Adenophostin A Can Stimulate Ca\(^{2+}\) Influx without Depleting the Inositol 1,4,5-Trisphosphate-sensitive Ca\(^{2+}\) Stores in the Xenopus Oocyte*

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Adenophostin A possesses the highest known affinity for the inositol 1,4,5-trisphosphate (Ins(1,4,5)P\(_3\)) receptor (InsP\(_3\)R). The compound shares with Ins(1,4,5)P\(_3\) those structural elements essential for binding to the InsP\(_3\)R. However, its adenosine 2'-phosphate moiety has no counterpart in the Ins(1,4,5)P\(_3\) molecule. To determine whether its unique structure conferred a distinctive biological activity, we characterized the adenophostin-induced Ca\(^{2+}\) signal in Xenopus oocytes using the Ca\(^{2+}\)-gated Cl\(^{-}\) current assay. In high concentrations, adenophostin A released Ca\(^{2+}\) from Ins(1,4,5)P\(_3\)-sensitive stores and stimulated a Cl\(^{-}\) current that depended upon the presence of extracellular Ca\(^{2+}\). We used this Cl\(^{-}\) current as a marker of Ca\(^{2+}\) influx. In low concentrations, however, adenophostin A stimulated Ca\(^{2+}\) influx exclusively. In contrast, Ins(1,4,5)P\(_3\) and (2-hydroxyethyl)-a-D-glucopyranoside 2',3,4-trisphosphate, an adenophostin A mimic lacking most of the adenosine moiety, always released intracellular Ca\(^{2+}\) before causing Ca\(^{2+}\) influx. Ins(1,4,5)P\(_3\) could still release Ca\(^{2+}\) during adenophostin A-induced Ca\(^{2+}\) influx, confirming that the Ins(1,4,5)P\(_3\)-sensitive intracellular Ca\(^{2+}\) stores had not been emptied. Adenophostin- and Ins(1,4,5)P\(_3\)-induced Ca\(^{2+}\) influx were not additive, suggesting that both agonists stimulated a common Ca\(^{2+}\) entry pathway, Heparin, which blocks binding to the InsP\(_3\)R, prevented adenophostin-induced Ca\(^{2+}\) influx. These data indicate that adenophostin A can stimulate the influx of Ca\(^{2+}\) across the plasma membrane without inevitably emptying the Ins(1,4,5)P\(_3\)-sensitive intracellular Ca\(^{2+}\) stores.

Stimulation of many plasma membrane receptors increases the intracellular concentration of the second messenger inositol 1,4,5-trisphosphate (Ins(1,4,5)P\(_3\)). In its best characterized

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§ The abbreviations used are: Ins(1,4,5)P\(_3\), inositol 1,4,5-trisphosphate; InsP\(_3\)R, Ins(1,4,5)P\(_3\) receptor; CRAC, Ca\(^{2+}\) release-activated Ca\(^{2+}\); CIF, Ca\(^{2+}\) influx factor; ADAN 1, (2-hydroxyethyl)-a-D-glucopyranoside 2',3,4-trisphosphate; ATP\(_S\), adenosine 5'-O-(thiotriphosphate).

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outside the Ins(1,4,5)P₃-binding domain. If so, then stimulating the InsP₃R with adenophostin A could result in a distinctive Ca²⁺ signal that may uncover novel aspects of the InsP₃R function. To begin to test this hypothesis, we microinjected adenophostin A into Xenopus oocytes and compared the resulting Ca²⁺ signal with that induced by Ins(1,4,5)P₃. Our results show that in high concentrations, adenophostin A and Ins(1,4,5)P₃ produce a similar Ca²⁺ signal. However, in low concentrations, adenophostin A stimulates extracellular Ca²⁺-dependent Cl⁻ current (Ca²⁺ influx) without first releasing intracellular Ca²⁺.

