Relationship Between Reduction in Food Intake and Amelioration of Hyperglycemia by Oral Vanadate in STZ-Induced Diabetic Rats

The insulin-like effects of vanadium compounds in streptozocin (STZ)-induced diabetic rats, including the amelioration of hyperglycemia, have been documented by a number of investigators (1–3). However, in the January issue of *Diabetes*, Malabu et al. (4) reported that the antihyperglycemic action of vanadate in the STZ-induced diabetic rat is attributable entirely to its suppression of feeding. Although in a recent study we also demonstrated that the "positive" effects of vanadate or vanadyl treatment (via drinking water) on the amelioration of hyperglycemia in STZ-induced diabetic rats might be secondary to the decreases observed in food and fluid intake (5), we disagree with some of the conclusions drawn by Malabu et al. (4). Because Malabu et al. (4) were previously unable to lower glycemia in STZ-induced diabetic rats without causing unacceptable side effects when vanadate was added to drinking water, in their recent study, vanadate was administered by gavage at doses of 2.94 $mg \cdot kg^{-1} \cdot day^{-1}$ for 3 weeks without observing severe toxic effects during vanadate treatment. These data disagree with our previous studies in which no improvement of glucose homeostasis in STZ-induced diabetic rats was found when sodium metavanadate was given by gavage for 28 days at doses of 2.5, 5, 10, and 20 $mg \cdot kg^{-1} \cdot day^{-1}$ for 4 weeks. Moreover, remarkable signs of vanadium toxicity were observed at all dose levels, including a significant mortality rate (50% at 2.5 $mg \cdot kg^{-1} \cdot day^{-1}$ vs. 12.5% in the control group) (6). Also, diabetic rats given vanadyl sulfate by gavage were not characterized by amelioration of hyperglycemia, whereas in contrast, several signs of vanadium toxicity could be observed (7). The reasons for the discrepancies between the results of Malabu et al. (4) and our results are unclear.

On the other hand, when Malabu et al. (4) compared their data with those from other studies, they stated that some discrepancies in side effects or efficacy could be attributable to the use of a variety of vanadium compounds that may differ in their solubility, bioavailability, and intrinsic toxicity. These authors seem to be unaware of the results of previous investigations that showed that improvement of glucose homeostasis by oral vanadium (metavanadate, orthovanadate, and vanadyl) administration to STZ-induced diabetic rats is accompanied by marked negative side effects that are independent of the form of vanadium used (8,9). Moreover, vanadium accumulated in a dose-dependent way in all of the tissues analyzed, which would imply an additional risk of vanadium toxicity (5–9).

In summary, although we agree with Malabu et al. (4) that the antihyperglycemic action of vanadate is attributable, at least in part, to the suppression of feeding, it should be taken into account that a number of studies showing improvement in the diabetic state by vanadium treatment via drinking water also report correction of plasma lipid levels, very significant improvement in glucose homeostasis, and reduced development of diabetic complications. Consequently, the antidiabetic action of vanadium compounds seems to be well established. However, because of the toxic effects derived from chronic vanadium administration and tissue accumulation of the element, coadministration of vanadium compounds with chelating agents has been suggested (10,11).

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