Outline of “The Wonders of Vanadium”

1. Multiple Physiological Actions

The following wealth of physiological actions have been confirmed for pentavalent vanadium ion water（V^{5+} water）.

A. Immediate Physiological Action

(1) Diuretic action → improves edema

(2) Promotes sweating and thermogenesis → improves sensitivity to cold, promotes metabolic turnover, promotes energy consumption

B. Early Onset Physiological Action

(3) Improvement of atonic constipation（covers approx. 60%）

(4) Uric acid reduction → improves gout, suppresses onset

C. Physiological Action One Month Before/After

(5) Reduces blood triglycerides (elevated HDL) → improves high and moderate blood triglycerides, blood pressure, improves insulin resistance that causes high and moderate blood triglycerides, prevents circulatory diseases

(6) Reduces blood glucose → improves diabetes, a cause of high and moderate blood triglycerides (50-60% total recovery)

(7) Reduces blood pressure → approx. 15% reduction confirmed in most patients.

(8) Improves the symptoms and inhibits the progression of Alzheimer’s-like cognitive impairment → Symptom improvement was striking, but only seen in 3 cases.

2.Principle (Mechanism of action)

The biological activities of V^{5+} ion are explained by the following integrated action mechanism without any contradictions, which arises from inhibition of Na^+, K^+-ATPase by free V^{5+} ion, and leads to increase of Ca^{2+} concentration in subcellular organelles such as mitochondria, endoplasmic reticulum and nuclear.

A. Principle

(1) The species of free V^{5+} ion is contained in the ingested vanadium ion water at about 35%, and V^{5+} inhibits the function of Na^+, K^+-ATPase in the cell membrane by competitively binding to the phosphate biding site on the enzyme. Therefore, an intake of the vanadium ion water in a certain level inhibits the function of the enzyme to excrete Na^+ from the cell, and to take K^+ into the cell. (Cantley happened to discover it in 1977.)

(2) Since extracellular Na^+ concentration is approximately 30 times higher than that of inside, Na^+ flows into the cell by osmotic pressure, and intracellular Na^+ concentration increases. Then the membrane potential of the cell gradually elevates from the resting state (-100mV to -70mV) to the depolarized state, which leads to opening of membrane potential-dependent Ca^{2+} channel, and the extracellular Ca^{2+} ion, of which concentration is one million times higher than that in the cell, flows into the cell. Since the higher level of Ca^{2+} concentration at 10^{-4} to 10^{-3} M is cytotoxic, Ca^{2+} ions are absorbed into mitochondria and endoplasmic reticulum in a moment. At the same time, the increased Ca^{2+} inactivates the channel, and the gate will be closed.

(3) Increased Na^+ is then excreted from the cell by Na^+, Ca^{2+}-pump activated by Ca^{2+} ion flow. Although the Ca^{2+} pump, which actively transports Ca^{2+} from inside to outside of the cell by using energy of ATP, exists in the cell membrane, this is naturally inhibited by V^{5+} ion, and the amount of Ca^{2+} transport decreases.

(4) Through the foregoing actions, the Ca^{2+} concentration in nucleus linked to mitochondria and endoplasmic reticulum increases. All of the biological activities of V^{5+} water, which we confirmed as described above, can be explained by the increase of Ca^{2+} concentration in three subcellular organelles[(1), (10) - (22)].

3.Detailed mechanisms of biological activities

(1) Diuretic action

Inhibition of Na^+, K^+-ATPase activity suppresses Na^+ resorption at distal tubule of renal nephron, thereby accompanying blood pressure lowering as well as diuretic action in the same manner of thiazide and loop diuretic[23), (24)].

(2) Enhanced pyrogenicity and sweating, Improvement of feeling of cold

When Ca^{2+} concentration in mitochondria is elevated, several enzymes of citric acid cycle are activated, and energy production increases. In a thermogenic tissue such as brown adipose tissue containing uncoupling protein-1(UCP-1), the produced energy is almost consumed as heat. In addition, there are several UCP family proteins for heat production, such as UCP-2 (in white adipose tissue, skeletal muscle, spleen, intestine and so on), UCP-3 (mainly in skeletal muscle), UCP-4 and UCP-5 (in brain), by which the living organisms can maintain their body temperatures at a very narrow constant range[25)].

(3) Improvement of atonic constipation

A fundamental cause of atonic constipation of aged people is decrease of intestinal peristaltic movement. The intestinal peristaltic movement carries ingested foods by the repeated contractions of longitudinal muscle and circular muscle, and finally excretes stool. According to the research by Kuemmele et al., it is reported that the longitudinal muscle contracts by Ca^{2+} release from endoplasmic reticulum responding on ADP-ribose, and the circular muscle contracts by Ca^{2+} release on inositol trisphosphate (IP3). Improvement of atonic constipation can be explain by this increase of Ca^{2+} concentration or release from endoplasmic reticulum caused by vanadium ion (V^{5+}) water[27), (28), (29)].

