Protein-tyrosine Kinases Activate while Protein-tyrosine Phosphatases Inhibit L-type Calcium Channel Activity in Pituitary GH3 Cells*

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The aim of this study was to evaluate the effect of protein-tyrosine kinase (PTK) and protein tyrosine phosphatase (PTP) inhibitors on Ca2+ channels in GH3 cells. The activity of Ca2+ channels was monitored either by single-cell microfluorometry or by the whole-cell configuration of the patch-clamp technique. Genistein (20–200 μM) and herbimycin A (1–15 μM) inhibited [Ca2+]i rise induced either by 55 mM K+ or 10 μM Bay K 8644. In addition, genistein and lavendustin A inhibited whole-cell Ba2+ currents. By contrast, daidzein, a genistein analogue devoid of PTK inhibitory properties, did not modify Ca2+ channel activity. The inhibitory action of genistein on the [Ca2+]i increase was completely counteracted by the PTP inhibitor vanadate (100 μM). Furthermore, vanadate alone potentiated [Ca2+]i response to both 55 mM K+ and 10 μM Bay K 8644. The possibility that genistein could decrease the [Ca2+]i elevation by enhancing Ca2+ removal from the cytosol seems unlikely since genistein also reduced the increase in fura-2 fluorescence ratio induced by Ba2+, a cation that enters into the cells through Ca2+ channels but cannot be pumped out by Ca2+ extrusion mechanisms. Finally, in unstimulated GH3 cells, genistein caused a decline of [Ca2+]i, and the disappearance of [Ca2+]i oscillations, whereas vanadate induced an increase of [Ca2+]i, and the appearance of [Ca2+]i oscillations in otherwise non-oscillating cells. The present results suggest that in GH3 cells PTK activation causes an increase of L-type Ca2+ channel function, whereas PTPs exert an inhibitory role.

It has been largely demonstrated that the activity of L-type Ca2+ channels can be regulated by different types of kinases, such as protein kinase A (PKA)1 (1, 2) and protein kinase C (PKC) (3, 4). These two kinases phosphorylate serine (Ser) and threonine (Thr) residues on the α- and β-subunits of these channel proteins (5, 6). Recently, a great deal of interest in the literature has been devoted to another class of kinases, the protein-tyrosine kinases (PTKs) (7–9). These enzymes, which exist both in transmembrane receptor-linked (7) or non-transmembrane forms (8, 9), phosphorylate tyrosine (Tyr) residues on several cellular proteins. Since it has been recently reported that in non-excitable cells such as T-lymphocytes the overexpression of PTK activity, obtained transfecting these cells with the PTK-encoding oncogene v-src, induces a remarkable increase of basal and stimulated [Ca2+]i levels (10), it appeared of interest to explore the possibility that PTKs could modulate the activity of L-type Ca2+ channels. For this purpose, the effect of the specific PTK inhibitors genistein (11, 12), herbimycin A (13), and lavendustin A (14) on the function of L-type Ca2+ channels was evaluated in pituitary GH3 cells (15) by single-cell microfluorometry and patch-clamp electrophysiology. On the other hand, since PTK activity is functionally counteracted by protein-tyrosine phosphatases (PTPs) (16, 17), the possible effect of the PTP inhibitor vanadate (18) on L-type Ca2+ channels was also investigated.

EXPERIMENTAL PROCEDURES

Cell Culture—GH3 cells were obtained from Flow Laboratories (Irvine, Scotland) and grown on plastic dishes in Ham's F-10 medium (Life Technologies, Inc., San Giuliano Milanese, Italy) with 15% horse serum (Flow, Irvine, Scotland), 2.5% fetal calf serum (HyClone, Logan, UT), 100 IU of penicillin/ml, and 100 μg of streptomycin/ml. Cells were cultured in a humidified 5% CO2 atmosphere. Culture medium was changed every 2 days. For microfluorometric studies, cells were seeded on glass coverslips (Fisher) coated with poly-L-lysine (30 μg/ml) (Sigma). All the experiments were performed 2–4 days after seeding. The cells were at a culture passage between 34 and 60.

