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RESPONSE TO COMMENT ON GIACCO ET AL.

GLP-1 Cleavage Product Reverses Persistent ROS Generation After Transient Hyperglycemia by Disrupting an ROS-Generating Feedback Loop. Diabetes 2015;64:3273–3284

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In their brief but disappointing letter, Ceriello and Genovese (1) erroneously describe the novel mechanism identified in the recent article by myself and my coauthors as "descriptive" (2). In fact, the article's novelty is that it is entirely mechanistic. This mechanism, which is the central point of the article, explains how hyperglycemic spikes too brief to affect the HbA_{1c} value cause continued overproduction of reactive oxygen species (ROS) for days of subsequent normal glucose homeostasis by activating a multicomponent feedback loop. This loop maintains a stable left shift of the glucose concentration–ROS dose-response curve for days of subsequent normal glycemia. Disruption of the feedback loop by normalizing any of the individual components rapidly normalizes multiple persistent posthyperglycemic abnormalities. These data suggest that hyperglycemic spikes high enough to activate persistent ROS production during subsequent periods of normal glycemia but too brief to affect the HbA_{1c} value may help explain the 89% of diabetes complications risk not captured by HbA_{1c} (3,4).

The glucagon-like peptide 1 (GLP-1) cleavage product GLP-1(9-36)^{amide} also reversed the persistent left shift, normalizing persistent overproduction of ROS and its pathophysiologic consequences, providing one example of potential novel therapeutic agents targeting the multicomponent feedback loop.

Our article was reviewed by three experts in the field, and none of these experts said anything about the self-citations contained in the letter by Ceriello and Genovese (1). This should not be surprising because none of these support their claim that the mechanism we have discovered is "just another piece of an already long story" (1). In less than 300 words, they demonstrate that they have failed to understand the central subject of our article, and they even manage to confuse the GLP-1 receptor–independent biologic actions of GLP-1(9-36)^{amide} with the GLP-1 receptor–dependent actions of intact GLP-1 (5).

If the concern of Ceriello and Genovese in writing is truly a scientific one, we cordially invite them to discuss substantive questions together, in the open spirit that defines the scientific enterprise. It is possible, however, that their comment may be just another example of the Dunning-Kruger effect (6).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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