208

Alpha-lipoic acid

"The antioxidant miracle." Lester Packer.

Like Vitamins C and K, natural elements that are essential to the normal functioning of the body, alpha-lipoic acid is an effective anticancer agent. Alpha-lipoic acid is a powerful antioxidant, synthesised in plants and animals, and found widely in nature.[964] It has much in common with vitamins, but is not an essential dietary requirement, since humans can create it internally.[a]

Alpha-lipoic acid prevents the development of cancer by acting as an antioxidant. It has the properties of an ideal anticancer drug since, at higher levels, it destroys cancer cells while leaving normal cells unharmed. Despite this, its use as a treatment has been overlooked for many years. The power of alpha-lipoic acid is illustrated in a case related by Dr Burt Berkson, which also shows the constraints involved in practising medicine. The full story can be found in his book *The Alpha Lipoic Acid Breakthrough*.[965] In 1977, Berkson was a physician in a Cleveland hospital. One weekend, a woman picked wild mushrooms and cooked them for herself and her husband. A short time later, the couple were rushed to hospital where they were treated for a stomach upset, before being sent home. Their son, a paramedic, asked them what they had eaten and, realising it could be mushroom poisoning, they returned to the hospital. It emerged they had eaten several mushrooms from a group known as destroying angels, in this case *Amanita verna*. The main prognostic indicator for poisoning is the amount of mushroom ingested: if a large amount is eaten, the person usually dies.[966] The husband had consumed several: enough to amount to a death sentence. The wife had eaten less than one, making it was possible that she might live. Berkson was given charge of the two patients and told to give them painkillers and fluids. He was expected to wait and see if they died of liver failure.

As luck would have it, Berkson was a trained scientist, with a PhD in the biology of fungi. He contacted a colleague from the US National Institutes of Health, who suggested that an experimental substance,

[a] Alpha-lipoic acid is sometimes called thioctic acid, 2-dithiolane-3-penatanoic acid or 1,2-dithiolane-3-valeric acid.

209

alpha-lipoic acid, might be helpful for treating the liver failure caused by mushroom poisoning. Berkson gave alpha-lipoic acid to the couple, who

recovered in a couple of days. Even the husband recovered most of his liver function. A senior doctor explained to Berkson that, although rare, such recoveries are sometimes reported.

The following week, another couple was admitted to the hospital with mushroom poisoning. Berkson was told they had no chance of survival, as the poisoning was severe. He was instructed *not to use alphalipoic acid* on these patients, as it was not a recommended treatment. He was not to order more alpha-lipoic acid until the hospital pharmacy committee had approved its use. By this time, the patients would be dead, killed by bureaucracy or fear of legal action. Berkson could not stand by and watch his patients die. He gave them the remainder of his alpha-lipoic acid supply and they went home, alive and well, 10 days later. Berkson expected to be in trouble, but he was saved by the National Institutes of Health's interest in the patients' recovery. The story illustrates the extent to which legal and other pressures on the modern-day practice of medicine can override scientific knowledge and the interests of patients. It also suggests that alpha-lipoic acid is a remarkable substance.

Chemical structure

Alpha-lipoic acid contains two sulphur atoms that can be reversibly oxidised and reduced. In addition to its properties as an antioxidant, alpha-lipoic acid is a cofactor for several essential enzymes.
There are two optical isomers of alpha-lipoic acid, called R-alphalipoic acid and S-alpha-lipoic acid, which have different properties. The term optical isomer refers to one of the main physical differences between the two forms: they rotate polarised light in opposite directions. Chemically, the two are identical and can be difficult to separate. However, as explained previously, such molecules are mirror images of each other, differing like the right and left hands of a pair of gloves. When alpha-lipoic acid is synthesised in a laboratory, the result is a 50/50 mixture of the R and S forms.[967] However, in living systems, optical isomers generally occur in only one form. Within the body, the two forms are processed differently. In biological systems, only the Rform appears to occur naturally. In this chapter, unless we wish to be specific about the form, we refer simply to alpha-lipoic acid.

