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Non-specific effects of calcium entry antagonists in mast cells

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Abstract. Calcium entry in non-excitable cells occurs through calcium-selective currents activated secondarily to store depletion and/or through non-selective cation channels (e.g., receptor- or second-messenger-activated channels). The driving force for calcium influx can be modified by chloride or potassium channels, which set the membrane potential of cells. Together, these conductances determine the extent of calcium entry. Mast cells are an excellent model system for studying calcium influx, because calcium-release-activated calcium currents (I_{CRAC}), second-messenger-activated non-selective currents and chloride currents are present in these cells. Whole-cell patch-clamp recordings were used to test the effects of the commonly used calcium entry blockers econazole and SK&F 96365, as well as the antiallergic and anti-inflammatory drugs tenidap, ketotifen and cromolyn on these channels. All tested drugs blocked the three different channel types with a similar order of magnitude (IC_{50} values ranging from micromolar to millimolar). Hence, these drugs cannot be used to discriminate between different calcium entry mechanisms.

Key words: Calcium-release-activated calcium current – Capacitative calcium entry – Non-selective channels – Chloride channels – Econazole – SK&F 96365 – Tenidap – Cromolyn

Introduction

Ca^{2+} entry plays an important role in signal transduction (e.g. stimulation of exocytosis) and in replenishing depleted Ca^{2+} stores. Unlike excitable cells, where Ca^{2+} entry can be provided by voltage-dependent Ca^{2+} channels, non-excitable cells seem to employ mainly two other influx mechanisms that account for Ca^{2+} entry: capacitative Ca^{2+} entry [6, 22, 23] and agonist-activated non-specific cation channels [6, 14]. The former mechanism is activated by the filling state of the internal Ca^{2+} stores; depletion of these stores results in activation of highly selective Ca^{2+} currents [5, 8, 9, 16, 21, 31]. This current has been termed I_{CRAC} (calcium-release-activated calcium current) in mast cells and rat basophilic leukemia (RBL) cells [5, 6, 8, 9, 22]. The other mechanism is provided by receptor-operated or second-messenger-operated cation channels [6].

Various Ca^{2+} entry blockers have been used as tools to study Ca^{2+} influx in non-excitable cells: the imidazol derivatives econazole [1, 26], SK&F 96365 [10, 17, 27], and tenidap [3] have been used in order to discriminate different influx pathways. Here we report that in mast cells from rat peritoneum these drugs inhibit I_{CRAC}, agonist-activated non-selective 50-pS cation channels, and cAMP-activated chloride channels with similar efficacy. Since mast cells are involved in allergic responses [18], we also tested the antiallergic compounds ketotifen [12, 29] and cromolyn [15]. None of these pharmacological agents affected the membrane currents in a specific manner. Similarly, agonists and antagonists of voltage-activated Ca^{2+} channels had no effects on the amplitude of I_{CRAC}. Together with the characterization of the blocking efficacy of divalent cations [9] the data of the present paper provide an extensive and detailed pharmacological profile of I_{CRAC}.

Materials and methods

Mast cells from rat peritoneum were obtained as described [9]. For experiments, cells were transferred to the recording chamber and kept in an external Ringer's solution of the following composition (in mM): NaCl 140, KCl 2.8, $CaCl_2$ 10, $MgCl_2$ 2, glucose 11, HEPES/NaOH 10, pH 7.2. External solution changes were made by pressure injection (10 cm H_2O) from a wide-tipped puffer pipette positioned about 10–20 μm from the cell. The standard intracellular solution contained (in mM): potassium glutamate 145,

