Time-Dependent Interaction of a New H2-Receptor Antagonist, IT-066, with the Receptor in the Atria of Guinea Pig

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ABSTRACT — 3-Amino-4-[4-[4-(1-piperidinomethyl)-2-pyridyloxy]-cis-2-butenylamino]-3-cyclobutene-1,2-dione hydrochloride (IT-066) showed a highly potent and long lasting H2-receptor blocking action in guinea pig atria. The inhibitory effect of IT-066 on the histamine-induced positive chronotropic response increased concentration- and time-dependently. A short period of treatment with IT-066 shifted the concentration-response curve of histamine to the right in parallel, without decreasing the maximal response to histamine. With prolongation of the treatment, the concentration-response curve shifted further to the right with time-dependent suppression of the maximal response to histamine. The inhibitory effect of IT-066 was irreversible. The dissociation constant for histamine (K_A) was not changed by prolongation of the time of incubation with IT-066. The dissociation constant for IT-066 (K_B) was decreased with the prolongation of the treatment. Kinetic analysis of the time-dependent inhibition showed a two-step reaction: the first was reversible and the second was irreversible. Preincubation of the atria with ranitidine, however, protected the H2-receptor from the apparently irreversible antagonism of IT-066. These results suggest that IT-066 has a time-dependent and irreversible interaction with the H2-receptor and that the interaction may be responsible for the potent and long lasting H2-receptor blocking action of IT-066.

The discovery of burimamide, a prototype H2-receptor antagonist (1), has prompted intensive investigations to clarify the physiological and pharmacological involvement of histamine in the regulation of gastric acid secretion (2–4). These have included a search for more useful H2-receptor antagonists for the treatment of peptic ulcer with gastric hyperacidity (5–7). A H2-receptor antagonist with the imidazole group in its structure, cimetidine, was the first drug to be used for the clinical treatment of ulcer patients. Since then, H2-receptor antagonists, ranitidine (8) and famotidine (9), which do not have the imidazole group in their structure have been used, and a series of diazothiadiazole oxide and dioxides (10, 11) have been reported. Recently, new H2-receptor antagonists, L-643,441, lamtidine (AH 22216), loxitidine (AH 23844) and BMY-25368 (SK&F 94482), which contain a piperidinomethylphenyl moiety in their structure have been reported (6, 7, 12). These compounds produced unsurmountable antagonism in guinea pig atria and showed very potent and long lasting inhibition of gastric acid secretion. The mechanism, however, has not
been clarified yet. More recently discovered is IT-066, a piperidinomethylpyridyl moiety-containing compound (3-amino-4-[4-[4-(1-piperidinomethyl)-2-pyridyloxy]-cis-2-butenylamino]-3-cyclobutene-1,2-dione hydrochloride) (Fig. 1), which has potent and long lasting anti-acid secretory and anti-ulcer actions (13–15).

In the present study, we investigated the mechanism of the potent and long lasting effects of IT-066 by studying the histamine-induced positive chronotropic action in guinea pig atria, compared with that induced by other H₂-receptor antagonists.

MATERIALS AND METHODS

Male Hartley strain guinea pigs weighing 300 to 450 g were sacrificed by a blow on the head. The spontaneously beating right atrium was dissected from the surrounding tissue and suspended in a glass chamber containing 20 ml of Krebs-Henseleit solution at 35°C, which was aerated with a mixture of 95% O₂ and 5% CO₂. Tissue was attached under 0.5 g of tension to an isometric force displacement transducer for rate recording and measurement, and it was allowed to stabilize for at least 60 min before the experiment commenced.

