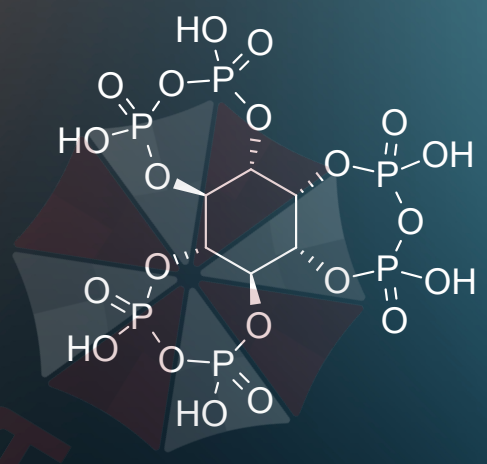

ITPP in Clinical Research - Potential Applications in Cardio-Vascular and Cancer Therapies

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History

In 2005, a study by a group of researchers from Boston medical school first reported the synthesis of myo-Inositol trispyrophosphate (ITPP, also known as OXY111A) and its effects in red blood cells. Since than, a number of studies have been published focusing on the metabolic effects of this compound.

ITPP closely related to other biological agents known as inositol phosphates. These compounds are important metabolic regulators and messengers in the body, especially inosityl trisphosphate (IP3) and Phosphatidylinositol 4,5-bisphosphate (PIP2). Inositol hexaphosphate (IP6) is the most abundant inositol phosphate isomer found. IP6 is solely involved in various biological activities such as neurotransmission, immune response, regulation of kinases and phosphatases as well as activation of calcium channels. ITPP itself can be seen as a direct product of IP6, which can be generated from it by dehydration.

ITPP itself was initially reported to influence the binding properties of O2 to hemoglobin, the main transport vehicle for oxygen in the body.[1] As an allosteric effector, it mildly reduces the affinity for hemoglobin for O2, which means that O2 can be more easily liberated into oxygen deficient tissues. On the other hand, it also reduces the oxygen uptake ability in the lungs slightly.

Cell Culture Data & Animal Experiments

The first report in 2005 had shown reduction of the oxygen binding affinity of red blood cells when ITPP was supplied.[2]

In a study on the metabolism of ITPP in horses, urine and blood plasma samples were collected up to 120 h post intravenous injection and analyzed for ITPP by LC-MS. ITPP was detected in post administration plasma samples up to 6 hours. The peak concentration was detected at 5 min post administration. In urine, ITPP was detected up to 24 h post administration. The peak concentration was detected at 1.5 h post administration. After around 5 hours, 90% of the compound had been eliminated from blood and urine of the horses.[3]

Cardiovascular Disease in Animals

In mice with artificial heart failure, ITPP at a dose between 0.5 and 3 g/kg supplied in the drinking water of the animals, was able to increase the excersize capacity of these animals by up to 63%. It had no effect on myocardial

contractility in isolated mouse cardiac myocytes and did not affect arterial blood pressure in vivo in mice. ITPP decreases the oxygen binding affinity of Hb, increases tissue oxygen delivery, and increases maximal exercise capacity in normal mice and mice with severe heart failure. ITPP is thus an attractive candidate for the therapy of patients with reduced exercise capacity caused by heart failure. The authors of this study concluded ITPP may be an attractive candidate for the therapy of patients with reduced exercise capacity caused by heart failure.[1] Another study in mice with heart failure have affirmed these results.[4]

A later study from 2020 investigated how ITPP affects rats suffering from an acute heart attack found ITPP supplementation results in protection from heart failure and demonstrated a positive effect on recovery of the heart tissue after the event had ended.[5]

Pulmonary hypertension, a serious form a high blood pressure in the lungs, was successfully alleviated in rats by supplementation of ITPP. It did also prevent the failure of the right ventricle of the heart, which is often associated with pulmonary hypertension.[6]

Cancer Models

A number of studies in rats and mice have focused on the potential applicability of ITPP in tumor therapy.