(4) Symptom improvement and progression control of Alzheimer type dementia (AD) A thesis about dementia symptoms and degenerative nerves of Alzheimer disease are published by Harvard Medical School research group of neurological disease on Nature (issued on July 2009). According to the study, the main cause on early stage of dementia symptoms and degenerative nerves of Alzheimer disease are on inactive presenilin of presynaptic terminal. It is considered that the obstruction of Ca^{2+}intracellular influx from voltage-gated calcium channels and the depletion of Ca^{2+}on endoplasmic reticulum are deeply related.

(5) Lowering of blood triglyceride

The lowering of blood triglyceride is a principal action of total metabolic improvements caused by pentavalent vanadium ion (V^{5+}) water. At first, when Ca^{2+} concentration in mitochondria is elevated, biologically activities of many enzymes in the mitochondria are significantly increased, and further enhances fatty acid metabolism such as β-oxidation. Some kinds of fatty acids, and fatty acid derivatives behave like a ligand, and activate nuclear receptors, peroxisome proliferator-activated receptors (PPARs). PPARs are transcription factors having DNA binding regions and ligand binding regions. Forty eight PPARs are found in human, and PPARδ has been discovered recently to be particularly important in lipid metabolism. PPARα is mainly expressed in liver, PPARγ is expressed in adipose tissue, and PPARδ is ubiquitously expressed in skeletal muscle etc. Activation of these transcription factors is dependent on Ca^{2+} concentration as is shown by the mechanism of fertilization and ovulation. Since the inner side of nuclear membrane is directly connected with the lumen of endoplasmic reticulum (ER), increase of Ca^{2+} concentration of ER reflects the activation

of PPARs. Ca^{2+} ion in the inner side of nuclear membrane flows to nucleoplasm by various routs via Ca^{2+} ATPase or IP3, and regulates the transcription. The activation of PPARα accelerates β-oxidation of fatty acid in the liver, suppresses triglyceride synthesis, and reduces the secretion of VLDL from the liver, which leads to lowering of blood triglyceride. Further, an agonist of PPARγ, fibrate, has been widely used over 20 years as a hypotriglyceridemic drug. PPARγ is a primary regulator of adipocyte differentiation, and enhances storage of lipid in the mature adipocyte by expressing master genes in the differentiation stage. An agonist of PPARγ, a thiazolidine derivative, is also widely used in the world as an anti-insulin resistant drug. PPARδ is known to activate the transcription of most genes of fatty acid catabolism such as transfer, activation, β-oxidation, and uncoupling protein (uCP) in skeletal muscle, enhance total lipid metabolism, and improve insulin resistance and abnormal glucose tolerance. The expression of PPARδ increases by continuous endurance exercise. We observed that muscular subjects are more easily activated by vanadium ion water than those of fragile subjects. Taken together, it is speculated that the activation of the PPARδ significantly contributes to the improvement of lipid metabolism by vanadium ion water[(30) - (37)].

(6) Improvement of diabetes derived from hypertriglyceridemia

Since diabetes is a common disease caused by a variety of factors such as genetic polymorphisms and lifestyles, insulin treatment does not necessarily result in good outcomes. Hyperglycemia based on the onset of insulin resistance derived from hypertriglyceridemia can be greatly improved by the above lowering of blood triglyceride. In addition, some serious cases of weak insulin secretion due to the long-term administration of sulfonylurea agent can be recovered to the normal insulin level by the lowering of blood triglyceride and regeneration of beta-cell due to the increase of Ca^{2+}

concentration in the endoplasmic reticulum caused by vanadium ion (V^{5+}) water[16, 38 – 43].

(7) Lowering of blood pressure

Excretion of Na^{+} based on diuretic effect by vanadium ion (V^{5+}) water appeared to be primary cause of blood pressure decrease. Other factors are also important effect, such as decrease of fat in the blood vessel and increase of motion effect of blood vessel muscle[44, 45].

(8) Improvement or retarded progression of dementia

Despite the small number of clinical results, Zhang et al. has been reported that the dysfunction of intracellular Ca^{2+} release in presynaptic terminals might be an early pathogenic event leading to dementia and neurodegeneration in Alzheimer's disease. The enhancement of store and release of intracellular Ca^{2+} by vanadium ion (V^{5+}) water may have an important role for improvement or retarded progression of dementia[46].

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