NEW VANADIUM-BASED MOLECULAR IMAGING PROBES FOR MAGNETIC RESONANCE IMAGING

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Abstract: We have developed a new vanadium-based contrast agent, *bis*(acetylacetonato)oxovanadium(IV) [$VO(acac)_2$], for magnetic resonance imaging. In separate experiments using 3T3-L1 adipocytes we have demonstrated that $VO(acac)_2$ enhances glucose uptake and tyrosine phosphorylation of the insulin receptor synergistically with insulin. In addition, it is taken up into cells through glucose transporters. We have further demonstrated that $VO(acac)_2$ has no adverse effect in rats after administration of a large dose. It's relaxivity is comparable to that of low molecular weight Gd^{3+}-complexes. Furthermore, it provided high-resolution T_2^*-weighted images of AT6.1 tumors in rats.

Introduction: Improved methods for early detection and accurate characterization of cancer are highly desirable for treatment of cancer. We developed a new magnetic resonance imaging (MRI) method for detecting cancer based on the use of a novel class of contrast agents that target insulin receptors and glucose transporters. Aggressive cancers are metabolically active glycolytically, resulting in increased uptake of glucose. An MRI contrast agent that enters in cells with high glycolytic activity could provide high-resolution *functional* images of tumor boundaries and internal structure.

Methods: To investigate the structural origins of the insulin-mimetic activity of VO^{2+}-chelates, namely $VO(acac)_2$ and *bis*(maltolato)oxovanadium(IV) [$VO(malto)_2$], we first determined the stability of the VO^{2+}-chelated compounds free in solution and complexed with serum albumins by application of EPR (electron paramagnetic resonance) and ENDOR (electron nuclear double resonance) spectroscopic methods. By employing cell biological techniques, we measured the influence of insulin and insulin-mimetic VO^{2+}-chelates on the uptake of 2-deoxy[1-^{14}C]glucose by 3T3-L1 adipocytes, and the effects of VO^{2+}-chelates on glycogen synthesis and glycogen synthase activity in cultured 3T3-L1 adipocytes. We have also performed *in vivo* MR imaging experiments with rats bearing highly invasive, metastatic AT6.1 tumors with 0.2 mM/kg of $VO(acac)_2$ as a contrast agent. Before MRI studies we monitored glucose level, heart rate, respiration, blood pressure, and blood gases after administration of a large dose (1 mM/kg) of $VO(acac)_2$ to ensure absence of short-term toxic effects.

Results: After incubation with 0.25 mM $VO(acac)_2$ in the presence of serum albumin 3T3-L1 adipocytes were carefully washed to remove extracellular vanadyl-chelate. Glycogen synthesis increased 20-fold in the washed cells, compared to a maximal 100-fold enhancement by 10 nM insulin. This suggests that $VO(acac)_2$ accumulated intracellularly. A high dose of $VO(acac)_2$ did not cause adverse reactions in rats either acutely, or 24 hrs after injection of $VO(acac)_2$. The relaxivity for $VO(acac)_2$ of 2.5 ± 0.2 $mM^{-1}s^{-1}$ is comparable to that of low molecular weight gadolinium complexes of 4.3 ± 0.2 $mM^{-1}s^{-1}$ at 4.7 Tesla. High MR images were obtained with $VO(acac)_2$ as a contrast agent. In the figure below, panel A illustrates MR images (3 slices) of a tumor prior to administration of $VO(acac)_2$; and panel B illustrates the difference between the post- and pre-contrast images of the same tumor. We compared these images with those obtained with Gd-DTPA in separate experiments. The results show that $VO(acac)_2$ provides excellent T_1 and T_2* contrast.

Discussion: The vanadium-based contrast agents discussed here have no adverse effect in rats. The preliminary biochemical, biophysical, and cell assay results suggest that VO^{2+}-chelates accumulate intracellularly and may be useful contrast agents that target insulin receptors and may be sensitive to the increased glycolytic metabolism of neoplasms. [Supported by a grant from the National Cancer Institute (CA089408)].