Calculation of dissociation constants of agonist (Kₐ) and antagonist (Kᵦᵦ)

First, a control concentration-dependent curve of the chronotropic response to histamine was obtained. After repeated washouts of the bath for more than 20 min, varying concentrations of IT-066 and H₂-receptor antagonists, cimetidine, ranitidine and famotidine, were introduced into the bath; and 5 min later, a histamine-induced response curve was obtained. Since IT-066 and famotidine showed apparent irreversible antagonism, the Kₐ and Kᵦ values were determined according to the method of Furchgott (16) and Kenakin (17), respectively. IT-066 and famotidine showed competitive and irreversible antagonism to the histamine-induced response time-dependently. Therefore, the rate of the rightward shift of the concentration-response curve by the antagonists was calculated by rectifying the maximal response to represent 100%, to obtain the apparent Schild regression line and dose-ratio value.

Certification of competitive antagonism of IT-066 and famotidine

Competitive antagonism of the inhibitory effect of IT-066 and famotidine on histamine-induced chronotropic action was confirmed on a concentration-response curve with no decrease of the maximum response to histamine at various pretreatment times, using following equation:

\[ \frac{[A]}{[A]_0} = 1 + \frac{[B]}{K_B} \]  

[A] is the concentration at which histamine shows a response of a certain degree in the presence of the antagonist IT-066 or famotidine. [A]₀ is the concentration at which histamine shows a response. [B] is the concentration of IT-066 or famotidine. Kᵦ is the dissociation constant of IT-066 or famotidine.

Irreversibility and receptor protection experiments

The response of guinea pig atria to a single dose (3 µM) of histamine was obtained before each antagonist addition, after incubation with
subsequent drugs, and then at 3 time intervals after washout of the antagonist from the bath. Eighteen-minute periods, each with three buffer washes at 5 min intervals, were allowed between each trial with histamine after the initial removal of the antagonist. Ranitidine and IT-066 were tested alone and in combination. When tested in combination, ranitidine was added 1 min before the addition of IT-066. The dose of IT-066 was selected on the basis of a previous study showing that at 3 μM, histamine produced approximately 50% of its maximal positive chronotropic response.

**Kinetic analysis of the time-dependent inhibition**

The response induced by a single concentration (100 μM) of histamine was considered to be the maximal response. First, the control response to histamine was obtained, and then the response after treatment with IT-066 or famotidine was obtained successively at 15-min intervals. The kinetics of the inhibition of the response showed the properties of first order decay. The apparent decay constant (k_{app}) increased with increasing concentrations of the compounds so that the values of k_{app} divided by the concentration of the compounds used gave approximately constant values for each time-dependent compound. This constancy was predicted from a single kinetic model for inhibition by time-dependent agents that act in two steps, as reported previously (18): a reversible binding followed by an irreversible decay, where R and R* are the normal and modified receptor, respectively, and I is the antagonist.

\[
\begin{align*}
R + I &\rightarrow [RI] \rightarrow ([R^*] + I) \text{ or } [R^*]; \\
K_i &= k_{f} / k_{i}
\end{align*}
\]

This kinetic formulation yields the following algebraic relationship in terms of the time-dependent loss of the response:

\[
\ln (\text{response in the presence of the drug}) = \ln \left( \frac{R_{\text{total}} - R^*}{R_{\text{total}}} \right) \\
= -k[I]t/(K_i + [I]) = -k_{\text{app}}t \quad (2)
\]

Thus, the properties described above for k_{app} are compatible to the situation in which the concentration of [I] is less than the value for K_i so that k_{app}/[I] = k · K_i. In the text, the logarithm of the remaining response is plotted against the preincubation time with famotidine and IT-066, as shown in Fig. 6.

**Drugs used**

IT-066 (19) was synthesized at our research center. Histamine dihydrochloride and (±)-isoproterenol hydrochloride were purchased from Wako Pure Chemical Industries and Sigma Chemical Company, respectively. Cimetidine, ranitidine and famotidine were obtained from commercially available pharmaceuticals. All other reagents were obtained commercially and were of the highest purity available.