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NaCl 8, $MgCl_2$ 1, MgATP 0.5, fura-2 pentapotassium salt (Molecular Probes) 0.1, HEPES/KOH 10, pH 7.2. Inositol trisphosphate ($InsP_3$) (Amersham; 10 μM), and BAPTA (Sigma; 10 mM), heparin (low molecular mass, Sigma; 500 μg/ml) or cAMP (Sigma; 100 μM) was added where indicated. The pharmacological agents were obtained from the following sources: econazole nitrate salt, ketotifen fumarate salt and cromolyn sodium salt all from Sigma (München, Germany), SK&F 96365 from Biomol (Hamburg, Germany), tenidap from Pfizer (Groton, USA), nedocromil from Fisons (Loughborough, UK), LOE 908 from Boehringer (Ingelheim, Germany) and Bay-K, nifedepine, PN-200-110 from Bayer (Frankfurt, Germany). Stock solutions of econazole nitrate salt, SK&F 96365, tenidap and ketotifen fumarate salt were dissolved in dimethylsulphoxide (DMSO) and diluted in the external Ringer's solution so that the final DMSO concentration did not exceed 1‰ (by vol.). Experiments were performed at room temperature (22−26° C) in the tight-seal whole-cell configuration of the patch-clamp technique using Sylgard-coated patch pipettes with resistances of 2−5 MΩ. Series resistances were in the range of 5−20 MΩ. Membrane currents were recorded as described [8, 9]. Variance analysis was used to identify the activation of 50-pS cation channels [14]. This was performed on-line at a rate of 0.5−1 Hz, by sampling 500-ms sections of membrane currents with a sampling rate of 5 kHz and signals were low-pass filtered at 500 Hz (effective bandwith: 2−500 Hz). All values are given as means ± SEM (number of experiments). Ramp currents in Figs. 1 and 4 were corrected by subtracting ramp currents obtained before activation of the respective conductances.

Results

Depletion-activated Ca^{2+} influx through I_{CRAC} is the major determinant of changes in $[Ca^{2+}]_i$ following receptor-mediated release of Ca^{2+} from internal stores, accounting for at least 70% of the plateau phase of $[Ca^{2+}]_i$ [4]. In order to obtain a dose/response curve for the inhibition of I_{CRAC} by the various drugs, different concentrations were applied after I_{CRAC} had been activated by perfusing the cell with $InsP_3$ and BAPTA. Figure 1 illustrates the effects of the substances on the inward current carried by I_{CRAC} at a potential of 0 mV. Examples of experiments employing concentrations that had no or little effect and concentrations that blocked almost 100% of the current are shown in Fig. 1A, B respectively. Figure 1C illustrates the membrane currents in response to voltage ramps (−100 mV to +100 mV, ramp duration = 50 ms) under control conditions and after application of the different drugs (same experiments as shown in Fig. 1B). The quantitative analysis of the data is shown in Fig. 2, where the percentage of inhibition is plotted against the drug concentrations. Data were fitted by dose/response curves yielding IC_{50} values of 0.6 μM (econazole), 4 μM (SK&F 96365), 13 μM (tenidap), and 200 μM (ketotifen). Cromolyn had only very weak effects when used at concentrations in the submillimolar range. Similarly, the cromolyn-derivative nedocromil was found to be ineffective at blocking I_{CRAC} at 100 μM (n = 3).

The same drugs were used at different concentrations to test the blocking effects on the non-selective 50-pS cation channels, which contribute to Ca^{2+} influx, although to a lesser extent than I_{CRAC} [4]. Since currents through 50-pS cation channels are transient and of variable duration [14], it was not possible to activate the

