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Insulinomimetic Activity of Vanadyl-Porphyrin Complexes

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Abstract:
Diabetes mellitus (DM) is one of the life style-related diseases as well as one of the widespread diseases in the world. DM is classified mainly into two types; type 1 insulin-dependent DM is associated with absolute insulin deficiency and type 2 non-insulin dependent DM is associated with lowering of insulin sensitivity in all organs, which ultimately follows absolute insulin deficiency. We first reported that vanadyl-cysteinemethylester complex with the $VO(S_2N_2)$ coordination mode is very useful in the treatment of streptozotocin (STZ)-induced type 1 diabetic rats by daily oral administrations in 1990. Since then, many types of insulinomimetic vanadyl complexes with different coordination modes around vanadyl, such as $VO(O_4)$, $VO(S_4)$, $VO(S_2O_2)$, $VO(S_2N_2)$ and $VO(N_2O_2)$ have been proposed, however, few complexes with the $VO(N_4)$ coordination mode have been examined. Recently, we found that meso-tetrakis({1-methylpyridinium-4-yl} porphyrinato)oxovanadium(IV), VOTMPyP, with the $VO(N_4)$ coordination mode, is a potential insulinomimetic vanadyl complex for the treatment of type 1 diabetic model STZ-rats in the presence of sodium ascorbate. This important finding promoted us to find more active insulinomimetic vanadyl-porphyrin complexes. In this study, we have synthesized, characterized and estimated *in vitro* insulinomimetic activity of the (protoporphyrinato IX) oxovanadium(IV), VOPP, and meso-tetrakis({4-sulfonatophenyl}porphyrinato) oxovanadium(IV), VOTPPS, complexes, comparing with those of previously proposed insulinomimetic VOTMPyP. VOTPPS was very stable in both 4% bovine serum albumin (BSA) and rat blood serum (RBS) for 48 h without ascorbate. The IC_{50} value, which is a 50% inhibitory concentration of the complex for FFA-release from the adipocytes, was estimated to be 488.3 ± 49.1 μM for VOTMPyP and 18.6 ± 13.0 μM for VOTPPS,

respectively. The EC_{50} value, which is a 50% enhancing concentration of the compound with respect to the maximal glucose-uptake concentration in epinephrine-treated adipocytes, was not detected for VOTMPyP, but found for VOTPPS as 46.3 ± 6.4 μM. The complex VOPP, which is insoluble in water, exhibited no *in vitro* insulinomimetic activity in the concentration range examined. Based on these observations, VOTPPS was proposed to be an insulinomimetic vanadyl porphyrin complex having a potential for treating insulin-dependent and noninsulin-dependent diabetic mellitus.

Key words: vanadyl-porphyrin, insulinomimetic, diabetes, rat adipocyte, free fatty acid, glucose-uptake

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