

Liver-diseases and myopathy substituted with sodium-pyruvate

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Pyruvic acid is formed by sugar and alanine during the metabolism process. The daily amount produced by one person, varies between 200 and 600 g pyruvic acid, depending on the degree of physical strain of the body. The produced quantity of pyruvate is rapidly metabolized or transformed quickly into other cell-particles. Pyruvate is the metabolite in cell metabolism which decomposition leads to the highest amount of mononucleotide triphosphate in a few reactions:

Under intact aerobic conditions, 14 mole of adenosine triphosphate and one mole of GTP are available for the organism for diaphragm seals, intracellular synthesis or muscular contraction, obtained via degradation of 88 g pyruvate into carbon dioxide and water. In calorimetric values: One mole pyruvic acid, 88 g, contains a calorific value of 282 calories or 1181 kJ. For all kinds of reactions in cell metabolism 15 x 8 calories or 502 kJ are preserved as unstable bonds of groups easily to split.

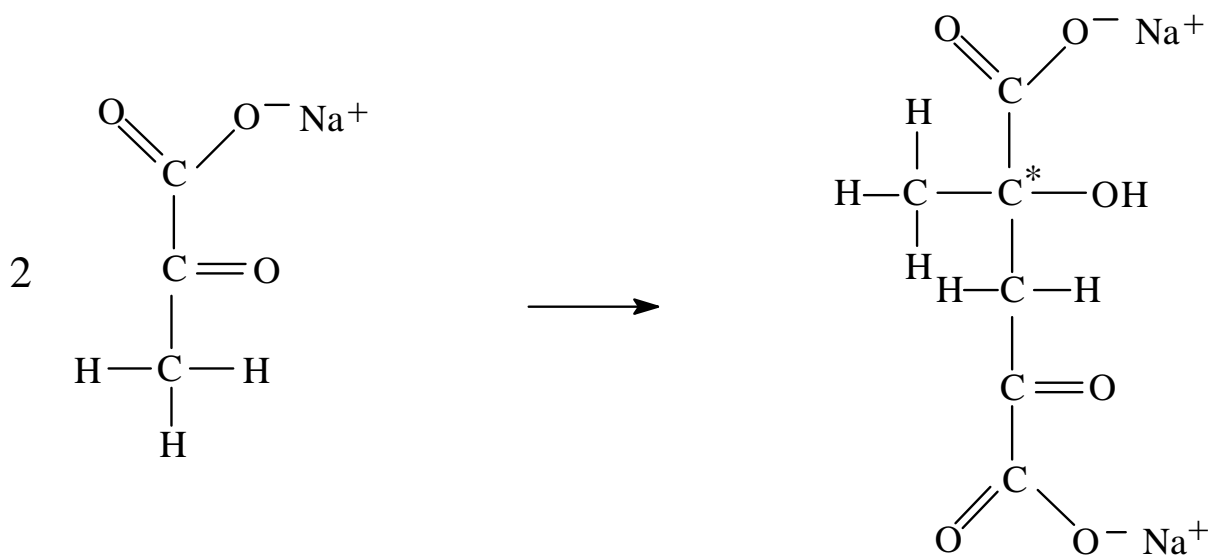
Furthermore, the hormonal controlled content of glycogen in an organ depends on its shape and is reduced or absent in undersupplied or injured cells and tissues. A supply via infusion of glucose is subject to hormonal control, too. In addition, for processing the glucose intracellular glycolysis of soluble enzymes right up to the level of pyruvic acid is required. It is only possible to reach the mentioned yield of mononucleotide triphosphate in combination with pyruvic acid's dehydrogenase, the citrate-cycle and the oxidative phosphorylation after this enzymatic pre-reaction. The long pre-reaction, such as the synthesis and mobilization of glycogen, will not be described.

The objective of the following program is the use of pyruvate for the substitution of undersupplied, injured or diseased cells and organs, due to its central and energetic dominated position in cellular metabolism. The application takes place in form of stable and freshly prepared solutions, which can be easily handled within the experiment. The pyruvate reaches well diffusible all human cells via the bloodstream.

Preparation, pyrogen and toxicological controls

Pyruvic acid itself is unsuitable for the focused procedure, but its sodium salt seems to suit perfectly. It is not hygroscopic, can be stored in dry ambient without any temporal limit and can easily and safely be used in the laboratory.