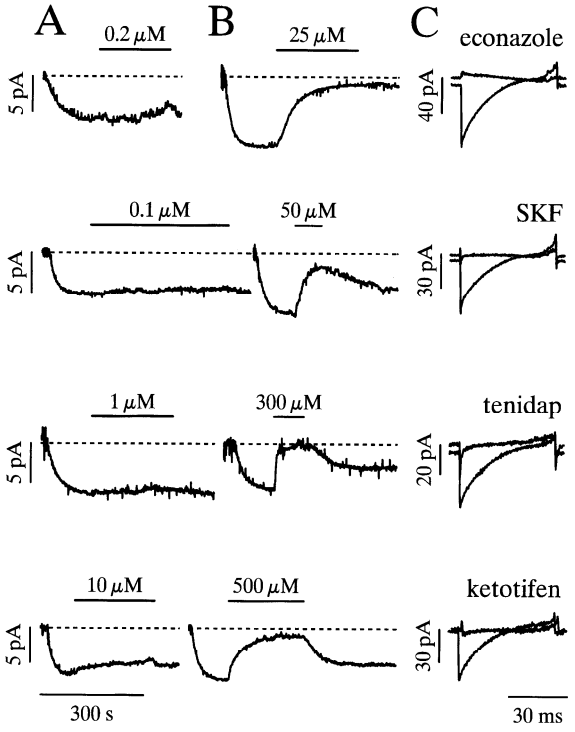

Fig. 1A–C. Block of calcium-release-activated calcium current (I_{CRAC}) by various drugs. The temporal pattern of I_{CRAC} at the holding potential (0 mV) is shown. Pipettes contained standard internal solution supplemented with inositol trisphosphate (10 μM) and BAPTA (10 mM) in order to activate the current. The application of the different pharmacological agents is indicated by the *bars*. Current spikes in response to voltage ramps (−100 mV to +100 mV, 50 ms duration) as shown in **C** were eliminated. **A**, **B** Two different concentrations for each drug are depicted. **C** High-resolution currents in response to the applied voltage ramps of the corresponding experiments in **B** before and after application of the pharmacological agents. Each trace represents the average of two to five leak-subtracted ramps

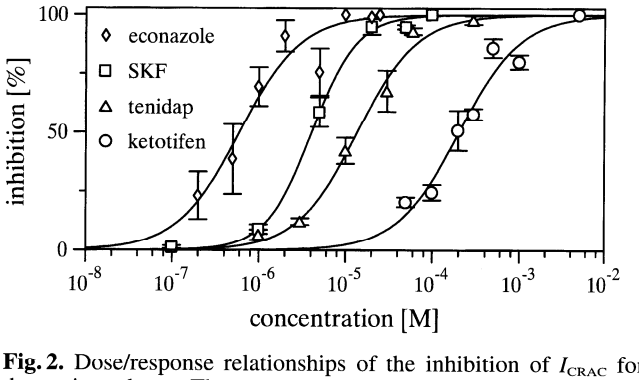

Fig. 2. Dose/response relationships of the inhibition of I_{CRAC} for the various drugs. The percentage inhibition of I_{CRAC}, taken at a membrane potential of −40 mV from the voltage ramps, is plotted against the drug concentrations on a semi-logarithmic plot. The mean values ± SEM (n = 2−7) are displayed. The data sets could be fitted by a sigmoidal function $100/[1+(IC_{50}/x)^h]$ yielding the following values: econazole (IC_{50} = 0.6 μM, h = 1.2); SK&F 96365 (IC_{50} = 4.0 μM, h = 1.7); tenidap (IC_{50} = 13.5 μM, h = 1.3); ketotifen (IC_{50} = 200 μM, h = 1.2)