**RESULTS**

**Effect of cimetidine, famotidine and IT-066 on the histamine-induced chronotropic response in guinea pig atria**

IT-066 inhibited the histamine-induced positive chronotropic response. Five minutes of pretreatment with 3 × 10^{-7} M IT-066 shifted the dose-response curve of the histamine-induced concentration-response curve to the right without decreasing the maximal response (Fig. 2). Five minutes of pretreatment with IT-066 inhibited the response at 5 × 10^{-7} and 1 × 10^{-6} M concentration-dependently with a decrease of the maximal response. Pretreatment with IT-066 at 3 × 10^{-5} M for 60 min shifted the histamine-induced concentration-response curve to the right without decreasing the maximal response, but no effect was observed in the concentration-response curve with 5 min pretreatment (Fig. 3). The pretreatment of IT-066 for 60 min at 5 × 10^{-8} M, however, shifted the curve to the right and decreased the maximal response. Pretreatment of the atria with famotidine for 60 min also strengthened the inhibitory effect observed after 5-min pretreatment, as did IT-066 (Figs. 2
Fig. 2. Effect of 5-min treatment with IT-066 and famotidine on the positive chronotropic action induced by histamine. Responses induced by $3 \times 10^{-4}$ M histamine were taken as 100%. Each value represents the mean ± S.E. obtained from 3–5 experiments. ○: Control, ●: $3 \times 10^{-7}$ M, □: $5 \times 10^{-7}$ M, ■: $10^{-7}$ M IT-066 or famotidine.

Fig. 3. Effect of 60-min treatment with IT-066 on the positive chronotropic action induced by histamine. Responses induced by $3 \times 10^{-4}$ M histamine were taken as 100%. Each value represents the mean ± S.E. obtained from 3–4 experiments. ○: Control, ●: $3 \times 10^{-7}$ M, □: $5 \times 10^{-8}$ M, ■: $10^{-7}$ M, △: $3 \times 10^{-7}$ M IT-066 or famotidine.
and 3). The suppression of the maximal response by prolonged treatment, however, was significantly greater for IT-066 compared with famotidine. Time-dependent augmentation of the inhibitory effect was not observed in the treatment of cimetidine (data not shown). Incubation of the atria with IT-066 did not alter either the basal atrial rate or the response of the tissue to isoproterenol. The basal atrial rates in the absence and presence of IT-066 (10^{-5} M) were 182.0 and 181.5 beats/min (each value represents the mean from 2 experiments), respectively. The basal and isoproterenol (10^{-9} - 3 \times 10^{-6} M) stimulated rates in the absence or presence of IT-066 (10^{-5} M) were 189.0 and 312.0 or 181.5 and 317.5 beats/min (each value represents the mean from 2 experiments), respectively. The inhibitory effects of IT-066 and famotidine on the histamine-induced response were accompanied by both a decrease of the maximal response and a shift of the concentration-response curve to the right. The extent of the shift of the concentration-response curve and the decrease of the maximal response for histamine induced by IT-066 and famotidine depended on the concentration and the duration of the treatment (Fig. 4). The $K_A$ value for histamine, however, was not changed by treatment with IT-066 or famotidine (Fig. 5a). For the same incubation period, no significant differences in $K_B$ values were observed for different concentrations of the antagonist. Therefore, the mean value of the different concentrations of the antagonist was considered as

**Fig. 4.** Time-dependent shift of the dose-response curve of histamine-induced positive chronotropic action due to IT-066 and famotidine. The dose-ratio indicates the degree of parallel shift of the concentration-response curve of histamine to the right in the presence of IT-066 or famotidine. Each value represents the mean ± S.E. obtained from 3–4 experiments. The dose-ratio was determined by the following equation: $ED_{50}$ (in the presence of drug)/$ED_{50}$ (in the absence of drug). IT-066: ●, 3 \times 10^{-7} M; ■, 10^{-7} M; ▲, 5 \times 10^{-8} M. Famotidine: ●, 10^{-6} M; ■, 3 \times 10^{-7} M; ▲, 10^{-7} M.
the KB value of the drug at the defined incubation period. The KB value of IT-066 decreased with the prolongation of the treatment and reached a plateau 60 min after the beginning of the incubation (Fig. 5b). The values obtained from treatment for 15 and 60 min were 3.90 × 10^{-8} M and 8.16 × 10^{-9} M, respectively. This means that the affinity of IT-066 increased 4.8 times by prolongation of the treatment period from 15 to 60 min. The KB value of famotidine also decreased with the prolongation of the treatment. The affinity of famotidine for the receptor increased about 2.6 times by the prolonging the treatment from 15 min to 60 min. The decrease of the KB for famotidine reached a plateau with 30-min pretreatment.