Pyruvate permanently exists intracellular in the organism and just a low amount reaches the extra cellular area and the blood. In our project the metabolite, offered indirectly (oral) or directly (intravenous), will be converted into a pharmacon, which diffuses into the cells. Pyrogenic and toxicogenic controls were necessary, because of the reverse reaction. Pure, sterile, neutral, water-based solutions of sodium-pyruvate freshly prepared are not toxic. They tend to aldol-addition during the storage. The main product, termed as para-pyruvate for simplification, can be detected soon after preparing the solution. Therefore, there had to be a toxicological control concerning the solutions` contents: Although sodium-pyruvate and the products obtained act neither pyrogenic nor toxic (controlled chromatographically and by NMR-measurements), it is recommended to use all infusion-solutions soon.



Sodium - pyruvate

Para - pyruvate

Oral and intravenous application of sodium-pyruvate

There are two possibilities for applying sodium-pyruvate. On the one hand there is the oral application, pure as a drink or mixed with other drinks or food. On the other hand there is the intravenous application, which requires a higher purity of the product (in this case, Musashino, Chemical Laboratory, Tokyo 104).

Results of testing the oral application show that the maximum single dose is already reached between 5 and 10 g. Even though test-persons recognized intestinal disorder and it is impossible to determine the resorbed part of pyruvate exactly. In order to still make use of the limited oral tolerability, 2g-pyruvate powder is added to drinks or food and offered multiple times a day.

Attempts to press tablets from pure pyruvate were not carried out, because of the required pressure and the dissolving time, which is too long. Additives such as accelerators endanger the stability and require storage tests for the tablets. By mixing pyruvate-powder we try to elongate an infusion-based therapy at home. Independent from the infusion, we try to build up a program based on ambulant and medical control, to which even diabetics and other groups may be integrated.

Intravenous therapy supplemented by oral applications seems to be the main field of application. Results concerning the treatment with limited oral doses only will be shown by time.

Infusion solutions, infusion time, sodium-pyruvate-dosages

Concerning all preliminary works and all decisions according to realization of test series with human patients, there were not any results and experiences in literature. It was proven advantageously to start with half a mole of sodium-pyruvate (55 g, 43,5 g pyruvate, 11,5 g sodium) as well in the production of solutions, as in testing well tolerated dosage.

In a 5,5 % solution of sodium-pyruvate, pH value 7,9, aldol-addition starts quickly. It is recommended to consume the solution soon. Carefully acidifying the solution right up to a pH level of 4,5 to 4,6 by adding hydrochloride acid repressed the aldol-addition. The solution remains stable up to four weeks. Changes caused by storage of the sterile solution were controlled chronographically and by NMR-measurements. The acidified solution is sterilisable. It resists steam sterilization up to 124 °C for 30 minutes.

Half a mole of sodium-pyruvate, 55 g in a 5,5 % solution infused in six hours, was well tolerated. This way we were able to acquire important details of the dosage, step by step. The utilization of the infused volume depends on the patient's demand of energy (muscle tension or relaxed lying) and on demand of pyruvate for the intracellular synthesis.

It is necessary to mention, that sodium-pyruvate in too high dosages does not necessarily help a lot but can strain as well.

For example, if you want to infuse the same amount in a shorter period of time:

We tested infusion-times of six hours on ten to fifteen following days at patients with medium up to serious liver-diseases without formation of edemas, based on former experiences. These data are just for orientation and further tests are still necessary to increase the quality of the application and to classify different ranges of application. There are first attempts on abuse of alcohol-based myopathy with infusion-times of four up to six hours.

Until now we have not dealt with short-time infusions given several times a day. In this context, at present we discuss about the wide range of muscular atrophy, where we are able to provoke an increasing zymogenesis with a high dosage of sodium-pyruvate.

Based on long-term experiments it is recommended to dose 150 to 200 mg per kg weight and hour of infusion, which means 10,5 to 14,5 g for a patient of 70 kg per hour. To get an overview about what amount of sodium-pyruvate was processed in metabolism, it is necessary to control the level of pyruvate measured in urine. Further, it is recommended to control the value of electrolytes in blood before the first infusion, to prevent hypokalemia.

Further information can be obtained by the producer Musashino Chemical Laboratory, Ltd and by Prof. Dr. Werner Thorn.

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