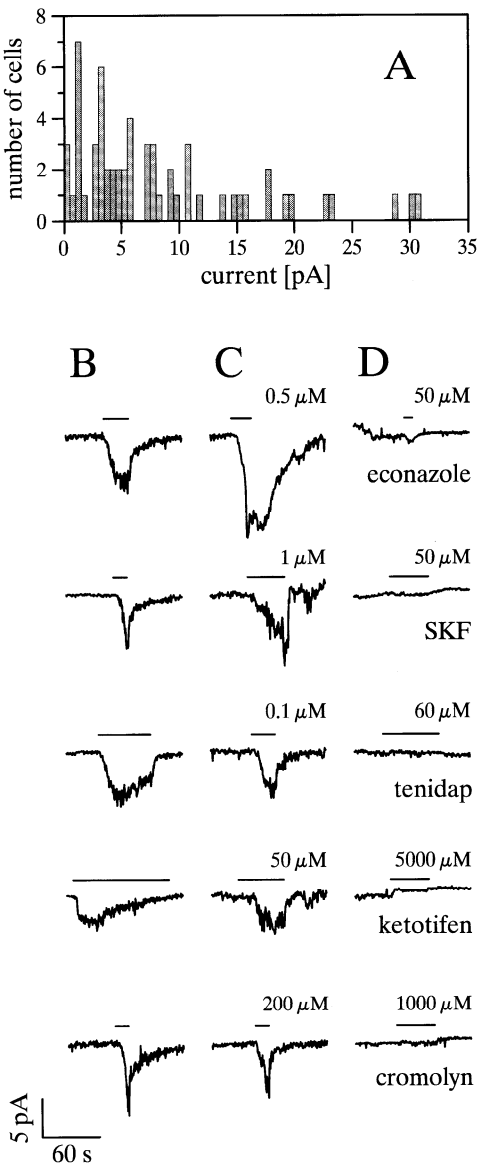

Fig. 3. Inhibition of current through 50-pS channels by the various drugs. **A** The distribution of the amplitude of the 50-pS currents from 60 experiments is shown. Currents were activated by application of compound 48/80 (50 μg/ml) in Ca^{2+}-free Ringer's solution about 200 s after whole-cell configuration. The standard internal solution contained heparin (500 μg/ml) in order to prevent activation of I_{CRAC}. The mean value of the current distribution is -8.3 ± 1.0 pA. The lower part of the figure shows several current traces measured under conditions described in **A**. **B** Control currents in response to application of compound 48/80 (50 μg/ml). **C** Experiments with drug concentrations that did not affect the current significantly. **D** Experiments with drug concentrations that blocked the current completely

channels first and subsequently apply the drugs to test the inhibitory effects. Hence, separate sets of experiments were carried out by applying the agonist 48/80 alone or by co-application of 48/80 and the drugs. Since there is a delay of 5.8 ± 0.7 s ($n = 52$) between application of 48/80 and activation of 50-pS channels, there is presumably sufficient time for the drugs to act on the channels. Figure 3A shows the amplitude distribution of

Table 1. Inhibition of 50-pS cation channels. Currents through the channels were activated by compound 48/80 (50 μg/ml) in external Ringer's solution (nominally Ca^{2+}-free external during application). Current amplitudes were recorded at a holding potential of −40 mV

Blocker	Concentration (μM)	Current (pA)	n
None (control)		-8.3 ± 1.0	60
Econazole	0.5	-10.2 ± 3.5	5
	20	-1.5 ± 0.8	5
SK&F 96365	1	-20.5 ± 8.1	3
	40–50	-0.1 ± 0.1	5
Tenidap	0.1–6	-3.0 ± 0.5	10
	60	-0.9 ± 0.5	4
Ketotifen	50	-9.0 ± 4.2	3
	5000	-0.6 ± 0.7	4
Cromolyn	200	-7.0 ± 2.4	4
	1000	-0.4 ± 0.3	3
LOE 908	1	-7.6 ± 2.3	3
	50	-5.1 ± 4.4	3

50-pS channels under control conditions. The mean amplitude of the current at −40 mV was -8.3 ± 1.0 pA ($n = 60$). Because of the very heterogeneous distribution, we resorted to using either very low concentrations of the drugs, which had almost no effects on the channel, or very high concentrations that blocked almost all of the channels, in order to get an idea in which concentration range the IC_{50} value for the drugs is located. Figure 3B shows examples of the activation of 50-pS channels under these conditions for all five drugs tested. The first column illustrates control experiments (Fig. 3B), the second column shows an example of an ineffective concentration (Fig. 3C) and the third column presents concentrations that block almost 100% of the current (Fig. 3D). The current amplitudes obtained for concentrations below and above the IC_{50} are summarized in Table 1. From these values it is possible to estimate the IC_{50} range for the different drugs (see Table 3).

Agonist stimulation of mast cells activates Cl^- currents which clamp the membrane potential to negative values (about −45 mV) and thus contribute to Ca^{2+} influx by providing a strong driving force. Even stronger activation of Cl^- currents is achieved by cAMP [13]. To see whether cAMP-activated chloride currents were also affected by the Ca^{2+}-influx-blocking agents, we chose to test blocker concentrations around the IC_{50} values obtained for the Ca^{2+} entry mechanisms. Substances were applied after the chloride current had been activated by intracellular perfusion of cells with cAMP (100 μM), and it was observed that the drugs also affected the chloride current, blocking about 50% of it. Examples of these experiments are shown in Fig. 4 and all experiments of this kind are summarized in Table 2. Cromolyn had almost no effects on the amplitude of the chloride channels when applied at concentrations ranging from 200 μM to 1000 μM.