The first study on this topic from 2011 experimented with ITPP treatment of a rat hepatocellular carcinoma (HCC) model with weekly intravenous injections. The results showed a high potency of ITPP for tumor growth inhibition, thus allowing long-term survival and even cure of almost all the treated animals. Under these conditions tumor growth hormones were down-regulated, and apoptosis of cancer cells was found to be increased. ITPP did not affect hematologic parameters during treatment.[7] A similar study found ITPP could also reduce the growth of colon cancer cells implanted in mice. This particular study did also focused on metabolic markers of tumor growth and provided hints on the matter of the signalling pathway of ITPP in controlling tumor growth.[8] Further studies have been undertaken to invest age ITPP effects on other tumor entities, such as black skin cancer and breast cancer. These studies also showed a positive effect of ITPP.[9,10] Some of these studies additionally reported that ITPP therapy has a positive effect on subsequent chemotherapy.[11]

Further studies include the impact of ITPP supplementation on brain[12,13], ,pancreatic [13,14], squamous cell[15], liver[7,16], connective tissue[17], gastric[18], colorectal[19], peritoneal[8] and muscle cancer.[20] The collective results from these studies are mixed, but generally promising. Some studies found a reduction in tumor mass or a prolonged survival time, while others did not. A positive effect on tissue oxygenation was found in every study though.

Human Clinical Trials

In 2016, ITPP was first used in a clinical trial for the treatment of solid tumors. Some of these tumors often lead to a general problem with oxygen supply in the body which leads to a generally increased morbidity and poor outcome for the patient. In addition, the tumor growth profits from chemical signalling that is produced by the body as a result of the poor oxygen supply. ITPP was theorized to counter the negative effects of low blood oxygen levels in cancer patients. A Phase I/II clinical trial has investigated the effects of ITPP supplementation at doses between 2,5 g and 20 g per day to patients suffering from tumor hypoxia. The primary objectives were assessment of the safety and tolerability and establishment of the maximum tolerated dose, while secondary objectives included assessment of pharmacokinetics, antitumor activity via radiological evaluation and assessment of circulatory tumor-specific and angiogenic markers. The maximum tolerated dose is 12,4 g/m2, and ITPP treatment resulted in 32 treatment-related toxicities (mostly hypercalcemia) that require little or no intervention. 52% of patients had disease stabilization under ITPP monotherapy. Following subsequent chemotherapy, 10% show partial responses while 60% have stable disease. Decreases in angiogenic markers are noted in ~60% of patients after ITPP and tend to correlate with responses and survival after chemotherapy.[21,22]

As ITPP was thought to be an attractive candidate for performance enhancement is various aerobic sports, first experiments for the detection of the compound in human urine were already published in 2014. Since the compound is relatively stable in aqueous solution, it is easy to detect with HPLC.[23]

Conclusion

The discovery of ITPP has been relatively recent, hence there are still a lot of open questions on how ITPP can be used most effectively.

At the present time, one can conclude ITPP has the ability to increase tissue oxygenation via a stronger release of oxygen from the blood cells into the body. This property has a number of different applications. Many pathological processes in the body are connected to a lower availability of oxygen. Often tissues are replaced by scar tissue or other non-functional tissue is formed when the body senses a low supply of oxygen. ITPP can inhibit these mechanism and prevent negative long term changes in the body. In addition the current state of knowledge, some authors propose that ITPP could have potential in the treatment of various cardiovascular diseases, as those conditions often go along with tissue hypoxia, which itself leads to a variety of further problems later.[24]

The evidence at the present time also strongly suggests ITPP can be used as an auxiliary component in the treatment of solid tumors, which often lead to a low oxygen supply in the body and in some cases depend in the low oxygen environment to thrive themselves. It is likely we will see an increased research activity in this field in the coming years. Research on the compound is still ongoing, as some clinical and non-clinical studies are being performed by mid-2024.

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