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BCH 410

QUESTIONS

1. Write a comprehensive note on the role of cisplatin as an anticancer agent
2. Write on the role of vanadium as an antidiabetic agent
3. Write on the role of selenium as an anticancer agent

ANSWERS

**CISPLATIN AS AN ANTICANCER AGENT**

Cisplatin was discovered fortuitously by Dr. Rosenberg in 1965 while he was examining the effect of electromagnetic field on bacterial cell growth. Since the active principle that inhibited bacterial cell division was identified to be cisplatin, he anticipated that it would also inhibit the proliferation of rapidly dividing cancer cells. Cisplatin was indeed demonstrated to possess antitumor activity in a mouse model and was first used in the clinical trial almost 30 years ago. Since its approval by the Food and Drug administration in 1978, cisplatin continues to be one of the most effective anticancer drugs used in the treatment of solid tumors.

Cisplatin has been used as a first-line therapy for several cancers, including testicular, ovarian, cervical, head, and neck and small-cell lung cancers either alone or in combination with other anticancer agents. It is also used as an adjuvant therapy following surgery or radiation. In addition to cisplatin, its analogs, such as carboplatin and oxaliplatin, are also currently being used in the clinic. However, patients who initially respond to cisplatin therapy often develop resistance to the drug during the course of the treatment.

The success of cisplatin therapy is compromised due to dose-limiting toxicity, especially nephrotoxicity as well as resistance by tumor cells to cisplatin. Cellular resistance to cisplatin could be either intrinsic or acquired. The clinically acquired resistance can be caused by decreased drug accumulation which includes reduced uptake or increased efflux of cisplatin, increased drug detoxification by cellular thiols, increased DNA repair or tolerance of cisplatin-damaged DNA and the ability of the cancer cells to evade cisplatin-induced cell death. Numerous studies have focused on the drug-target interactions, cellular pharmacology, and pharmacokinetics of cisplatin. Another active area of research has been to develop analogs of cisplatin to minimize toxicity and circumvent cisplatin resistance.

The antitumor activity of cisplatin is believed to be due to its interaction with chromosomal DNA. Only a small fraction of cisplatin, however, actually interacts with DNA and the inhibition of DNA replication cannot solely account for its biological activity. In addition, the efficacy of chemotherapeutic drugs depends not only on their ability to induce DNA damage but also on the cell's ability to detect and respond to DNA damage. Following DNA damage, cells may either repair the damage and start progressing through the cell cycle or if they cannot repair the damage, cells proceed to die. Cisplatin, like many other chemotherapeutic drugs, can induce apoptosis. Thus, the signaling pathways that regulate apoptosis have significant impact on deciding cellular responsiveness to cisplatin. There are many excellent reviews on cisplatin and its analogues.

**VANADIUM AS AN ANTIDIABETIC AGENT**

Compounds of the trace element vanadium have been shown to mimic insulin in *in vitro* and *in vivo* systems. These compounds have been found to exert anti-diabetic effects in rodent models of type 1 and type 2 diabetes mellitus as well as in a limited number of studies in human diabetic subjects. Thus, vanadium compounds have emerged as agents for potential use in diabetes therapy. However, treatment of diabetic animals with inorganic vanadium salts has also been associated with some toxic side-effects such as gastrointestinal discomfort and decreased body weight gain. In addition, vanadium salts have been reported to exert toxic effects on the liver and kidney. More recently, it was shown that organic vanadium compounds were much safer than inorganic vanadium salts and did not cause any gastrointestinal discomfort, hepatic or renal toxicity.

