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Radiographic contrast media-induced histamine release: A comparative study with mast cells from different species

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Abstract

Radiographic contrast media in clinical use cause unwanted allergic and pseudoallergic reactions. To investigate the mechanisms of these reactions, studies on isolated mast cells from different species and sites are necessary. In this study, the effect of six commonly used contrast media on rat (peritoneal, lung) and human (lung) mast cells was investigated. The three preparations with low osmolalities (Hexabrix, Solutrast, Ultravist) released little or no histamine from the cells examined. In contrast, the three preparations with high osmolalities (Angiographin, Telebrix, Rayvist) were potent releasing agents. However, the degree of release and the order of potency was different depending on the cells investigated. Indeed, rat peritoneal mast cells required much higher concentrations before release was observed. Since the contrast media with low osmolality also cause histamine release and reactions *in vivo*, other systems (e.g. complement) must be additionally involved.

Introduction

Unwanted allergic/pseudoallergic reactions with histamine release after the administration of radiographic contrast media have been observed since the introduction of these useful diagnostic aids. A reduction of both the incidence and severity of these reactions was expected with the development of products with low osmolalities, since a number of in vitro studies have shown that basophils release histamine after exposure to some solutions with high osmolalities and release increased amounts of histamine on subsequent challenge with antigen or anti-IgE [1]. However, these reactions still occur with the newer products [2, 3]. In order to recommend suitable prophylactic measures or to improve these agents, investigations on the reaction mechanisms with mast cells from different species and sites are necessary. In this study, we wish to report preliminary results investigating the action of six commonly used radiographic contrast media on mast cells from the rat (peritoneal, lung) and man (lung).

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Materials and methods

Female Sprague-Dawley rats (150–250 g) were used and mixed peritoneal cells recovered by direct lavage with heparinized Tyrode's buffer as previously described [4]. Pulmonary cell suspensions were prepared from freshly excised rat lungs and macroscopically normal human tissue obtained from surgical resections using a collagenase dispersion procedure essentially as described by Ennis [5]. All cells were prewarmed for 5 min at 37 °C and

Table 1
Histamine release from rat and human pulmonary mast cells induced by radiographic contrast media.

Radiographic contrast media (μl/ml cell suspension)		Histamine release (%)	
		Rat pulmonary cells	Human pulmonary cells
Angiographin	300	13.7±2.5	14.2±5.6
	200	5.8±1.7	5.2±1.8
	100	3.0±1.7	2.7±0.8
Hexabrix	300	3.2±1.3	2.5±1.4
	200	2.7±0.9	2.5±1.1
	100	3.3±1.2	2.9±0.9
Rayvist	300	38.9±4.6	16.7±2.0
	200	27.8±5.0	9.5±1.3
	100	9.8±1.8	4.0±1.2
Solutrast	300	2.3±1.4	3.4±0.8
	200	0.9±0.7	2.5±0.8
	100	1.0±0.8	1.3±0.4
Telebrix	300	18.7±2.5	9.2±1.6
	200	8.1±0.9	5.2±1.3
	100	3.9±1.4	2.4±0.8
Ultravist	300	1.3±1.0	2.8±1.2
	200	2.0±1.2	3.3±1.2
	100	1.9±1.1	2.4±0.8

Rat pulmonary mast cells, $n=4$; human pulmonary mast cells, $n=5$.

Table 2
Histamine release induced by radiographic contrast media from rat peritoneal mast cells.

Radiographic contrast media (μl/ml cell suspension)		Histamine release (%)
Angiographin	500	34.0±6.4 (4)
	400	4.4±0.3 (4)
	300	3.7±0.9 (8)
Hexabrix	500	−3.0±1.3 (5)
Rayvist	500	46.1±4.6 (4)
	400	15.5±4.5 (4)
	300	6.8±1.1 (7)
Telebrix	500	49.3±4.9 (4)
	400	14.8±3.1 (4)
	300	2.5±1.0 (6)
Solutrast	500	−1.6±1.4 (5)
Ultravist	500	3.2±1.4 (5)

Negative values arise because histamine releases less than the spontaneous release occurred. The number of experiments is given in parenthesis.

then challenged for 10 min with various concentrations of the radiographic contrast media, as shown in the tables. Histamine was determined in both supernatants and cell pellets using an automated procedure (Technicon autoanalyser). All results are expressed as the percent histamine release and given as means ±SEM for the number of experiments noted. The histamine release occuring in the absence of any stimulus (spontaneous: 3–8%) was subtracted in all cases.

