Insulin-Like Effects of Vanadium Pentoxide (V_2O_5) on Glucose Consumption in Primary Human Fibroblasts

Abstract

Mt. Fuji subsoil water contains high levels of vanadium pentoxide (V_2O_5) and seems to be effective in diabetes mellitus therapy. Therefore, the insulin-like effects of V_2O_5 were investigated in primary human fibroblasts. To evaluate the insulin-like effects, glucose consumption in culture medium and cell growth based on cellular protein content were measured, and cytotoxic effects on cells were assessed. In addition, vanadium ions were used for comparison with vanadium pentoxide in the same experimental system. A significant acceleration of glucose consumption was observed at 250-5,000µg/l vanadium pentoxide, and almost the same acceleration was observed for 1,000µg/l vanadium ions. However, vanadium pentoxide as well as vanadium ions at 1,000-5,000µg/l had a significant cytotoxic effect. Thus, vanadium pentoxide at low concentrations (100-500µg/l) seems to have a potential role in diabetes mellitus therapy.

Keywords: Glucose; Diabetes mellitus therapy; Cytotoxic effects; Vanadium pentoxide; V_2O_5

Short Communication

Volume 5 Issue 4 - 2017

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Received: July 14, 2017 | **Published:** July 25, 2017

Introduction

The prevalence of diabetes mellitus (DM) is increasing throughout the world. If left untreated, DM can lead to a complication of diabetes. It is well known that vanadium compounds have insulin-like effects in vivo [1-8] and *in vitro* [9,10], but medicinally-useful vanadium compounds have not yet been developed. One of reasons is that vanadium is cytotoxic at high concentrations. Kistuta found that subsoil water from Mt. Fuji, Japan, containing vanadium pentoxide (V_2O_5) seemed to be effective in diabetes mellitus therapy [11]. Recently, we investigated the effects of vanadium ions and Mt. Fuji subsoil water on glucose consumption in established cultured cell lines [12], and it was clarified that Mt. Fuji subsoil water may have potential for diabetes mellitus therapy [12]. The present study was designed to confirm this possibility, using primary human fibroblasts, because it has been generally thought that primary cultured cells are more sensitive toward various chemical compounds than the established cell lines used previously.

Materials and Methods

Cultured medium was prepared by dissolving RPMI-1640 powder (GIBCO, Invitrogen Corporation, Gland Island, NY, USA) into Milli-Q water. Vanadium pentoxide (V_2O_5) and vanadium standard solution (V 1000), consisting of metal ions for atomic absorption spectroscopy, in 0.2M HCl and 0.5 M HNO_3 were purchased from Wako (Tokyo, Japan). Primary human fibroblasts (NHDF) were purchased from Kurabo (Tokyo, Japan). The cells were initially cultured to amplify cell numbers in a manufacture recommended medium (FibroLife® S2 LifeFactor), which contains 7.5mM L-glutamine, 5ng/ml hFGFβ, 5µg/ml insulin, 50µg/ml ascorbic acid, 1µg/ml hydrocortisone, and 2% (v/v) fetal bovine serum. Cells were cultured in RPMI-1640 for subsequent experiments. The amplified cells were dispersed with 0.3% trypsin, and then inoculated into 24-well plates. After cells reached confluence, they were cultured in RPMI-1640 medium in the presence or absence of vanadium compounds.

The glucose concentration in the medium was measured according to the previously reported method [12], using a Glucose Assay Kit purchased from Wako (Tokyo, Japan). Cellular protein concentrations were assessed by the Bradford method [13].

Results and Discussion

It was reported that the vanadium compound in the Mt. Fuji subsoil water is vanadium pentoxide (V_2O_5) [11]. In fact, Mt. Fuji subsoil water that contained vanadium oxide also accelerated glucose consumption in established cell lines [12]. Water bottled at Mt. Shasta in California, USA, also contains vanadium (50.4µg/l), and accelerated glucose consumption [12]. However, as this vanadium concentration was lower than that in the Mt. Fuji subsoil water (56-144µg/l), its effect on glucose consumption was lower than that of the Mt. Fuji water [12]. These results clearly indicate that the vanadium concentration in the water sample is important for the insulin-like effects, and that the effect is independent of where the water is collected. However, although there are many volcanos which produce or produced basalt containing vanadium compounds as lava, water samples drawn from their vicinities do not always possess insulin-like effects because of different vanadium concentrations. These different vanadium concentrations seem to be based on the time for which rain or snow water has contacted with the basalt, because of low water solubility of vanadium compounds. Thus, the Mt. Fuji subsoil water seems a very rare natural product.

The effect of V_2O_5 on glucose consumption was investigated using NHDF. V_2O_5 at 500µg/l significantly accelerated glucose consumption, and the effect almost plateaued at 500-1,000μg/l (Figure 1A). Similar effects were observed when using 1,000μg/l vanadium ions with NHDF, although the molar concentrations differed slightly between vanadium ions and V_2O_5. The results were consistent with those obtained from rat fibroblasts (Py-3Y1-S2) [12].

Vanadium oxide as well as vanadium ions at concentrations >1,000μg/l showed great cytotoxicity on NHDF (Figure 1B). In our previous study [12], using established cell lines such as Py-3Y1-S2 and human esophageal cells (ET-13), serious cytotoxic effects were not observed even at 1,000μg/l vanadium ions, while vanadium ions at 200-400μg/l accelerated cell growth. Thus, primary human fibroblasts are more sensitive to high vanadium concentrations.

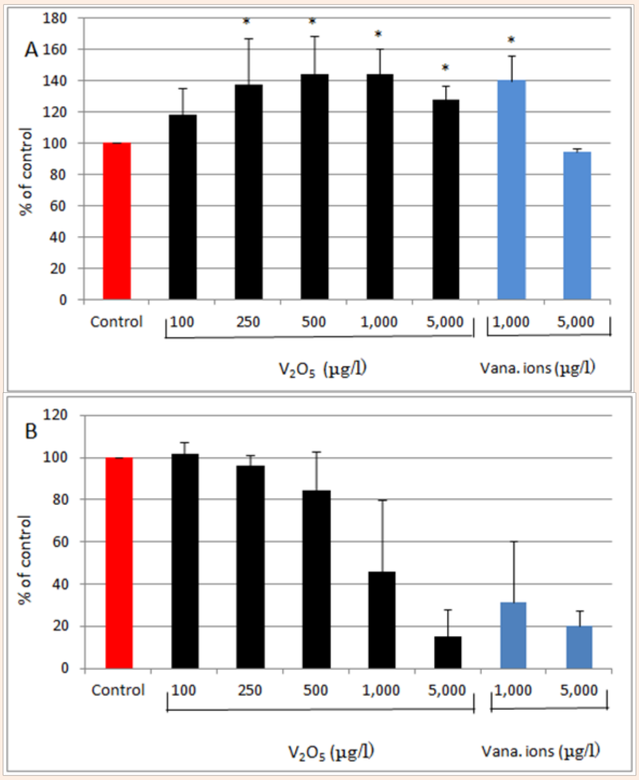

Figure 1: Effect of vanadium pentoxide on glucose consumption (A) and cellular protein levels (B) of primary human fibroblasts. Data are expressed as the mean ±S.D. of 3-4 separate experiments using 2-4 wells. *p < 0.05.

Conclusion

Vanadium pentoxide (V_2O_5) at 100-500μg/l has a potential future role in diabetes mellitus therapy.

Acknowledgment

We thank James Allen, DPhil, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

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