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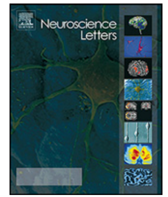

Inhibition of histamine release by local and intracerebroventricular infusion of galanin in hypothalamus, hippocampus and prefrontal cortex of awake rat: A microdialysis study

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HIGHLIGHTS

- ► Galanin decreases histamine release in the rat brain in vivo.
- ► Different effects of local versus intracerebroventricular infusions of galanin.
- ► Measurement of histamine in brain microdialysis samples.

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ABSTRACT

The neuropeptide galanin is co-localized with histamine in subpopulations of neurons in the tuberomammillary nucleus suggesting its involvement in modulating histaminergic neurotransmission. The purpose of the present study was to investigate, by use of microdialysis, the effects of local intraparenchymal (combined infusion and microdialysis probe), and intracerebroventricular (i.c.v.) infusions of galanin on extracellular levels of histamine in its major projecting areas, ventromedial hypothalamic nucleus ventrolateral part (VMHVL), CA3 area of ventral hippocampus (vHipp) and medial prefrontal cortex (mPFC) in separate groups ($n = 5$ rats/each) of freely moving rats. Galanin (0.5 nmol and 1.5 nmol) dose-dependently decreased the basal histamine levels in the VMHVL to 77.1% (i.c.v.) at 40 min and to 82.1% (intra-VMHVL infusion) already at 20 min, of the control group (32.6 ± 3.5 fmol/10 µl), whereas only 1.5 nmol i.c.v. galanin and not the local infusions deceased the histamine levels in the vHipp (8.4 ± 0.6 fmol/10 µl) to 82.8% and in mPFC (9.8 ± 0.9 fmol/10 µl) to 87.5%. It is concluded that central administration of galanin decreased the basal extracellular histamine levels in major histamine projecting areas, however, these effects were less prominent than those observed for 5-HT (Kehr et al., 2002 [12]) and ACh (Yoshitake et al., 2011 [38]) in the ventral hippocampus following i.c.v. and/or local galanin infusions.
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1. Introduction

The neuropeptide galanin [33] is widely distributed in the mammalian central nervous system including the rat brain [18,27–29] where it often coexists in the neurons expressing the classic neurotransmitters acetylcholine (ACh), serotonin (5-HT), noradrenaline (NA), GABA and histamine [14,18,19]. A body of evidence exists for the role of galanin in mediating, cognitive function, affective behaviour, addiction, epilepsy, pain, neuronal injury and neurodegeneration, food intake, sexual behaviour, as well as in modulation of peripheral actions, for review, see [9,10]. Using the microdialysis technique, we and others have demonstrated that intracerebroventricular (i.c.v.) or intracerebral infusions of galanin reduced the basal extracellular levels of ACh [16,23,38], 5-HT and NA [12,13,37,39] in the ventral hippocampus of awake rats and mice. These findings support a notion that galanin acts predominantly as an inhibitory neuropeptide via its three receptors, which all are coupled to Gi/o and inhibit adenylyl cyclase [3]. In addition, galanin receptor 2 (GalR2) also signals via Gq/11 to activate phospholipase C and protein kinase C [30]. Subsequently, a differential

Abbreviations: ACh, acetylcholine; aCSF, artificial cerebrospinal fluid; vHipp, CA3 area of the ventral hippocampus; GalR, galanin receptor; i.c.v., intracerebroventricular; mPFC, medial prefrontal cortex; NA, noradrenaline; TMN, tuberomammillary nucleus; VMHVL, ventromedial hypothalamic nucleus ventrolateral part.

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distribution of galanin receptors in the rat brain was demonstrated for GalR1 [6,22], GalR2 [22] and for GalR3 [31].

Besides numerous studies on galanin modulating ACh, 5-HT and NA neurotransmission, less attention was paid to investigation of possible interactions between galanin and other coexisting neurotransmitters including histamine. Galanin has been shown to be co-localized with histamine in subpopulations of neurons in the tuberomammillary nucleus (TMN), suggesting its involvement in modulating histaminergic neurotransmission [14,15,32]. Histamine together with its four receptor subtypes is implicated in mediating important physiological functions such as sleep–wakefulness, circadian rhythm, thermoregulation, food intake, as well as behavioural functions involving cortical arousal, cognitive function, affective behaviour, and nociception, for review, see [1,7,8]. Consequently, histamine and its receptors, have been implicated in the pathophysiology of neurological and psychiatric disorders including cognitive impairment associated with Alzheimer's disease and Parkinson's disease, ADHD, schizophrenia, sleep–wakefulness disorders including narcolepsy, eating disorders, neuroinflammation and pain, for review, see [8,24,34].

The purpose of the present study was to investigate, by use of microdialysis in freely moving rats, the effects of local, and i.c.v. infusion of galanin on extracellular histamine levels in major histamine projecting areas: ventromedial hypothalamic nucleus, CA3 area of ventral hippocampus (vHipp) and medial prefrontal cortex (mPFC).

2. Materials and methods

2.1. Animals

Adult male Sprague-Dawley rats, weighing 230–330 g at the time of the experiment (Charles River Laboratories, Japan) were used in all studies. The rats (three animals/cage) were maintained at free access to food and water, on a 12-h light–dark cycle (light at 7:00 AM), room temperature $22 \pm 2\,^{\circ}C$ and humidity 50–55%. All animal experiments were approved by the local ethical committee following "Guidelines for Proper Conduct of Animal Experiments" (Science Council of Japan) and the directives of the "Principles of Laboratory Animal Care" (NIH publication No. 8023). All efforts were made to minimize animal suffering and the number of animals used for the study.

