proceedings

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Extended Abstract

Design and Synthesis of a cADPR Mimic as a Novel Tool for Monitoring the Intracellular Ca^{2+} Concentration †

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† Presented at the 1st International Electronic Conference on Biomolecules: Natural and Bio-Inspired Therapeutics for Human Diseases, 1–13 December 2020; Available online: https://iecbm2020.sciforum.net/.

Cyclic ADP-ribose (cADPR, **1**, Figure 1) is a naturally occurring metabolite of NAD^+ capable of mobilizing Ca^{2+} ions from intracellular stores. It was firstly isolated from sea urchin egg extract, but it was later established that it is also produced in many other mammalian cells, including pancreatic β-cells, T-lymphocytes, smooth and cardiac muscle cells, and cerebellar neurons, acting as a Ca^{2+}-mobilizing agent. For this activity, cADPR has been classified as a second messenger that, by activating the ryanodine receptors of the sarcoplasmatic reticulum, is able to mobilize the calcium ions from intracellular stores. cADPR is involved in many physiological processes related to variation in the Ca^{2+} concentration, such as synaptic homeostasis in neurons as well as fertilization and cellular proliferation. This cyclic nucleotide, characterized by a very labile glycosidic bond at N1, is also rapidly hydrolysed in neutral aqueous solutions to inactive ADP-ribose. Matsuda and co-workers [1] were the first to synthesize new analogues of cADPR in which the adenine base is replaced by a hypoxanthine ring. This kind of modification produced the cyclic inosine diphosphate ribose (cIDPR), which proved to be stable in hydrolytic physiological conditions and showed significant Ca^{2+} mobilizing activity. Many modifications regarding the northern and southern ribose, as well as the purine base of cADPR, have been proposed so far. In our laboratories, we have synthesized several analogues of cIDPR [2–7]. In particular, the analogue with the northern ribose replaced by a pentyl chain (cpIDP) showed interesting Ca^{2+} mobilizing activity on the neuronal PC12 cell line [2]. Starting from these results, we report here the synthesis of the novel analogue **2**, in which the "northern" ribose of cIDPR is replaced by a 2″,3″-dihydroxy pentyl chain. The effect of the presence of the diol moiety on the intracellular Ca^{2+} release will be assessed in due course.

Citation: D'Errico, S.; Borbone, N.; Falanga, A.P.; Marzano, M.; Terracciano, M.; Greco, F.; Piccialli, G.; Oliviero, G. Design and Synthesis of a cADPR Mimic as a Novel Tool for Monitoring the Intracellular Ca^{2+} Concentration. *Proceedings* **2021**, *83*, 5. https://doi.org/10.3390/IECBM2020-08578

Published: 30 November 2020

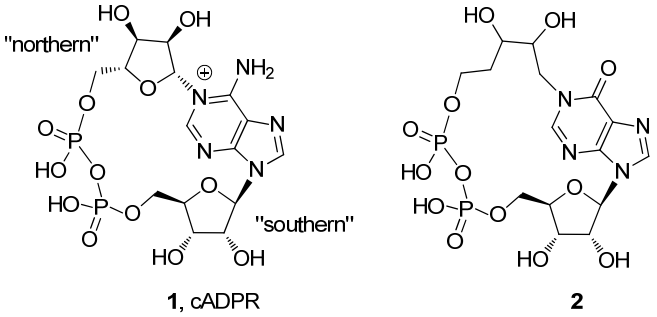

Figure 1. The structures of cADPR (**1**) and of the novel analogue **2**.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available in Supplementary Material

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