The six radiographic contrast media were used in the commercially available clinical formulations. Four were ionic:

Angiographin (Schering, Berlin), INN name Amidotrizoate, 1530 mOsm/kg, iodine content 306 mg/ml; Hexabrix (Byk Gulden, Konstanz), INN name Ioxaglate, 600 mOsm/kg, iodine content 320 mg/ml; Rayvist (Schering), INN name Ioglicate, 1790 mOsm/kg, iodine content 300 mg/ml; Telebrix (Byk Gulden), INN name Ioxithalamate, 1860 mOsm/kg, iodine content 300 mg/ml; and two were non-ionic:

Solutrast (Byk Gulden), INN name Iopamidol, 616 mOsm/kg, iodine content 300 mg/ml; Ultravist (Schering), INN name Iopromide, 610 mOsm/kg, iodine content 300 mg/kg.

All other reagents and methods were as described in Ennis [5] and Pearce et al. [4].

Results

The radiographic contrast media with low osmolalities (Hexabrix, Solutrast, Ultravist) were inactive on all 3 cell populations tested (Tables 1 and 2). Incubation with media of higher osmolality produced a dose-dependent histamine release from all cell types; however, rat peritoneal mast cells required higher concentrations before release was observed (Tables 1, 2). The order of release was as follows: rat peritoneal mast cells: Telebrix ≙ Rayvist > Angiographin; rat pulmonary mast cells: Rayvist ⩾ Telebrix > Angiographin; and human pulmonary mast cells: Rayvist ≙ Angiographin > Telebrix.

Discussion

As with adverse reactions to other drugs, the reported incidence of allergic/pseudoallergic reactions after the administration of radiographic contrast media varies greatly, depending on the route of administration, the agent used and the type of

report (controlled clinical trial, case reports etc.). The advent of the newer non-ionic contrast media with lower osmolalities has reduced but not abolished these adverse reactions. Beyer and coworkers [2] found an incidence of 14% for reactions requiring treatment after the intravenous administration of an ionic contrast medium (amidotriozate) for digital subtraction angiography, whereas arterial administration of a nonionic agent (iopromide) only caused an incidence of 3.2% for such reactions. The role of histamine release as a causal factor for these adverse reactions and hence also the use of a prophylaxis with H_1 and H_2 receptor antagonists has been controversely discussed [2, 6]. In this study histamine release induced by 6 commonly used radiographic contrast media was investigated with 3 mast cell populations. Unexpectedly, rat peritoneal mast cells proved to be the most refractory to these agents, with much higher concentrations being required before release was observed (Table 2). These concentrations are achieved clinically, where large volumes (up to *ca.* 400 ml) of contrast media are administered into the circulation. The three contrast media with high osmolalities (Angiographin, Rayvist, Telebrix) released histamine from all 3 mast cell populations; however, the degree and order of activity depended on the individual cell type (Tables 1 and 2). The three contrast media with low osmolalities (Hexabrix, Solutrast, Ultravist) released little or no histamine from the 3 cell populations investigated (Tables 1 and 2). Thus, a direct histamine release is probably not the causal factor involved in the *in vivo* reactions to agents with low osmolalities. It should, however, not be forgotten that for example the activation of the complement system (a favoured mechanism in the literature [7]) also leads to histamine release. The experiments described here were carried out in the absence of complement and other serum factors. Additionally, other mast cell populations may react differently and, for example, canine liver mast cells release histamine after challenge with Hexabrix [8]. Further work is necessary to resolve these questions.

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