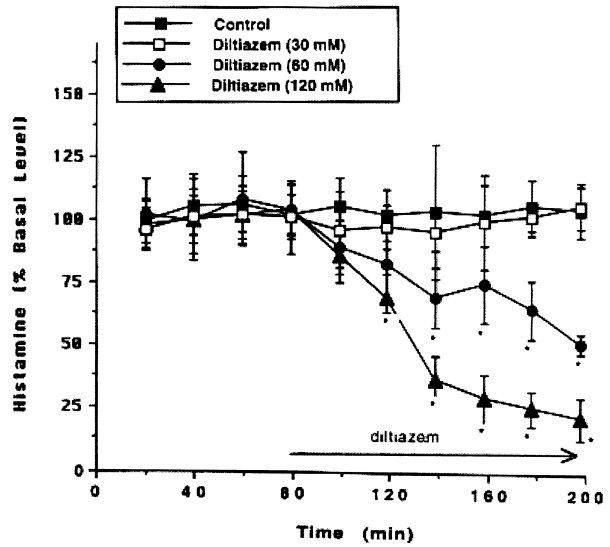

Fig. 1. Dose-dependent effect of diltiazem on histamine release in rat cerebral cortex. Diltiazem was continuously administered into the cerebral cortex through the dialysis membrane (indicated by arrow). Histamine concentration in the dialysate is expressed as percentage of mean basal levels taken at four time points prior to administration of the drug (error bars = ±S.E.M.). N = number of animals: control ($n = 6$); 120 mM ($n = 5$); 60 mM ($n = 5$); 30 mM ($n = 4$). $^{*}P < 0.05$ vs. control.

experimental values and basal control values. A significance level of < 0.05 was considered statistically significant.

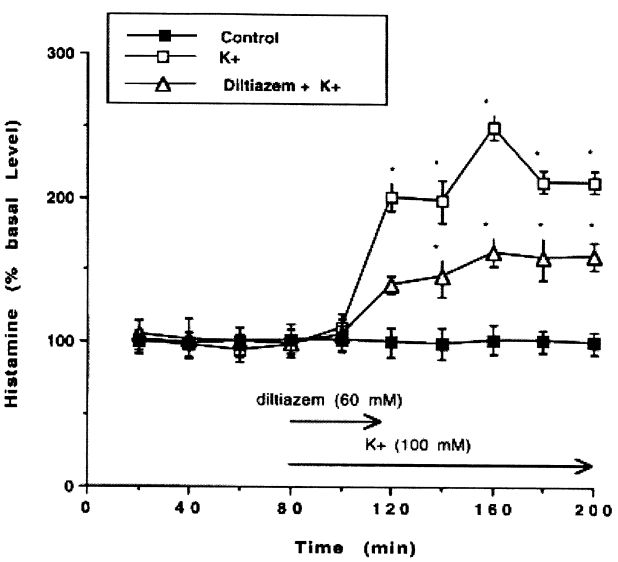

Fig. 2. Effect of continuous perfusion of elevated K^+ (100 mM) on extracellular histamine in dialysate samples. After collection of four (20 min) basal samples, the cerebral cortex was perfused with elevated K^+ or diltiazem (60 mM) for 40 min plus K^+. Arrows indicate perfusion of drugs. Data are expressed as the percentage of the mean ± S.E.M. basal levels. $N = 5$, which indicate the number of animal per experiment. Statistics were calculated by ANOVA followed by Dunnett's test. $^{*}P <$ 0.05 vs. control.

3. Results

To substantiate the stability of our experimental preparation, basal histamine release was measured at 20-min intervals throughout the duration of all experiments. Basal histamine release after 60 min was determined to be 0.67 ± 0.02 pmol/10 μl of dialysate ($n = 12$ animals) and at 180 min basal histamine (0.65 ± 0.06 pmol/10 μl) was not significantly different from basal release determined at 60 min.

Histamine release overtime was not different from basal levels when perfused with 30 mM of diltiazem. The