EXPERIMENTAL PROCEDURES

Materials—Adenophostin A was isolated (10) and ADAN 1 was synthesized (11) as described before. The purity of adenophostin A was more than 90% by high pressure liquid chromatography analysis, and no contaminating signal was observed by NMR spectrometry. ADAN 1 was purified by ion exchange chromatography and was used as the triethylammonium salt. Ins(1,4,5)P₃ was obtained from Calbiochem. Adenophostin A was isolated (10) and ADAN 1 was synthesized (11) as described before. The purity of adenophostin A was more than 90% by high pressure liquid chromatography analysis, and no contaminating signal was observed by NMR spectrometry. ADAN 1 was purified by ion exchange chromatography and was used as the triethylammonium salt. Ins(1,4,5)P₃ was obtained from Calbiochem. BAPTA was from Molecular Probes (Eugene, OR). All other chemicals were from Sigma. Oocyte harvesting, micropipette calibration, and cytosolic microinjections were performed as described previously (13). Injection pipettes were back-filled with adenophostin A, ADAN 1, or Ins(1,4,5)P₃. The injection volume was kept at 0.7 nl, as determined by measuring the diameter of a droplet microinjected under oil.

Electrophysiology—We assayed changes in free cytosolic Ca²⁺ concentration ([Ca²⁺]) by measuring Ca²⁺-activated Cl⁻ currents with the two-electrode voltage clamp technique as described before (13). This assay has been extensively validated using Ca²⁺-sensitive electrodes (14–16) and fluorescent Ca²⁺ indicators (13, 17–21). For most experiments, oocytes were initially stimulated in a bath solution containing 116 mM NaCl, 2 mM KCl, 6 mM CaCl₂, 1 mM MgCl₂, 5 mM HEPES, pH 7.4. We assessed Ca²⁺ influx by measuring the change in Ca²⁺-gated Cl⁻ current induced by either lowering the Ca²⁺ (from 6 to 0.1 mM CaCl₂) or increasing the concentration of the inorganic ions Mn²⁺ (4 mM), Ni²⁺ (5 mM), or La³⁺ (5 mM) in the bath. Both Ni²⁺ and La³⁺ block Ca²⁺ channels. Although Mn²⁺ may go through Ca²⁺ influx channels, it does not activate the Ca²⁺-gated Cl⁻ channel in the oocyte (22). We preferred using the inorganic ions to reversibly inhibit the Ca²⁺-gated Cl⁻ current caused by Ca²⁺ influx (22–24) because the plasma membrane electrical resistance often decreases in low external [Ca²⁺], making some of the recordings difficult to interpret (24). The Ca²⁺-gated Cl⁻ current reflects [Ca²⁺] just beneath the cytoplasmic membrane; changes in [Ca²⁺] occurring deeper in the cell are not measured (25, 26). Thus, this assay inherently measures [Ca²⁺], in the cellular area most likely to be affected by Ca²⁺ influx. The assay also integrates the submembranous [Ca²⁺], changes across the oocyte’s entire plasma membrane surface, thereby maximizing our ability to detect Ca²⁺ influx. Although the extracellular Ca²⁺-dependent Cl⁻ current assays Ca²⁺ influx indirectly, for clarity, we use the terms “extracellular Ca²⁺-dependent Cl⁻ current” and “Ca²⁺ influx” interchangeably.