The increased plasma free fatty acid levels due to the deregulated lipolysis in adipocytes are considered as one of the major risk factors for developing type II diabetes. Vanadium compounds are well-known for their antidiabetic effects both on glucose and lipid metabolism, but the mechanisms are still not completely understood. There is a present study which suggests a mechanism for how vanadium compounds exert antilipolytic effects. It demonstrates that all the three vanadium compounds, bis(acetylacetonato)-oxovanadium(IV) (VO(acac)2), bis(maltolato)-oxovanadium(IV) (VO(ma)2) and sodium metavanadate (NaVO3), attenuated basal lipolysis in 3T3L1 adipocytes in a dose- (from 100 to 400 μM for VO(acac)2and VO(ma)2, 1.0 to 4.0 mM for vanadate) and time-dependent (from 0.5 to 4 h) manner using the glycerol release as a marker of lipolysis. In addition, the three compounds inhibited lipolysis to a different extent. Among them, VO (acac)2 (from 100 to 400 μM) exerted the most potent effect and reduced the lipolysis to ∼60–20% of control after 4 h treatment. The antilipolytic effects of vanadium compounds were further evidenced by a decrease of the levels of phosphorylated HSL at Ser660 and phosphorylated perilipin, which were counteracted by inhibitors of PI3K or Akt but not by an MEK inhibitor. This indicates that though both Akt and ERK pathways are activated by the vanadium compounds, only Akt activation contributes to the antilipolytic effect of the vanadium compounds, without the involvement of ERK activation. We previously demonstrated that VO(acac)2 can block cell cycle progression at the G1/S phase *via* a highly activated ERK signal in human hepatoma HepG2 cells. Together with this study, we show that similar activated pathways may lead to differential biological consequences for cancer cells and adipocytes, indicating that vanadium compounds may be used in the prevention and treatment of both diabetes and cancer.

**SELENIUM AS AN ANTICANCER AGENT**

It is generally accepted that selenium (Se) plays an important role in maintaining equilibrium of a healthy organism. It also participates in processes related to carcinogenesis such as inhibition of tumor formation and regression. Scientific data accumulated so far using experimental animal models and from clinical studies devoted to investigating the effects of Se confirm strong relationship or correlation between Se supplementation and tumor frequency of prostate, lungs, liver and colon. Many of these experimental models demonstrated that inorganic and organic [selenium](https://www.sciencedirect.com/topics/medicine-and-dentistry/selenium" \o "Learn more about Selenium from ScienceDirect's AI-generated Topic Pages) (Se) compounds may have an [anticancer activity](https://www.sciencedirect.com/topics/medicine-and-dentistry/antineoplastic-activity" \o "Learn more about Antineoplastic Activity from ScienceDirect's AI-generated Topic Pages). However, large clinical studies failed to demonstrate that Se supplementations may prevent the outcome of cancers. Moreover, there are few randomized trials in cancer patients and there is not yet any Se compound recognized as [anticancer drug](https://www.sciencedirect.com/topics/medicine-and-dentistry/anticarcinogen" \o "Learn more about Anticarcinogen from ScienceDirect's AI-generated Topic Pages). There is still a need to develop new Se compounds with new strategies. For that, it may be necessary to consider that Se compounds may have a dual role, either as [anti-oxidant](https://www.sciencedirect.com/topics/chemistry/antioxidant-agent" \o "Learn more about Antioxidant Agent from ScienceDirect's AI-generated Topic Pages) or as [pro-oxidant](https://www.sciencedirect.com/topics/medicine-and-dentistry/pro-oxidant" \o "Learn more about Pro-Oxidant from ScienceDirect's AI-generated Topic Pages). Experimental studies demonstrated that it is as pro-oxidant that Se compounds have anticancer effects, even though cancer cells have a pro-oxidant status. The oxidative status differs according to the type of cancer, the stage of the disease and to other parameters. We propose to adapt the doses of the Se compounds to markers of the [oxidative stress](https://www.sciencedirect.com/topics/medicine-and-dentistry/oxidative-stress" \o "Learn more about Oxidative Stress from ScienceDirect's AI-generated Topic Pages), but also to markers of [angiogenesis](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/angiogenesis" \o "Learn more about Angiogenesis from ScienceDirect's AI-generated Topic Pages), which is strongly related with the oxidative status. A dual role of Se on angiogenesis has also been noted, either as pro-angiogenesis or as [anti-angiogenesis](https://www.sciencedirect.com/topics/medicine-and-dentistry/antiangiogenic-activity" \o "Learn more about Antiangiogenic Activity from ScienceDirect's AI-generated Topic Pages). The objective for the development of new Se compounds, having a great selectivity on cancer cells, could be to try to normalize these oxidative and angiogenic markers in cancer patients, with an individual adaptation of doses.