**Confirmation of competitive antagonism of IT-066 and famotidine**

The pA2 value was obtained from the data of the concentration-response curve, which shifted to the right in parallel, as shown in Figs. 2 and 3. In this case, the pA2 value should be considered the KB value. The degree of the parallel shift of the concentration-response curve to the right (dose ratio) coincided with the value determined by equation (1) for different concentrations of IT-066 and different pretreatment times with IT-066 (data not shown). The coincidence was also observed when the KB value of Fig. 5b was applied to equation (1). This suggests that IT-066 and famotidine show competitive antagonism at the receptor site when depression of the maximum response is not observed.

**Time-dependent inhibition of the maximal response to histamine by IT-066 and famotidine**

IT-066 and famotidine decreased the maximal response of histamine time-dependently. The decrease of the maximal response to histamine caused by IT-066 was about 70%, while the decrease caused by famotidine was about 25% after 60-min treatment with 3 × 10^{-7} M of the drugs. The time-dependent inhibitions of the maximal chronotropic response to histamine by IT-066 and famotidine are illustrated in Fig. 6. The kinetics of the inhibition of the maximal response to histamine showed the properties of first order decay. The constancy of this decay is predicted from a single kinetic model which is divided into a two-step reaction. The initial reaction is reversible and the second one is irreversible, as described in the Methods section above. The dissociation constant (K_i) of IT-066 and famotidine in the initial reversible reaction was 4.25 × 10^{-7} M and 2.67 × 10^{-7} M, respectively, which is similar to the KB value obtained from
the 5-min treatment (IT-066: $3.08 \times 10^{-7}$ M, famotidine: $2.13 \times 10^{-7}$ M) (Table 1). The irreversible reaction constant of IT-066 in the second step was $4.17 \times 10^{-2}$·min$^{-1}$ and was about 4 times greater than that of famotidine ($1.02 \times 10^{-2}$·min$^{-1}$) (Table 1).

**Table 1. Reversible and irreversible reaction constants of IT-066 and famotidine with H$_2$-receptor of guinea pig atria**

|                | Reversible reaction dissociation constant ($K_i$, $\times 10^{-7}$ M) | Irreversible reaction decay constant ($k$, $\times 10^{-2}$·min$^{-1}$) |
|----------------|------------------------------------------------------------------------|---------------------------------------------------------------------|
| IT-066         | 4.25 ± 2.32                                                             | 4.17 ± 1.70                                                          |
| Famotidine     | 2.67 ± 0.57                                                             | 1.02 ± 0.10                                                          |

Each value represents the mean ± S.E. obtained from 3 different concentrations of IT-066 and famotidine.

**DISCUSSION**

In the present study, IT-066 inhibited histamine-induced positive chronotropic action in guinea pig atria. The inhibitory effect of IT-066 was enhanced in a time-dependent manner with suppression of the maximal response to histamine, and it was not removed by washing the tissue. Ranitidine protected against the...
irreversible inhibition of IT-066. These results suggest that IT-066 interacts with the H2-receptor as its antagonist. The inhibition was initially competitive but became noncompetitive due to its irreversible action at the H2-receptor, time-dependently. Therefore, it could be considered that IT-066 is not a noncompetitive antagonist for the H2-receptor, but instead a competitive and irreversible antagonist that interacts with the receptor time-dependently.