Intracellular Calcium Measurements—Intracellular calcium levels were measured using a microfluorometric technique, as reported previously (19). Briefly, the cells, grown on glass coverslips, were loaded with 5 μM fura-2/AM for 1 h at room temperature in Krebs-Ringer saline solution (5.5 mM KCl, 160 mM NaCl, 1.2 mM MgCl2, 1.5 mM CaCl2, 10 mM glucose, 0.2% bovine serum albumin, and 10 mM Hepes/NaOH, pH 7.4). At the end of fura-2/AM loading, the coverslip was mounted in a perfusion chamber (Medical System Co., Greenville, NY) on an inverted Nikon Diaphot fluorescence microscope. Throughout the experiment, the cells were superfused continuously with Krebs-Ringer saline solution using a peristaltic pump (Gilson, France) and a microtube, positioned with a macromanipulator on the cells under observation (Narishige, Japan). The perfusion medium was removed continuously from the perfusion chamber by suction using a microaspirator (Medical System Co.) connected with a vacuum pump (Hofer, San Francisco). All drugs tested were introduced into the superfusion line using an injection loop and a two-way valve (Thomson, Springfield, VA). A 100-watt xenon lamp (Osrarn, Germany) with a computer-operated filter wheel bearing two different interference filters (340 and 380 nm) illuminated the microscopic field with uv light alternatively at the wavelength of 340 and 380 nm, with an interval of 500 ms between lighting at 340 and 380 nm. The interval between each couple of lighting and the next was chosen according to the experimental protocol. Emitted light was passed through a 400 nm dichroic mirror, filtered at 510 nm, and collected by a CCD camera (Photonic Science, Robertsbridge, East Sus-

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§The abbreviations used are: PKA, protein kinase A; PKC, protein kinase C; PTK, protein tyrosine kinase; [Ca2+]i, cytosolic free calcium; PTP, protein tyrosine phosphatase; fura-2/AM, fura-2 acetoxymethylester.
Figure 1. Effect of genistein and herbimycin A on K⁺-induced [Ca²⁺]i increase in GH₃ cells. Panel A shows the effect of genistein (200 µM), added to the perfusion 7 min before and throughout the whole second K⁺ pulse. The mean peak after the second 55 mM K⁺ pulse was significantly lower than the first one (p < 0.01). In addition, genistein significantly reduced basal [Ca²⁺]i (124 ± 4 versus 104 ± 3 nM Ca²⁺; p < 0.01). In panel C the concentration dependence of the inhibitory effect of genistein on the [Ca²⁺]i increase induced by 55 mM K⁺ is represented. Each point is the mean of 10–30 single-cell recordings. The solid line is the fit of the experimental points to the equation $y = \max (1/(x + K_n))^n$, where $K_n$ is the $K_n$ for the block and $n$ is the Hill coefficient. Panel D shows the effect of different concentrations of herbimycin A on the 55 mM K⁺-induced [Ca²⁺]i increase. * = p < 0.01 versus control group.

Figure 2. Effect of genistein on [Ca²⁺]i increase induced by 10 µM Bay K 8644 in GH₃ cells. Panel A shows the effect on [Ca²⁺]i of two 10 µM Bay K 8644 pulses delivered with an approximately 25-min interval. During the resting period between the two stimulations, the cells were perfused with Krebs-Ringer saline solution. Panel B shows the effect of 200 µM genistein added to the superfusion medium 5 min before and throughout the second Bay K 8644 pulse. Each trace is the mean of at least 30 single-cell recordings obtained during a single experiment representative of at least three other experimental sessions.

RESULTS

Inhibition of Ca²⁺ Channel Activity by Genistein, Herbimycin A, and Lavendustin A—In GH₃ cells, genistein, which inhibits PTKs by competing with ATP for the binding on these enzymes (11), caused a dose-dependent (20–200 µM) inhibition of [Ca²⁺]i elevation elicited by a superfusion medium containing 55 mM K⁺ (Fig. 1, A–C). The apparent IC₅₀ of genistein effect (30 µM) on [Ca²⁺]i is similar to that on PTK activity (11). Herbimycin A, another PTK inhibitor that acts on these enzymes by a completely different mechanism, namely by direct binding on its reactive SH groups (13), exerted a similar concentration-dependent inhibition on the [Ca²⁺]i increase induced by 55 mM K⁺ (Fig. 1D).

