Does des-acyl ghrelin improve glycemic control by decreasing acylated ghrelin levels?

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Dear Editor,

In a recent paper on infusion of des-acyl ghrelin (DAG) in type 2 diabetic subjects, Özcan *et al.* (1) reported improvement in glycemia accompanied by a decrease in circulating acyl ghrelin (AG) levels. While the results clearly demonstrate the anti-diabetogenic potential of DAG, they also bring to mind Dr Tong's DAG infusion studies (2) in which we did not observe a decline in AG. We note that in (1), a C-terminal capture sandwich assay was used for ghrelin assay and, in (2), we used an N-terminal AG-specific capture antibody. It is therefore possible that the differences between the two studies are due to the specificity of the assay methodology. In particular, when high concentrations of DAG are present, they may compete for capture at the C-terminal assay antibody and interfere with the detection of AG, which is not the case if an N-terminal capture assay is used.

In (1) and (2), DAG was infused at pharmacological doses such that circulating levels exceeded those of AG by 500- to 1000-fold. In (1), the units for DAG concentrations during the infusion appear to be erroneous: they were listed as pg/ml but were probably meant to be ng/ml. Therefore, depending on the assay parameters, and more specifically on the binding capacity of the capture antibody, competition at the C-terminal antibody is possible. In (2), no suppression of AG was observed during infusion of DAG producing similar levels and time course to those reported in (1) (see Fig. 1). One notable difference is that overweight type 2 diabetic patients were studied in (1), while non-obese healthy subjects were studied in (2).

This problem of assay capture competition has been previously reported in the supplement of our paper

Figure 1

Plasma AG levels during DAG infusion. Data from ref.

(1) (A) and ref. (2) (B). Panel A represents an overnight infusion while panel B is only 210 min, but ref. (1) also reports similar AG suppression at 240 min.

characterizing our own ghrelin assay (3) and is the reason why we have always used a specific N-terminal AG capture antibody. Similarly, in the AG infusion studies in (2), we found that, when assaying DAG with a C-terminal capture antibody, the high levels of AG did inhibit the detection of DAG. We have therefore switched to N-terminal-specific capture for the DAG assay as well (2).

In conclusion, competition by pharmacological levels of DAG for the C-terminal capture antibody in the AG assay used in (1) may produce an artifact of AG suppression by DAG not observed in studies using specific N-terminal AG capture antibody. Therefore, while the results on improvement in glycemia remain extremely interesting and important, they are not necessarily due to suppression of AG by DAG.

References

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