Concerning the time-dependent inhibitory actions of IT-066 and famotidine, there is a possibility that the cause is due to the time-dependent diffusion of the drug. In the present study, however, the apparent Schild regression line for histamine following treatment with IT-066 or famotidine did not shift to the left in a parallel fashion following prolongation of the incubation period (data not shown), nor was it different at inadequate equilibration, as reported previously (20). Furthermore, the extent of the shift of the concentration-response
curve of histamine to the right depended on the concentration and the duration of the treatment. This also means that the present results are different from those obtained when the drug diffusion is rate limiting, as reported previously (21). Therefore, the time-dependent inhibitory effect of IT-066 and famotidine may be caused by the time-dependent interaction of H₂-receptor and its antagonist, and not by inadequate equilibration time.

Concerning the mode of the interaction between the unsurmountable H₂-receptor antagonist and the receptor, Sung et al. (22) have suggested the two binding sites of SK&F94482, which is a compound structurally similar to IT-066. In the atria, they observed reversible and irreversible inhibition of the H₂-receptor-mediated chronotropic response by SK&F94482. Furthermore, they observed two distinct binding sites of high and low affinity for [³H]SK&F94482 in the cerebral cortex, in which washout revealed two phases of dissociation consisting of fast and slow components. In the present study, kinetic analysis of the equation showed that the Kᵢ value of IT-066 in the initial reversible reaction was two thirds that of famotidine, but the rate constant of the second reaction of IT-066 was significantly higher than that of famotidine. Pendleton et al. (23) showed the unsurmountable antagonism of famotidine, suggesting the cause to be the slow dissociation of the drug from the binding site. In the present study, IT-066 and famotidine showed time-dependent and unsurmountable inhibitory action on histamine, but the time-dependent irreversible effect was more significant for IT-066. This difference may be because the rate constant for the second irreversible reaction of IT-066 may be greater than that of famotidine. From these results, three types of antagonism are suggested for H₂-receptor antagonists in the blockade of the receptor: One is competitive and reversible (e.g., cimetidine); the second is competitive and slowly dissociatable (competitive > irreversible, e.g., famotidine); and the third is competitive and slowly dissociatable (competitive < irreversible and apparently irreversible, e.g., IT-066) in the reaction. Concerning the unsurmountable inhibition of SK&F94482, Roberts et al. (24) have recently suggested an allosteric interaction between the H₂-receptor antagonist and the receptor. This allosteric interaction between the H₂-receptor and IT-066 may be involved as a cause of the time-dependent unsurmountable inhibitory effect of IT-066.

The inhibitory potency of IT-066 on [¹⁴C]aminopyrine accumulation in the parietal cells induced by histamine was also strengthened by a prolongation of the incubation time (14). The administration of IT-066 both orally and intravenously was very effective in the inhibition of gastric acid secretion evoked by various stimulants, histamine, carbachol, gastrin and 2-deoxy-D-glucose, in dogs and rats (15, 25). It has been reported that L-643,441 and BMY-25368, novel H₂-receptor antagonists, which contain the piperidinomethylphenyl group in their structures, produced unsurmountable antagonism in the guinea pig atrium against dimaprit stimulation and that recovery of their responsiveness by washing was difficult (12, 26). Furthermore, the antisecretory actions of these compounds were shown to be very potent for a prolonged duration (12, 27). The prolonged inhibitory effect on the H₂-receptor of the compounds appears to correlate reasonably well with the duration of their antisecretory action in vivo. The structure of IT-066 does not contain the piperedinomethylphenyl group, but contains a similar group, piperidinomethylpyridyl.

Taking these data into consideration, it is suggested that the interaction between the IT-066 molecule and the H₂-receptor, which is a competitive, irreversible or slow offset binding to the receptor is responsible for the prolonged duration and high potency of the pharmacological action of IT-066. To clarify the interaction between the H₂-receptor and IT-066, we are now studying the binding of IT-066 to the receptor.
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