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Feedback Regulation of ATP-induced Ca^{2+} Signaling in HL-60 Cells

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In HL-60 cells, extracellular ATP increases intracellular Ca^{2+} ($[Ca^{2+}]_i$) in a concentration-dependent manner with the maximal response occurring around 10 μM. However, above the maximal responsive concentration ATP elicits different patterns of Ca^{2+} signaling. While the initial $[Ca^{2+}]_i$ increase is similar over a range of 30 μM, 100 μM, and 300 μM ATP, the rate of the return to basal $[Ca^{2+}]_i$ level is faster in cells treated with higher concentrations of ATP. This probably results from differences in Ca^{2+} influx rather than Ca^{2+} release, since the influx of the unidirectional Ca^{2+} surrogates Ba^{2+} and Mn^{2+} also exhibit similar responses. Furthermore, while 300 μM ATP had an inhibitory effect on the thapsigargin-induced capacitative Ca^{2+} entry, 30 μM ATP potentiated the response. However, the inhibitory action of 300 M ATP was blocked by protein kinase C (PKC) inhibitors, such as GF 109203X and chelerythrine, and the potentiating action of 30 μM ATP was blocked by protein kinase A (PKA) inhibitors, H89 and Rp-cAMPS. The PKC inhibitors also slowed the decay rate of the Ca^{2+} response induced by 300 μM ATP, and the PKA inhibitors increased it when induced by 30 μM ATP. The variation in the decay rate may be dependent on the difference between activating PKC and PKA according to the concentration of ATP, since 30 μM ATP activates only PKA, while 300 μM ATP activates both kinases. Taken together, these data suggest that the changes in the ATP-induced Ca^{2+} response result from differential modulation of ATP-induced capacitative Ca^{2+} entry by PKC and PKA in HL-60 cells.