RESULTS AND DISCUSSION

When injected in high concentration (10⁻⁵ M in the pipette), adenophostin A causes a biphasic response; there is an initial, short lived increase in [Ca²⁺], followed by a slow increase (Fig. 2A, n = 16). This response pattern is similar to that generated by high concentrations of Ins(1,4,5)P₃ (10⁻⁴ M in the pipette, n = 8; and see Ref. 22). Both components of the response to adenophostin A are due to an increase in [Ca²⁺], because they can be completely blocked by the Ca²⁺ chelator BAPTA (1 nmol, n = 6, flat tracings not shown). The initial transient increase of [Ca²⁺] caused by both agonists persists in the presence of extracellular Mn²⁺ (4 mM) (Fig. 2C and D) or in low extracellular [Ca²⁺] (n = 5 for adenophostin A, n = 6 for Ins(1,4,5)P₃; see also Ref. 23) and represents the release of Ca²⁺ from the intracellular stores. In contrast, the slow in-
Fig. 2. Adenophostin A releases Ca\textsuperscript{2+} from Ins(1,4,5)P\textsubscript{3}-sensitive intracellular stores. On each tracing of this report, Ca\textsuperscript{2+}-gated Cl\textsuperscript{-} current (y axis) is expressed as a function of time (x axis). For clarity, the parallel bars delineate the portion of the tracing that has been blanked to remove the artifacts caused by removal and reinserstion of the microinjection pipettes. Inward current (downward deflection) represents an increase in [Ca\textsuperscript{2+}], injection (arrow) of adenophostin A (10^{-5} M in the pipette) (A) or Ins(1,4,5)P\textsubscript{3} (10^{-4} M in the pipette) (B) causes a transient increase in [Ca\textsuperscript{2+}], which reflects the release of intracellular Ca\textsuperscript{2+} (see “Results and Discussion”), followed by a slow increase in [Ca\textsuperscript{2+}], which can be blocked by adding Mn\textsuperscript{2+} to the bath (bar) and therefore represents Ca\textsuperscript{2+} influx. C, following an injection of adenophostin A (left arrow), Ins(1,4,5)P\textsubscript{3} no longer releases intracellular Ca\textsuperscript{2+} (right arrow). D, the converse experiment is also true, illustrating that Ins(1,4,5)P\textsubscript{3} and adenophostin A cross-desensitize for the release of intracellular Ca\textsuperscript{2+}. Note that these experiments are performed in the continued presence of Mn\textsuperscript{2+} (bar) to block Ca\textsuperscript{2+} influx.

Fig. 3. Whole cell current-voltage relationship for the Ni\textsuperscript{2+}- or Mn\textsuperscript{2+}-inhibitable current induced by adenophostin A (closed circles, each representing the average ± S.E. of nine cells) or Ins(1,4,5)P\textsubscript{3} (open circles, each representing the average ± S.E. of seven cells).

Ins(1,4,5)P\textsubscript{3}-sensitive Ca\textsuperscript{2+} pools. Taken together, our data are consistent with adenophostin A stimulating the InsP\textsubscript{3}R (10).

When we compared the functional potency of many inositol phosphates, we noticed that in low concentrations, they only released intracellular Ca\textsuperscript{2+}; they did not cause Ca\textsuperscript{2+} influx (29, 30). Based on these results, we anticipated that when injected in threshold concentrations, adenophostin A would strictly release intracellular Ca\textsuperscript{2+}. As the tracing in Fig. 4A shows, a low concentration of adenophostin A (10^{-7} M in the pipette) caused a slow increase in Cl\textsuperscript{-} current. Contrary to what we had pre-
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**Fig. 4.** Adenophostin A stimulates \(Ca^{2+}\) influx without emptying the Ins(1,4,5)P_3-sensitive \(Ca^{2+}\) stores. **A**, injection of a low concentration of adenophostin A (10^{-7} \text{M} in the pipette) causes a slow increase in [\(Ca^{2+}\)], that can be blocked by adding extracellular Mn^{2+} (bar). Note the absence of an initial transient release of intracellular \(Ca^{2+}\). **B**, adenophostin A (10^{-7} \text{M} in the pipette) (arrow) does not increase [\(Ca^{2+}\)] until Mn^{2+} is removed from the extracellular bath (bar interruption). **C**, experiment similar to A except for an injection of Ins(1,4,5)P_3 (right arrow) performed during the course of adenophostin A-induced \(Ca^{2+}\) influx. Ins(1,4,5)P_3 causes a transient increase in [\(Ca^{2+}\)], that is due to the release of intracellular \(Ca^{2+}\), since it occurs despite the presence of extracellular Mn^{2+} (bar).