On the other hand, when GH₃ cells were superfused with two 10 µM consecutive pulses of the dihydropyridine activator of L-type Ca²⁺ channels Bay K 8644 (20, 21), two equivalent elevations of [Ca²⁺]i occurred (Fig. 2A). However, if genistein (200 µM) was superfused 5 min before the second pulse with the L-type Ca²⁺ channel activator, a 40% reduction of the [Ca²⁺]i increase was observed (Fig. 2B).

To identify more directly the target of PTK inhibition, Ba²⁺ currents through Ca²⁺ channels were recorded in GH₃ cells by means of the whole-cell configuration of the patch-clamp technique. From the holding potential of ~90 mV the cells were depolarized to various potentials at a frequency of 0.2 Hz to minimize Ca²⁺ channel rundown. The compensation of capacitative transients and leakage currents was performed both on-line by the clamp amplifier settings and off-line by subtracting Cd²⁺-insensitive currents (200 µM Cd²⁺).

Materials—All chemicals were of analytical grade and were purchased from Sigma. Genistein was obtained from BIOMOL Research Labs Inc. (Plymouth, PA). Lavendustin A, herbimycin A, Bay K 8644, daidzein, and fura-2/AM were purchased from Calbiochem. Nifedipine was a kind gift of Bayer AG (Germany).

Statistical Analysis—Data were analyzed by means of Students’ t test for paired data or by analysis of variance followed by Scheffé test. Data are expressed as mean values ± S.E.
of the whole-cell Ba²⁺ currents (Fig. 4C). Perfusing GH₃ cells with the PTK inhibitor genistein (100 μM) caused a 50% reduction of the currents at all potentials tested (Fig. 3B). Complete suppression of the currents was achieved with 200 μM Cd²⁺ (Fig. 3C). Upon extensive washout (5 min) Ba²⁺ currents recovered (Fig. 3D). The extent of genistein-induced inhibition of Ba²⁺ currents was comparable to that observed in microfluorometric studies (Fig. 4D). Lavendustin A (25 μM), another PTK inhibitor which could not be studied microfluorometrically because of its intrinsic fluorescence, also inhibited Ba²⁺ currents (Fig. 4, A and D). By contrast, daidzein, the inactive analogue of genistein (12), did not exert any influence on Ba²⁺ currents (Fig. 4, C and D). It should be underlined that although nifedipine inhibition of Ba²⁺ currents occurred with a very short latency (10 s), the effect of genistein required a longer period of time (30 s) (Fig. 4E).

**Effect of Genistein on the Fura-2 Fluorescence Ratio Increase Induced by Extracellular Ba²⁺**—It is well known that Ba²⁺ ions enter into the cells through Ca²⁺ channels, bind fura-2, increase its fluorescence ratio, and cannot be extruded through Ca²⁺ efflux pathways (22, 23). For this reason, an increase in the fura-2 fluorescence ratio after extracellular Ba²⁺ exposure is a specific index of cation influx through Ca²⁺ channels. When GH₃ cells were superfused in a Ca²⁺-free medium, two consecutive exposures to 1 mM extracellular Ba²⁺ caused comparable increases in the fura-2 fluorescence ratio. When genistein (200 μM) was superfused 5 min before and during the second Ba²⁺ exposure, a significant decrease in the fura-2 fluorescence ratio occurred. In fact, the S₂/S₁ ratio was 0.99 ± 0.001 in control cells and 0.73 ± 0.001 in genistein-treated cells (p < 0.01).

**The PTP Inhibitor Vanadate Enhances the [Ca²⁺] Increase**
Elicited by L-type Ca$^{2+}$ Channel-activating Stimuli and Reversal Genistein Inhibition of 55 mM K$^+$-induced [Ca$^{2+}$]i Increase—When the PTP inhibitor vanadate (100 μM) was superfused for 15 min before the 55 mM K$^+$ pulse, a 30% increase of the [Ca$^{2+}$]i response was observed (Fig. 5A). A similar potentiation of the [Ca$^{2+}$]i response was also observed when the cells were exposed to 10 μM Bay K 8644 (Fig. 5B).

In addition, the superfusion of GH3 cells with 100 μM vanadate for 15 min completely abolished the inhibition of the [Ca$^{2+}$]i response to 55 mM K$^+$ which follows the exposure of these cells to 200 μM genistein for 2 min (Fig. 6, A and B).

