Effects of histamine on neuropeptide release into the knee joint perfusate and cerebrospinal fluid in rats

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Abstract

In the present study we examined the effect of histamine injection on neuropeptide release in vivo in rats. Rats were injected with histamine either into the left knee joint or intraperitoneally. Concentrations of substance P (SP)-, neurokinin A (NKA)-, calcitonin gene-related peptide (CGRP)- and neuropeptide Y (NPY)-like immunoreactivity (LI) were examined in the knee joint perfusates and cerebrospinal fluid at 2, 6 and 24 h following injection, by radioimmunoassay. Results show that intraarticular injection of histamine induced a bilateral release of SP-, NKA- and CGRP-LI in the knee joint perfusates while intraperitoneal injection of histamine induced a release of SP-, NKA- and CGRP-LI into the cerebrospinal fluid. No changes in concentrations of NPY-LI were observed following histamine injection. Results of the present study indicate that histamine selectively stimulates sensory neurons without affecting sympathetic. The increased concentrations of sensory neuropeptide-LI in the cerebrospinal fluid following intraperitoneal administration of histamine indicate a new mechanism by which histamine may exert systemic effects during inflammation and allergy.

Keywords: Substance P; Neurokinin A; Calcitonin gene-related peptide; Histamine; Cerebrospinal fluid; Rats

Histamine, released by mast cells, is known to be one of the major mediators of inflammation and allergy. Due to its potent vasoactive effects histamine induces vasodilatation and plasma extravasation (cf. [20]). It also promotes leukocyte rolling [12] and recruitment [24]. It has been shown that administration of mast cell mediators leads to stimulation of peripheral sensory nerve afferents, acting through H1- and H2-receptors [1]. Another histamine receptor, H3-receptor, is suggested to be localized on nerve terminals (cf. [8]) and to have a regulatory role on the feedback loop between histamine and sensory nerves interaction. This suggestion is supported by a study shown that a H3-receptor agonist inhibits plasma extravasation elicited by electrical stimulation of vagal nerves in airways [15]. Numerous morphological observations show the existence of close anatomical localization between sensory nerves and mast cells in skin [2], thymus [25], spleen [10], lung [2] and jejunum [19] indicating a direct communication between mast cells and sensory nerves. This is supported by fact that neuropeptides such as substance P (SP), neurokinin A (NKA), neurokinin B, dynorphin, somatostatin [3], neuropeptide Y (NPY) [13] and pituitary adenylate cyclase activating polypeptide [18] are able to induce histamine release from peritoneal mast cells of the rat in vitro. Sensory nerves are known to contribute to inflammation through the release of neuropeptides, i.e. SP, NKA and calcitonin gene-related peptide (CGRP) (cf. [17]). Therefore, interactions between histamine and neuropeptides are considered to be of significant interest in inflammation and allergic disorders. In the present study we examined the effect of a single histamine injection on the nervous system, by studying neuropeptide release in the cerebrospinal fluid and knee joint perfusates in the rat. To study local and general release of neuropeptides, histamine was administered either intraarticularly (i.a.) or intraperitoneally (i.p.).
The study was carried out on male albino Sprague–Dawley ALAB rats, weighing 250–300 g, allowed to become habituated to the laboratory for at least 7 days before experimentation. All rats were maintained under identical conditions which included alternate cycles of 12 h light and 12 h darkness, temperature of 24°C, 60% relative humidity, and food and water ad libitum. On the day of the experiment rats were anaesthetized with chloralhydrate (0.4 g/kg) i.p. Anaesthesia lasted for 1–2 h. The rats were grouped as follows: eight rats were inoculated with 0.05 ml vehicle containing 50 pmol of histamine (Sigma Chemical Co., St. Louis, MO, USA) i.a. into the left knee joint and eight rats were given the same histamine injection i.p. Injected dose of histamine corresponded to a dose used to provoke itch in healthy subjects [9]. The same number of rats were injected with 0.05 ml saline either i.a. or i.p. and were used as control groups. Each rat received only one injection.

At 2, 6 or 24 h rats were anaesthetized again. Cerebrospinal fluid was collected from the IV ventricle (100–200 μl). Knee joint perfusate (2–3 ml) was collected by using a syringe pump set at 0.2 ml/min. Samples were frozen immediately and analyzed for SP-, NKA-, CGRP- and NPY-like immunoreactivity (-LI) as previously described [4,5].

Statistical analysis was carried out using the SPSS software (release 6). ANOVA one-way test (post-hoc Bonferroni test within and between treatments) was used to test differences in concentrations of neuropeptide-LI in the knee joint perfusate and cerebrospinal fluid following i.a. and i.p. injections of either histamine or saline. Wilcoxon rank sum test was used to compare concentrations of neuropeptide-LI between the right and the left knee joint perfusate. The coefficient of Spearman correlation test was calculated between neuropeptide-LI in cerebrospinal fluid and knee joint perfusate. A P value of less than 0.05 was considered as significant.