Predicted, this current is caused by \(Ca^{2+}\) influx, since it can be blocked by either adding Mn^{2+} (n = 9) or Ni^{2+} (n = 7) to the extracellular bath or by decreasing bath [\(Ca^{2+}\)] (n = 4). The absence of a fast initial component of the response suggested that threshold concentrations of adenophostin A did not release intracellular \(Ca^{2+}\). To test this possibility further, we injected adenophostin A in the continued presence of Mn^{2+} or Ni^{2+}. As the example in Fig. 4B shows, adenophostin A did not elicit a response in the presence of Mn^{2+} in the bath, whereas subsequent removal of the Mn^{2+} confirmed that adenophostin had stimulated \(Ca^{2+}\) influx (n = 3). We also considered the possibility that we failed to observe intracellular \(Ca^{2+}\) release because it did not yield a sufficiently high [\(Ca^{2+}\)] to stimulate the \(Ca^{2+}\)-gated Cl\^\,- channels. However, the smallest possible increase in [\(Ca^{2+}\)], caused by an inositol phosphate is higher than the threshold [\(Ca^{2+}\)], required to open the Cl\^\,- channels (29, 31). Moreover, the absence of an initial release of intracellular \(Ca^{2+}\) implied that adenophostin A had not depleted the Ins(1,4,5)P_3-sensitive \(Ca^{2+}\) stores. To verify this prediction, we injected a low concentration of adenophostin A, blocked the resulting \(Ca^{2+}\) influx with Mn^{2+}, and then injected Ins(1,4,5)P_3. As shown in Fig. 4C, injection of Ins(1,4,5)P_3 during adenophostin-stimulated \(Ca^{2+}\) influx causes a transient release in intracellular \(Ca^{2+}\) (n = 10). These results indicate that adenophostin A can stimulate \(Ca^{2+}\) influx without emptying the oocyte's Ins(1,4,5)P_3-sensitive \(Ca^{2+}\) stores. These results also argue against adenophostin A acting as an ATP inhibitor to cause \(Ca^{2+}\) influx: if adenophostin A inhibited the \(Ca^{2+}\) ATPases, then we would have expected the Ins(1,4,5)P_3-sensitive intracellular \(Ca^{2+}\) stores to be empty, and they were not. Furthermore, we could not cause \(Ca^{2+}\) influx with other purine compounds expected to inhibit ATPases, such as ADP (10 mM in the pipette, n = 5) or ATP/3S (10 mM in the pipette, n = 6).

Given that adenophostin A has an extremely high affinity for the InsP_3R and that it cross-desensitizes with Ins(1,4,5)P_3 for the release of intracellular \(Ca^{2+}\), our working hypothesis was that adenophostin A acted through the InsP_3R to cause \(Ca^{2+}\) influx. This hypothesis predicted that adenophostin A and Ins(1,4,5)P_3 should stimulate a common \(Ca^{2+}\) entry pathway. To test this prediction, we first injected a high concentration of Ins(1,4,5)P_3 (10^{-4} \text{M} in the pipette). When \(Ca^{2+}\) influx reached its maximum, we injected adenophostin A (10^{-7} \text{M}). As shown in Fig. 5A, adenophostin A caused \(Ca^{2+}\) influx to return to the maximal value that had been reached with Ins(1,4,5)P_3 alone but not to exceed this value (n = 4). This lack of additivity is consistent with Ins(1,4,5)P_3 and adenophostin A ultimately stimulating a common \(Ca^{2+}\) entry pathway. Contrary to the lack of additivity for \(Ca^{2+}\) influx, the working hypothesis predicted that adenophostin A and Ins(1,4,5)P_3 would act additively to release intracellular \(Ca^{2+}\). Microinjections of adenophostin A in concentrations sufficient to cause \(Ca^{2+}\) influx, but below the threshold for \(Ca^{2+}\) release, lowered the threshold for Ins(1,4,5)P_3-induced \(Ca^{2+}\) release (Fig. 5B, n = 6). The working hypothesis also predicted that heparin, which prevents Ins(1,4,5)P_3 (32) and adenophostin A (9) from binding to the InsP_3R, should prevent adenophostin A from inducing \(Ca^{2+}\) influx. When we preinjected oocytes with heparin (10 mg/ml in pipette, 30-nl injection volume), adenophostin A (10^{-7} \text{M}) no longer stimulated \(Ca^{2+}\) influx (n = 5, Fig. 5C). Although heparin could prevent \(Ca^{2+}\) influx through other mechanisms, our aggregate data nevertheless suggest that adenophostin A binds to the InsP_3R to stimulate \(Ca^{2+}\) influx.

