Involvement of histamine H₄ receptor in the development of chemotherapy-induced anorexia in mice

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Introduction

Cancer chemotherapeutic agents often induce anorexia in patients and its insufficient control impairs their quality of life and leads to an increased risk of malnutrition. It is known that inflammatory cytokines such as Interleukin-1 β and tumor necrosis factor (TNF)- α and subsequent signal transduction pathways are thought to be involved in the development of chemotherapy-induced anorexia.

Histamine is known as an inflammatory mediator. Among its four different types of receptors (H₁, H₂, H₃, and H₄), the H₄ receptor was expressed in immune cells such as mast cells, eosinophils and monocytes, and it was involved in inflammatory cytokine release.

Recent studies revealed that H₄ receptor antagonists inhibited TNF- α production in mice. From the findings mentioned above, we hypothesized that TNF- α production via the H₄ receptor is associated with cancer-therapy-related anorexic effects.

Methods

1. Automatic food measurement system

FDM300SW (Melquest) is an apparatus used to automatically determine cumulative amounts food intake. This apparatus consists of an acrylic home cage, a container and a controller equipped with a weight sensor. Food intake was measured automatically to 0.01 g and the data was stored using a PC.

2. General procedure

Male DBA/2 mice was obtained from Japan SLC. Throughout the experiment, all of the mice had free access to standard laboratory chow pellets (CE-2) and tapped water. Mice were adapted to the experimental environment for 7 days. On the day of the experiment, mice received cisplatin (7.5 mg/kg, i.p.) and their daily food consumption was measured for 3 day following injection of cisplatin. The controls were treated with saline.

3. Behavioral experiments

Mice were injected with a serotonin 5-HT₃ receptor antagonist (granisetron, 0.1 and 0.5 mg/kg, s.c.), a corticosteroid (dexamethasone, 0.1 and 0.5 mg/kg, s.c.), and a histamine H₄ receptor antagonist (JNJ7777120, 10 and 20 mg/kg, s.c.) at 15 min before cisplatin (7.5 mg/kg) injection. Granisetron, dexamethasone, or JNJ7777120 was then administered every 24 h for the observation period.

4. TNF- α mRNA expression experiments

At 2, 26 and 50 h after cisplatin (7.5 mg/kg, i.p.) administration, brains were removed, and total RNA was extracted. The extracted RNA was converted to first-stranded cDNA and the cDNA was then used as a template for the RT-PCR with TNF- α and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) specific primers. The PCR products were separated on agarose gels by electrophoresis analysis and the band density was analyzed for quantification.

Additionally, we examined the effect of JNJ7777120 on the cisplatin-induced expression of TNF- α mRNA.

Purpose

- We chose cisplatin as a representative chemotherapeutic agent and examined the effects of H₄ receptor antagonists on cisplatin-induced anorexia in mice.
- We also investigated the expression of TNF- α mRNA in the hypothalamus or spleen of cisplatin-treated mice with or without a selective H₄ receptor antagonist.

Results

Cisplatin-induced anorexia occurred within 24 h of administration and continued for 3 days. The early phase (day 1), but not the delayed phase (days 2 and 3), of anorexia was inhibited by the daily injection of granisetron. However, dexamethasone or JNJ7777120 abolished the delayed phases of anorexia (Fig. 1).

Cisplatin significantly increased TNF- α mRNA expression in the hypothalamus, and the period of expression increase paralleled the onset period of anorexia. In addition, pretreatment with JNJ7777120 completely inhibited the increased expression (Fig. 2).

Fig.1: The effects of a 5-HT₃ receptor antagonist (granisetron), corticosteroid (dexamethasone), and H₄ receptor antagonist (JNJ7777120) on cisplatin-induced anorexia in mice.

Fig 2: Expression of TNF- α mRNA in the hypothalamus of mice treated with cisplatin

Conclusion

These results suggest that TNF- α mRNA expression via H₄ receptors may contribute to the development of cisplatin-induced anorexia, and that H₄ receptor antagonists are potentially useful treatments.