In another series of experiments LOE 908, a substance that was reported to inhibit non-selective cation channels in the nanomolar concentration range [10], was

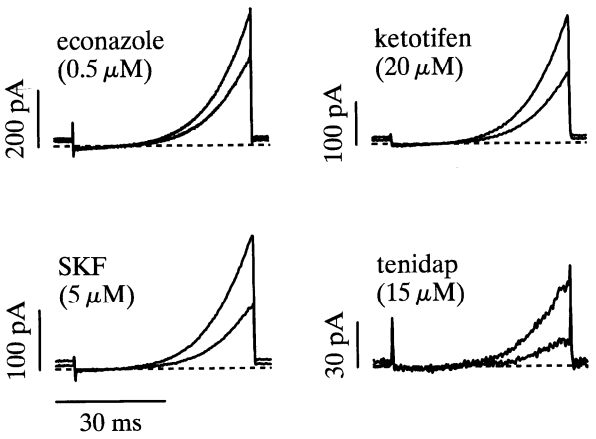

Fig. 4. cAMP-activated chloride currents were also blocked by the drugs. Examples of the blocking effect of the pharmacological agents used. Each trace shows an average of two to five current responses evoked by voltage ramps from −100 mV to +100 mV (50 ms duration). The overlayed traces were recorded from the same cell and show the maximal chloride current and the maximal inhibition reached with the given concentration of each drug

Table 2. Inhibition of chloride channels. Chloride currents were activated by intracellular perfusion of cAMP (100 μM). Pharmacological agents were applied after complete activation of the current. Current amplitudes were recorded at a holding potential of +40 mV

Blocker	Concentration (μM)	Inhibition (%)	*n*
Econazole	0.5	55 ± 9	11
SK&F 96365	5	83 ± 7	4
Tenidap	15	72 ± 14	3
Ketotifen	2	11 ± 11	3
	20	74 ± 13	4
	200	84 ± 1	3
Cromolyn	200	23 ± 22	3
	1000	23 ± 9	4

tested on both I_{CRAC} and 50-pS channels. Only weak effects of LOE 908 on the amplitude of I_{CRAC} or 50-pS currents could be observed even at concentrations up to 50 μM. The corresponding values for the 50-pS currents are sumnmarized in Table 1. I_{CRAC} was not affected at all by 50 μM LOE 908 ($n = 3$).

In addition, agonists and antagonists of voltage-dependent Ca^{2+} channels were tested on I_{CRAC}. None of these agents affected the amplitude of I_{CRAC} (data not shown) at the following concentrations: Bay-K (5 μM, $n = 3$), nifedepine (50 μM, $n = 4$), or PN-200-110 (5 μM, $n = 3$).

Discussion

The data presented in this study indicate that the compounds tested on various mechanisms that contribute to Ca^{2+} influx in rat peritoneal mast cells appear not to be specific. However, since non-excitable cell types express different Ca^{2+} influx mechanisms and since even different mast cell types exhibit heterogeneous pharmacological properties [20], our results may or may not apply to other cell types. Nevertheless, we consider the effects of the drugs, at least on I_{CRAC}, to be more general, as this mechanism appears to be rather ubiquitous [6, 22].

Table 3. IC_{50} values (or value ranges). I_{CRAC} calcium-release-activated calcium curents

Blocker	I_{CRAC} (μM)	Cation currents (μM)	Chloride currents (μM)
Econazole	0.6	0.5− 20	≈ 0.5
SK&F 96365	4	1 − 40	< 5
Tenidap	13	6 − 60	≈ 15
Ketotifen	200	50 −5000	2−20
Cromolyn	>500	200 −1000	>200
LOE 908	> 50	≈50	ND

As summarized in Table 3, most of the tested drugs affect I_{CRAC}, non-selective 50-pS, and chloride channels in the same concentration range. The main conclusion from this table is that none of these drugs is a specific blocker of Ca^{2+} entry, since they all have similar effects on the different currents. Furthermore blocking in the micromolar range is not considered to be specific. It is striking that the compounds tested exert their inhibitory effects in the same concentration range on ion channels as diverse as the ones investigated here. This makes it unlikely that they interact specifically with the ion channel proteins. Since most compounds are lipophilic, their lack of specificity might be related to sterical membrane effects, affecting proteins inside the lipid membrane environment.