Effect of the PTK Inhibitor Genistein and of the PTP Inhibitor Vanadate on Basal [Ca$^{2+}$]i—In unstimulated conditions, 20% (12/53) of GH3 cells displayed oscillations of [Ca$^{2+}$]i, defined as an increase of [Ca$^{2+}$]i above the mean of the basal values ± 2 S.D. occurring with a frequency higher than one peak every 3 min. The remaining cells (41/53, i.e. 80%) that did not display these characteristics were defined as non-oscillating. In non-oscillating cells, the superfusion of 200 μM genistein caused a 30% decline of basal [Ca$^{2+}$]i (Fig. 7A). In oscillating cells, this PTK inhibitor produced the interruption of [Ca$^{2+}$]i oscillations and a decline of baseline [Ca$^{2+}$]i values (Fig. 7B). By contrast, the PTP inhibitor vanadate (100 μM) induced an increase in the frequency (1.11 ± 0.2 versus 0.6 ± 0.06 peaks/min; p < 0.05) and amplitude (45.9 ± 3.8 versus 33.1 ± 3.4% increase over basal values; p < 0.05) of [Ca$^{2+}$]i oscillations in spontaneously oscillating GH3 cells. In addition, vanadate induced the appearance of [Ca$^{2+}$]i oscillations in 66.6% of GH3 cells that were non-oscillating (frequency: 1.32 ± 0.1 versus 0.2 ± 0.02 peaks/min; p < 0.05; amplitude: 44.7 ± 4.1 versus 37.2 ± 3.4% increase over basal values, p < 0.05) (Fig. 7, C and D).

DISCUSSION

The results of the present study, obtained by means of single-cell microfluorometry and whole-cell patch-clamp techniques, demonstrate that the activity of Ca$^{2+}$$^+$ channels in GH3 cells can be influenced by the interplay between PTK and PTP activity: PTK activation seems to cause an increase, whereas PTP activation appears to exert an inhibitory role on this ion channel. The hypothesis that the L-type Ca$^{2+}$ channel is the target of PTK and PTP modulation derives from the results showing that the increase of [Ca$^{2+}$]i elicited by the specific L-type Ca$^{2+}$ channel activator Bay K 8644 and high K$^+$ concentrations was reduced by the PTK inhibitor genistein and enhanced by the PTP blocker vanadate. A further support to this idea is the ability of genistein and lavendustin A to inhibit Ba$^{2+}$ currents through Ca$^{2+}$ channels that displayed biophysical and pharmacological features of the L-type. On the other hand, the possibility that the action of PTK inhibitors is exerted on the T-type Ca$^{2+}$ channels, which have been described in GH3 cells, seems unlikely since this Ca$^{2+}$ channel type does not play a significant role in the [Ca$^{2+}$]i elevation elicited by strong activating stimuli (55 mM K$^+$ or Bay K 8644) (24, 25). In addition, the biophysical features of Ba$^{2+}$ currents recorded in GH3 cells in the present study do not show the presence of a significant population of this Ca$^{2+}$ channel type. Furthermore, the remarkable inhibition of Ba$^{2+}$ currents by the L-type blocker nifedipine suggests that the largest population of Ca$^{2+}$ channels is represented by the L-type.

The possibility that the genistein-induced reduction of the [Ca$^{2+}$]i increase elicited by high K$^+$ concentrations could be due to an increase of Ca$^{2+}$ removal from the cytoplasm to the
extracellular space or into the intracellular Ca\textsuperscript{2+} stores seems not to be compatible with the results of the present study. In fact, genistein also reduced the entrance of Ba\textsuperscript{2+} ions, a cation that is known to be unable to substitute for Ca\textsuperscript{2+} in the extrusion mechanisms. In support of this interpretation, the entity of the genistein-induced inhibition of the [Ca\textsuperscript{2+}], rise induced by 55 mM K\textsuperscript{+} and 10 \mu M Bay K 8644 was comparable to the inhibition observed in electrophysiological experiments.