Injection of histamine into the left knee joint enhanced release of SP-LI into the knee joint perfusates at 2 h as compared to saline or to i.p. injection (Fig. 1). Following i.a. injection of histamine, concentrations of NKA-LI were enhanced in the right and left knee joint perfusate at 2, 6 and 24 h as compared to saline injection and to i.p injection of histamine (Fig. 1). Release of CGRP-LI in these rats was enhanced at 24 h as compared to saline injection. In rats

Fig. 1. Concentrations of SP-, NKA-, CGRP- and NPY-LI in the perfusates of the right and left knee joints of either intraarticularly (i.a.) or intraperitoneally (i.p.) treated rats are presented as mean ± SEM. Open columns represent saline injected control rats and closed columns represent histamine injected rats.

*Significant difference between injections (histamine vs. saline), P < 0.05; +significant difference between the injected sites (i.p. vs. i.a.), P < 0.05. n = 8 animals in each group.
given histamine injection into the left knee joint no significant differences in SP-, NKA-, CGRP- and NPY-LI were found between the left and the right knee joint perfusate. Injection of both histamine and saline into the left knee joint induced increased release of NPY-LI into the knee joint perfusate as compared to respective i.p. injections (Fig. 1). Injection of histamine into the left knee joint did not affect neuropeptide-LI release into the cerebrospinal fluid, except that CGRP-LI was increased at 2 h as compared to saline injection (Fig. 2).

Injection of histamine i.p. did not affect neuropeptide-LI release into the knee joint perfusate (Fig. 1). A significant increase in SP- and NKA-LI was found in the cerebrospinal fluid at 2, 6 and 24 h following i.p. injection of histamine as compared to saline injection and to i.a. injection of histamine (Fig. 2). Release of CGRP-LI was enhanced at 2 and 6 h as compared to saline injection and at 24 h as compared to saline injection and to i.a. injection of histamine (Fig. 2). Injection of both histamine and saline i.p. induced increased release of NPY-LI into the cerebrospinal fluid as compared to respective i.a. injections (Fig. 2). No significant correlation was found in neuropeptide-LI between the knee joint perfusate and cerebrospinal fluid (not presented).

In the present study injection of histamine into the rat either i.a. or i.p. induced increased release of sensory neuropeptides into the knee joint perfusate and cerebrospinal fluid depending on the site of injection. It has been previously reported that histamine application to the nasal mucosa in guinea pigs induces release of SP and CGRP from peripheral terminals of trigeminal ganglion [22]. Tani et al. demonstrated that in vitro this effect of histamine was due to an action on the sensory neurons and depending on the extracellular calcium concentrations [23]. The present study is the first evidence indicating that in vivo histamine in a specific way activates sensory nervous system resulting in an increased release of neuropeptide-LI. No effect on NPY-LI was found in the present study, suggesting that histamine has no effect on the sympathetic nervous system. However, injection of a vehicle per se (both histamine and saline) induces a non-specific activation of the sympathetic nervous system resulting in a release of NPY-LI.

In the present study i.p. injection of histamine increased neuropeptide concentrations in the cerebrospinal fluid. Recently it has been demonstrated that neuropeptides administered intracerebroventricularly regulates activity of hypothalamo-pituitary-adrenal axis [14,16]. Moreover, histaminergic neurons has been shown to be important in the regulation of the hypothalamo-pituitary axis [11] and histaminergic neurons in the hypothalamus received synaptic inputs from SP and NPY afferents [21]. These interactions between neuropeptides and histamine in the central nervous system indicate an involvement of the peripheral mechanisms in the regulation of the hypothalamo-pituitary axis following host defence responses.

Recently we reported that i.p. injection of IL-1α [6] and subcutaneous (s.c.) injection of a low dose of Freund’s adjuvant [7] induced neuropeptide release into the cerebrospinal fluid, plasma and knee joint perfusate. Moreover, an i.a. injection of pro-inflammatory substance induced release of neuropeptide-LI in the cerebrospinal fluid, plasma and bilaterally into the synovial fluid [4,5]. The acute bilateral release of neuropeptides following unilateral injection of a pro-inflammatory substance further support a general activation of the nervous system. This bilateral release of neuropeptides is mediated through the neural mechanisms as nerve sectioning abolished the release of neuropeptides on the contralateral side (Bileviciute et al., in preparation). Our studies indicate that injection of a non-specific challenge activates sensory and sympathetic nervous systems resulting in a generally increased release of neuropeptides. Therefore, activation of the sensory nervous system and release of neuropeptides following histamine injection may be considered as a part of host defence response.

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