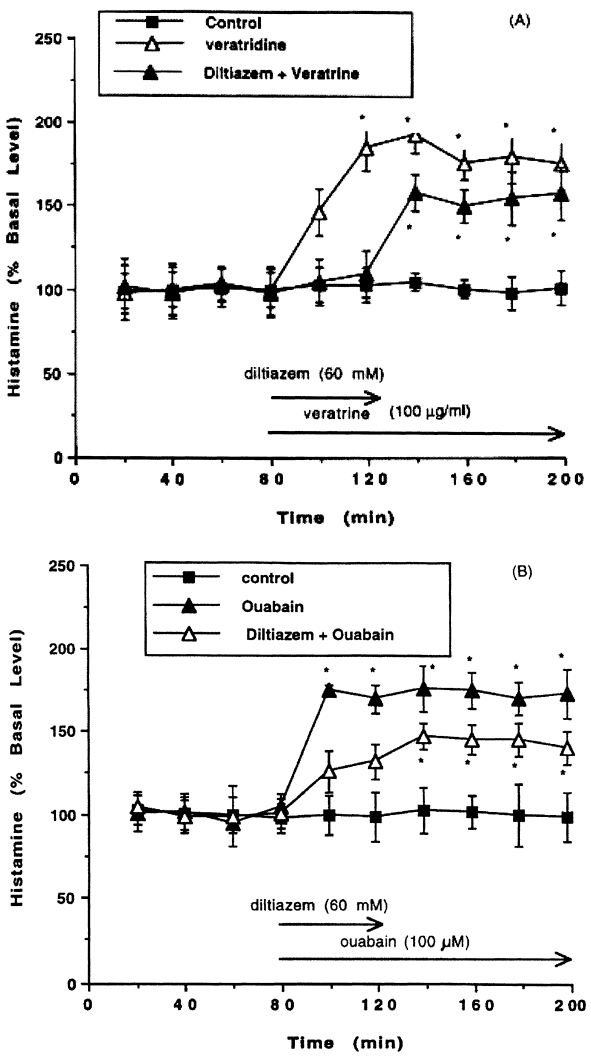

Fig. 3. Effect of veratridine and ouabain on evoked release of histamine in rat cerebral cortex. Veratridine (100 μg/ml) or ouabain (100 μM) continuously perfused or diltiazem (60 mM) for 40 min followed by (A) veratridine (100 μg/ml) or (B) ouabain (100 μM). Arrows indicate perfusion of drugs. Data are expressed as the percentage of the mean ± S.E.M. basal levels. $N = 4$, which indicate the number of animal per experiment. Statistic were caculated by ANOVA followed by Dunnett's test. $^{*}P < 0.001$ vs. control.

amounts of 60 and 120 mM of diltiazem, however, induced a time-dependent decrease in histamine concentration (Fig. 1). Maximum reduction of dialysate histamine after 2 h of perfusion of the drug was $51 \pm 4\%$, and $80 \pm 8\%$ when perfused with 60 and 120 mM of diltiazem, respectively.

Perfusion with elevated K^+ (100 mM) in the perfusion medium increased basal histamine levels to $223 \pm 24\%$ of baseline within 60 min (Fig. 2). This K^+-evoked increase in basal histamine release was reduced when the cerebral cortex was perfused with diltiazem (60 mM) prior to perfusing with elevated K^+.

Forty minutes after the beginning of perfusion with veratridine (100 μg/ml), histamine release increased $93 \pm 24\%$. On the other hand, after 20 min perfusion with ouabain (100 μM), baseline histamine release increased $76 \pm 23\%$. A $30 \pm 10\%$ reduction in veratridine-evoked release occurred within 60 min when diltiazem was perfused prior to veratridine and a $20 \pm 8\%$ reduction in ouabain-evoked histamine release was achieved by perfusing the cerebral cortex with diltiazem prior to ouabain (Fig. 3A and B).

Perfusion of tetrodotoxin (3 μM) reduced basal histamine levels by $48 \pm 6\%$ within 40 min of perfusion. However, histamine levels returned to baseline values even though the cerebral cortex was continuously perfused with tetrodotoxin (Fig. 4). Perfusion with a Ca^{2+}-free medium reduced histamine levels in a time dependent manner. After 2 h, histamine concentration was reduced by $38 \pm 11\%$.

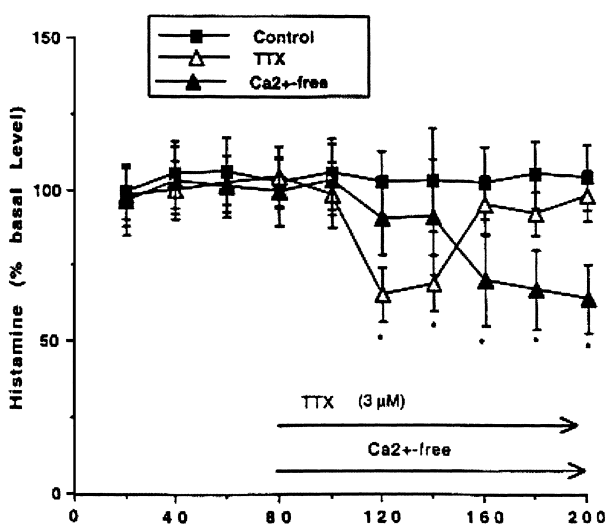

Fig. 4. Effect of tetrodotoxin or Ca^{2+}-free medium on histamine release in rat cerebral cortex. After collection of four (20 min) basal samples, the cerebral cortex was continuously perfused with 3 μM of tetrodotoxin or a Ca^{2+}-free medium. Arrows indicate perfusion of drug. Data are expressed as the percentage of the mean ± S.E.M. basal levels. $N = 3$, which indicate the number of animal per experiment. Statistics were calculated by ANOVA followed by Dunnett's test. $^{*}P < 0.001$ vs. control.