2.2. Chemicals and solutions

Galanin (porcine) trifluoroacetate salt was purchased from Bachem, Bubendorf, Switzerland. Histamine dihydrochloride, *o*-phthalaldehyde (OPA), sodium 1-octanesulfonate, methanol (CHROMASOLV® Plus) and all other salts and chemicals were purchased from Sigma–Aldrich (St. Louis, MO, USA). The reagents were used without further purification. Deionized water, purified with a Barnstead EASYpure RF (Hansen Co., Hyogo, Japan) system, was used for preparation of all aqueous solutions.

Galanin was dissolved in freshly made aCSF (NaCl 123.4 mM, $NaHCO_3$ 23.4 mM, KCl 2.4 mM, KH_2PO_4 0.5 mM, $CaCl_2{\cdot}2H_2O$ 1.1 mM, $MgCl_2{\cdot}6H_2O$ 0.8 mM, Na_2SO_4 0.5 mM and glucose 5.8 mM, pH 7.1), which also served as the control. The concentration of galanin was calculated as a free base and corrected for the purity (water content) of the each batch as declared in the corresponding information sheet provided by the supplier. For the microdialysis perfusions the aCSF solution contained 148 mM NaCl, 4 mM KCl, 0.8 mM $MgCl_2{\cdot}6H_2O$, 1.4 mM $CaCl_2{\cdot}2H_2O$, 1.2 mM Na_2HPO_4, 0.3 mM NaH_2PO_4, pH 7.2.

2.3. Microdialysis surgery and sampling

The microdialysis experiments were carried out on awake rats following the protocol described elsewhere [11,38]. Briefly, the animals were anaesthetized with isoflurane and placed into a stereotaxic frame (Narishige Co., Ltd, Tokyo, Japan) in a flat skull position with the incisor bar set to −3.2 mm, the body temperature of the rat was controlled by a rectal thermometer and maintained at +37 °C using a CMA/150 temperature controller (CMA/Microdialysis, Stockholm, Sweden). After exposing the skull, a hole for a probe, for an i.c.v. cannula and two holes for the fixing screws were drilled using a fine trephine drill. Animals were implanted each with a guide cannula for a combined microdialysis/infusion probe (Eicom, Kyoto, Japan) or the separate groups combining the i.c.v. infusion with a microdialysis probe (Eicom) implanted into the ventromedial hypothalamic nucleus ventrolateral part (VMHVL), mPFC, and the vHipp at the following coordinates: VMHVL: AP −2.5 mm; L −0.7 mm; V −8.6 mm; vHipp: AP −4.3 mm; L −4.6 mm; V −5.8 mm, and mPFC: AP 3.2 mm; L −0.5 mm; V −1.4 mm; all coordinates were relative to bregma and the dura surface, according to the stereotaxic atlas of Paxinos and Watson [25]. The placement of the combined microdialysis/infusion probes in the respective areas is illustrated in Fig. 1 for (A) VMHVL, 0.5 mm membrane length, (B) vHipp, 1 mm membrane length and (C) mPFC, 3 mm membrane length. In experiments including i.c.v. infusions of galanin, a second guide cannula for the infusion needle (Eicom) was implanted into the lateral ventricle (AP −1.3 mm; L −1.8 mm; V −3.3 mm). The guide cannulae were fixed to the skull using two anchor screws and dental cement. Seven days after surgery, the microdialysis probe with the injection cannula (MI-A-I series: 0.22 mm o.d., 0.5 mm, 1 mm or 3.0 mm membrane length, molecular weight cut-off 50,000 Da) or microdialysis probe (A-I series: the same membrane lengths as for MI-A-I) and the i.c.v. infusion cannula (AMI series) were inserted into the respective guide cannulae in awake, freely moving rats. The dialysis probes were perfused with aCSF at a flow rate of 1.0 μl/min. Dialysates were collected every 20 min and the first four samples were used for estimation of basal extracellular histamine levels. Galanin (0.5 nmol/0.5 μl or 1.5 nmol/0.5 μl) or aCSF in control groups was infused via the respective injection cannulae of the combined microdialysis probes or via a separate i.c.v. cannula in the lateral ventricle at the flow rate of 0.5 μl/min. After finalizing the experiment, the animals were sacrificed by an overdose of isoflurane and dislocation of the neck. The brains were removed, frozen on dry ice and stored at −20 °C for histological examination of the probe position and the infusion site.

2.4. Measurement of histamine

Concentrations of histamine in the microdialysis samples were measured by high-performance liquid chromatography (HPLC) with postcolumn OPA derivatization and fluorescence detection. Briefly, the HPLC system included three L-2130 isocratic pumps, each with an inbuilt degasser unit, a L-2300 temperature oven, a L-2200 Refrigerated Microsampler and a fluorescence detector L-2480, all purchased from Hitachi (Tokyo, Japan). The fluorescence detector was equipped with a 12-μl flow cell and operated at an excitation wavelength of 340 nm and an emission wavelength of 450 nm. The chromatograms were recorded and integrated by use of the computerized data acquisition system EZChrom Elite (Hitachi). A HPLC column EICOMPAK SC-5ODS (3.0 mm, i.d. × 150 mm) and a precolumn PREPAKSET CA-ODS (3.0 mm, i.d. × 4 mm) were purchased from Eicom (Kyoto, Japan). The mobile phase (Pump A) was a mixture of 0.1 M NaH_2PO_4 buffer and methanol (9:1, v/v) and containing sodium 1-octanesulfonate at a final concentration of 0.786 mM, the flow-rate was 500 μl/min. The

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