Since it has been reported that genistein, besides inhibiting PTKs, can also block other protein kinases such as PKA and PKC (11, 12), which are known to modulate L-type Ca\textsuperscript{2+} channels (1–4), the possibility exists that its effects on the activity of L-type Ca\textsuperscript{2+} channels could occur via PKA or PKC inhibition. However, this hypothesis seems unlikely since herbimycin A and lavendustin A, two other specific PTK inhibitors devoid of PKA or PKC inhibitory action (14, 26) and structurally unrelated to genistein, effectively inhibited Ca\textsuperscript{2+} channel activity in GH\textsubscript{3} cells. This evidence strongly suggests that PKA or PKC inhibition is not involved in the genistein action on Ca\textsuperscript{2+} channels. In addition, the IC\textsubscript{50} for genistein inhibition of Ca\textsuperscript{2+} channels (30 \mu M) was very similar to that for PTK inhibition and much lower than that for PKA and PKC blockade (11). The specificity of genistein action on Ca\textsuperscript{2+} channels via PTKs was confirmed further by the inability of the genistein analogue daidzein, which lacks PTK inhibitory properties, to modify Ca\textsuperscript{2+} channel activity in electrophysiological recordings.

The existence of a PTK regulation of L-type Ca\textsuperscript{2+} channels in GH\textsubscript{3} cells is also supported by the fact that PTPs, which physiologically counteract the activity of PTKs (16, 17), exert an opposite modulation on L-type Ca\textsuperscript{2+} channel activity. In fact, the inhibition of PTPs by orthovanadate, a well-known inhibitor of these enzymes (18), was able to enhance the [Ca\textsuperscript{2+}] increase induced by high K\textsuperscript{+} concentrations and to counteract the inhibitory effect of genistein on this response.

The modulation exerted by PTKs and PTPs seems to occur not only when L-type Ca\textsuperscript{2+} channels are activated by high depolarizing stimuli, but also in resting conditions. In fact, the inhibition of PTKs by genistein caused a decline of [Ca\textsuperscript{2+}], and a disappearance of [Ca\textsuperscript{2+}] oscillations in oscillating GH\textsubscript{3} cells, whereas the blockade of PTPs by vanadate induced an increase of [Ca\textsuperscript{2+}] or the appearance of [Ca\textsuperscript{2+}] oscillations. These findings were not unexpected since in unstimulated conditions, L-type Ca\textsuperscript{2+} channels of GH\textsubscript{3} cells are spontaneously active, as shown by the fact that spontaneous action potentials have been detected (27) and that these potentials are coupled to oscillations of [Ca\textsuperscript{2+}], which can be abolished by the specific L-type Ca\textsuperscript{2+} channel blocker nifedipine (15).

The results of the present study showing that PTKs exert a stimulatory modulation on L-type Ca\textsuperscript{2+} channels are in line with the recent report that genistein induces a concentration-dependent inhibition of Ca\textsuperscript{2+} channel currents in vascular smooth muscle cells (28). In addition, evidence has been provided that the inhibition of PTKs can also reduce Ca\textsuperscript{2+} influx through plasma membrane “refilling” channels (29–31) and that different types of receptor-operated channels, like the nicotinic, N-methyl-D-aspartic acid, and \gamma-aminobutyric acid receptor channels, can be modulated by PTKs (32–34).

The results of the present study could be of interest to explain the Ca\textsuperscript{2+} dependence of certain biological responses elicited by some growth factors (35). In fact, the stimulation of many growth factor receptors, such as those for the epidermal growth factor, recognize as a signaling pathway the activation of a receptor-linked PTK (7). Since the results of the present study indicated that PTK activation leads to Ca\textsuperscript{2+} entrance through L-type Ca\textsuperscript{2+} channels into the cells, the Ca\textsuperscript{2+}-dependent epidermal growth factor-induced differentiation of GH\textsubscript{3} cells toward the lactotroph phenotype (36) could be the consequence of the activation of L-type Ca\textsuperscript{2+} channels, especially if one considers that in a different pituitary cell line, epidermal growth factor induces an increase of [Ca\textsuperscript{2+}], which is independent of phospholipase C\textsubscript{y1}-dependent inositol 1,4,5-trisphosphate generation (37).
In conclusion, all of these results suggest that L-type Ca^{2+} channels are modulated by the PTK/PTP system in GH3 cells. The molecular mechanism of this modulation remains to be clarified. However, a possible working hypothesis to explain the effect of PTK inhibitors on Ca^{2+} channel function could be that phosphorylation by PTKs exerts a permissive role on the activation of Ca^{2+} channels elicited by both the dihydropyridine agonist Bay K 8644 and depolarizing stimuli. Such a model has already been proposed by Armstrong et al. (2) to explain the effect of PKA on Ca^{2+} channel activation.

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