4. Discussion

Studies of microdialysis basal histamine levels in various brain regions of conscious free moving rats have shown some discrepancies. Also, there have been reports of differences in basal histamine levels from animal to animal and in the methodology of measurements. The reasons for these differences are unclear. Chikai et al. (1993) reported basal extracellular histamine concentration in striatum estimated to be approximately 6.2 nM which agree with other studies (4.7–6.7 nM). Extracellular concentration of histamine in the periaqueductal gray was estimated to be 37.7 nM (Barke and Hough, 1994) which appeared to have higher extracellular histamine levels than reported for the hypothalamus, e.g., 7.8 (Itoh et al., 1991) and 11.2 nM (Mochizuki et al., 1991). Methodological differences may account for some of the discrepancies between these values (Barke and Hough, 1994). The value of extracellular histamine (50 nM in the striatum) obtained by Cumming et al. (1991) seems extremely high which is very similar to values reported in the present study.

It has been shown that perfusion of the hypothalamus of rat with elevated K^+ significantly increased histamine output to 175% of basal levels. The K^+-evoked release of histamine was greatly reduced when the hypothalamus was perfused with a Ca^{2+}-free medium although the basal levels were not influenced by the omission of Ca^{2+} (Itoh et al., 1991). It appears that Ca^{2+} potentiated the action of K^+ which facilitated the release of histamine. In the striatum and bed nucleus of stria terminalis, the omission of Ca^{2+} from the perfusion solution decreased basal histamine levels 20% (Cumming et al., 1991) suggesting that histamine release is Ca^{2+} dependent in the striatum and bed nucleus of stria but not in the hypothalamus (Itoh et al., 1991).

Similarly, the present study demonstrates that when the cerebral cortex of rats was perfused with diltiazem, a marked reduction in basal histamine release occurred implicating the involvement of L-type voltage sensitive Ca^{2+} channels in the release of histamine in the cerebral cortex. In addition, perfusion of the cerebral cortex with a Ca^{2+}-free medium reduced basal histamine levels by 38%. These results are consistent with previous reports by others where a Ca^{2+}-free medium only partially reduces histamine levels. Furthermore, the marked Ca^{2+} sensitivity of the release process evoked by veratridine and ouabain indicates that voltage-dependent L-type Ca^{2+} channels are involved in histamine release.

Cumming et al. (1991) reported that tetrodotoxin (3 nM) had no effect on histamine basal output in rat striatum and bed nucleus of stria terminalis. In the present study, however, perfusion with 3 μM of tetrodotoxin partially reduced histamine release in the cerebral cortex. The reduction in basal histamine output observed by perfusing with tetrodotoxin suggests that voltage-dependent Na^+ channels (Ulbricht, 1969; Ohta et al., 1973; Li and White,

1977) aid in regulating histamine output. Alternatively, inhibiting Na^+ channels has been shown in excitable tissue to reduce intracellular Ca^{2+} concentration due to increased efflux of Ca^{2+}. Mast cells are possible sources of tetrodotoxin-insensitive histamine release. Although mast cells are major sources of histamine in the rat thalamus, few mast cells are present in other brain areas (Goldschmidt et al., 1985). It is possible, however, that mast cells may infiltrate the brain as a result of probe implantation (Cumming et al., 1991). Prast et al. (1994) results indicated that tetrodotoxin reduced the release rate of histamine by 50% in rat hypothalamus. Furthermore, their results indicated that in the anterior hypothalamus, extracellular histamine does not originate from mast cells. It remains to be clarified whether, under in vivo condition, histamine released from glial cells might contribute to the total amount of histamine found in the perfusate.

In summary, the use of the drugs, diltiazem, veratridine, and ouabain have allowed the modulating effects of both Na^+ and Ca^{2+} channels on histamine release in the cerebral cortex to be investigated using microdialysis. Diltiazem is one of the L-class Ca^{2+} channel antagonist drugs that are used clinically to decrease vasoconstriction, cardiac arrhythmic, and/or heart rate (Janis and Triggle, 1991). The results not only indicate that histamine release in the cerebral cortex is sensitive to Ca^{2+} but also implicate the L-class Ca^{2+} channels as a possible source for entry of Ca^{2+} during this process. Further studies are being conducted to determine the potential role N- and T-type Ca^{2+} channels may play in the release of histamine in the cerebral cortex.

Acknowledgements

The authors thank Dr. Elaine Sander-Bush, Department of Pharmacology, Vanderbilt University, for her helpful comments regarding the manuscript. This research was supported by the RIMI Grants # RR11808-03 from NIH and the IMPASSE Program, Gwathmey.

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