Imidazole antimycotics, like econazole and SK&F 96365, are known to inhibit cytochrome *P*-450 in the micromolar range [25]. The observation that both cytochrome *P*-450 and capacitative Ca^{2+} entry are blocked by econazole and other imidazole antimycotics in the same concentration range has led to the hypothesis that cytochrome *P*-450 might be involved in the activation cascade of capacitative Ca^{2+} entry [1]. However, since the imidazole antimycotics block three types of currents (I_{CRAC}, 50-pS current and chloride current) that are important for Ca^{2+} influx in mast cells, there seems to be no basis for assuming a link between cytochrome *P*-450 and I_{CRAC}. Also, econazole has been reported to block voltage-activated Ca^{2+} channels [30] and potassium channels [2] in the same concentration range as that required to block Ca^{2+} entry [26]. Furthermore, econazole is known to release histamine from rat peritoneal mast cells by a "non-selective" mechanism [7], an effect probably unrelated to ionic currents.

SK&F 96365, which is probably the most frequently used blocker of receptor-activated Ca^{2+} influx [10, 17, 27], and tenidap, which has recently been found to inhibit Ca^{2+} influx in RBL-2H3 cells [3], are both reported to have non-specific effects. SK&F 96365 seems also to block voltage-operated Ca^{2+} channels [10] and potassium channels [10, 27]. It has moreover been reported to release Ca^{2+} from internal stores [17] when applied

at micromolar concentrations. Our data add to this list and further discredit SK&F 96365 as a selective blocker of Ca^{2+} influx. Tenidap seems to have additional effects on Ca^{2+} stores, causing a partial release of Ca^{2+} from these stores [3].

Cromolyn and ketotifen are both known to inhibit IgE-induced histamine release in mast cells [15, 29] although their efficacy on non-antigenic agonists is doubtful. For cromolyn it has been suggested that the mediator release is inhibited at an early, antigen-dependent and extracellular Ca^{2+}-independent stage [11]. This suggestion also fits with the detection of a "cromolyn-binding protein" [15], which seems to be involved in the immunological response of mast cells prior to the Ca^{2+} influx. Our data suggest that the antiallergic action of cromolyn is probably not at the level of ion channels, although the drug has been reported to inhibit "intermediate" Cl^- channels [24].

As we observed a concentration-dependent inhibition of the Ca^{2+} currents only with high concentrations of ketotifen, its main antiallergic effects could also be due to interaction with other steps in the signal transduction pathway, e.g. the inhibition of the calmodulin-dependent phosphodiesterase or interaction with calmodulin itself [19], or to antihistaminic effects in target cells resulting in inhibition of histamine-induced bronchospasm [12]. The hypothesis that the inhibition of histamine release by cromolyn and ketotifen is due to a direct block of Ca^{2+} influx in mast cells could not be supported by our results. In contrast to Sydbom [28] we even failed to observe a block of 48/80-induced degranulation when incubating mast cells with 100 μM cromolyn or nedrocromil for periods ranging from several seconds up to 20 h.

LOE 908, which has been reported to block non-selective cation channels in the nanomolar concentration range [10], seemed to have only weak if any effects on I_{CRAC} and non-selective 50-pS channels in the micromolar concentration range in mast cells. This would suggest that cation channels in different cells have different pharmacological profiles.

In summary, the pharmacological characterization of the different influx mechanisms did not reveal blocking agents that are highly selective for one entry mechanism or that discriminate between the different channels. Thus, these drugs do not seem to be powerful tools to study Ca^{2+} entry and we must await the development of other compounds before we are able to modulate Ca^{2+} influx mechanisms differentially in order to assign physiological functions to certain influx mechanisms.

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