Despite evaluating 47 of the 64 possible positional isomers, we have not encountered an inositol phosphate that stimulates \(Ca^{2+}\) influx exclusively (30). Instead, all of the inositol phosphates, including Ins(1,4,5)P_3, released intracellular \(Ca^{2+}\) before causing \(Ca^{2+}\) influx (22). The most obvious structural difference between adenophostin A and Ins(1,4,5)P_3 is that the former possesses a large adenosine 2'-phosphate moiety. We therefore asked if this moiety was responsible for adenophostin A's unique ability to preferentially stimulate \(Ca^{2+}\) influx. After establishing that d-glucose (n = 3) and glucose 1,6-diphosphate (n = 3) were inactive, we injected the polyphosphorylated d-glucose derivative ADAN 1 (11), which also possesses the glucose 3,4-bisphosphate moiety of adenophostin A (Fig. 1C). When injected in high concentrations, ADAN 1 (10^{-4} \text{M} in the pipette, n = 6) caused a biphase \(Ca^{2+}\) signal similar to that of
adenophostin A (Fig. 6A). However, when injected in threshold concentrations (10^{-6} M in the pipette), ADAN 1 did not behave like adenophostin A; it did not cause Ca^{2+} influx. Instead, ADAN 1 behaved like Ins(1,4,5)P_3, causing an oscillatory release of intracellular Ca^{2+} (Fig. 6B). The results with ADAN 1 suggest that the glucose 3,4-bisphosphate moiety of adenophostin A is sufficient to release intracellular Ca^{2+} but that the adenosine 2'-phosphate moiety is required for adenophostin A to preferentially stimulate Ca^{2+} influx. However, we do not think that the adenosine 2'-phosphate moiety is sufficient to...
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Adenophostin A stimulates Ca\(^{2+}\) influx, because the following compounds, which form an increasing part of the moiety, neither stimulated Ca\(^{2+}\) release nor elicited Ca\(^{2+}\) influx: d-ribose (n = 3), adenine (n = 3), adenosine (n = 4), and adenosine 2'-phosphate (n = 6).

Using a small phosphorylated polar compound, adenophostin A discloses some of the key properties attributed to the CIF partially purified from Jurkat cells (6, 7, 33). Like adenophostin A, CIF stimulates Ca\(^{2+}\) influx through the InsP\(_3\)R. In contrast to some studies showing that adenophostin A stimulates Ca\(^{2+}\) release in isolated heart, adipocytes, and smooth muscle, we find that adenophostin A stimulates Ca\(^{2+}\) influx without affecting the release of intracellular Ca\(^{2+}\). This is consistent with the following compounds, which neither stimulated Ca\(^{2+}\) influx: D-ribose (6), and adenophostin A is not (7). Thus, if CIF and adenophostin A both interact with the InsP\(_3\)R, they may do so through different mechanisms. Also, CIF was found to be active when added extracellularly (6), and adenophostin A is not (6, Fig. 5D).

In summary, our results suggest that adenophostin A can stimulate Ca\(^{2+}\) influx without depleting the Ins(1,4,5)P\(_3\)-sensitive intracellular Ca\(^{2+}\) stores. Although definitive proof must await a specific InsP\(_3\)R binding inhibitor, our results also suggest that adenophostin A stimulates Ca\(^{2+}\) influx by binding to an InsP\(_3\)R. When considered along with the recent finding that overexpression of type 3 InsP\(_3\)R markedly increases the magnitude of Ca\(^{2+}\) influx without affecting the release of intracellular Ca\(^{2+}\) (35), our results raise the possibility that the InsP\(_3\)R influences Ca\(^{2+}\) influx through mechanisms that extend beyond its ability to release intracellular Ca\(^{2+}\).

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