Both plants and animals can synthesise R-alpha-lipoic acid. The method of manufacture is not known, but it may be made in the mitochondria,[991] and some may be derived from bacteria in the gut. Normal synthesis does not lead to large amounts of free alpha-lipoic acid

in the bloodstream.[987] The alpha-lipoic acid we obtain from food is usually bound to proteins. Offal such as kidney, heart and liver is rich in alpha-lipoic acid. Spinach, broccoli and tomatoes also contain large amounts, and it is found in rice, peas, Brussel sprouts and bran.[968] The amount absorbed from a typical diet is unknown. Dietary alpha-lipoic acid may be bound to the amino acid lysine, which may explain its apparent absence in the blood of unsupplemented individuals.[987]

Supplements

Alpha-lipoic acid is available as a dietary supplement. Many supplements consist of the synthetic form and contain a mixture of R- and S-alpha-lipoic acid.[b] The naturally occurring form, R-alpha-lipoic acid, is also available as a supplement. Supplements of alpha-lipoic acid are rapidly absorbed, metabolised and excreted. Because of their short retention in the body, supplements should be taken in divided doses throughout the day. The absorption of a 200 mg oral dose is 20-40% that of an intravenous dose.[969,970,971] As with vitamin C, large doses are likely to be more effective if given intravenously. Oral doses can decrease oxidative stress,[972] and alpha-lipoic acid supplements act as an effective antioxidant. A notable action of alpha-lipoic acid is that, like vitamin C, it inhibits replication of the HIV virus and may be beneficial in AIDS.[973] Synthetic supplements of alpha-lipoic acid are less effective than the natural form. The synthetic form is less well absorbed and the Salpha-lipoic acid it contains is less biologically active. Outside the mitochondria, but inside the cell, S-alpha-lipoic acid may be reduced to dihydrolipoic acid (DHLA) about twice as fast as R-alpha-lipoic acid. However, this conversion rate may be misleading as, when taken orally, natural R-alpha-lipoic acid is more readily absorbed than S-alpha-lipoic acid,[969] so there is less of the L form to be reduced.

It has been suggested that R-alpha-lipoic acid has antiaging properties. This is because oxidation damage to mitochondria may be an important factor in aging. Within the mitochondria, R-alpha-lipoic acid is reduced to DHLA, which is a more potent antioxidant than alpha-lipoic acid. The conversion is nearly 30 times faster with R-alpha-lipoic acid

[b] RS-alpha-lipoic acid is sometimes called racemic or DL-alpha lipoic acid.

than with the S- form. This is consistent with the R- form having a more powerful antioxidant effect within the body.

Alpha-lipoic acid supplementation may be beneficial for diabetics, as it increases glucose uptake and metabolism. This is relevant to cancer treatment, because of the relationship between glucose and cancer,

emphasised previously. In insulin-resistant rat skeletal muscle, natural Ralpha-lipoic acid is more effective than the synthetic form at enhancing glucose uptake and metabolism.[1011]

R-alpha-lipoic acid is a critical cofactor for several important enzymes, related to energy metabolism.[974] In the body, R-alpha-lipoic acid binds closely to proteins, forming a lipoamide. One reason for the binding may be to retain alpha-lipoic acid in the body, as the unbound form has a short half-life, and is rapidly excreted. The rate of excretion has implications for the use of alpha-lipoic acid in diabetes and cancer.

Toxicity

There appear to have been no reports of overdose with alphalipoic acid. Doses of 600 mg/day are well tolerated. In patients with diabetic nerve damage (neuropathy), higher doses, such as 1,200 mg/day for two years or 1,800 mg/day for three weeks, have been taken without adverse effects.[975] In dogs, the LD50 (lethal dose, leading to death in half the subjects) is 400-500 mg/kg after oral doses.[974,976] In rodents, the LD50 is estimated to be 500-1000 mg/kg. These figures equate roughly to 35-70 g in a 70kg human. However, lower dosages may be fatal in rats that are severely deficient in the B vitamin, thiamine.[977] The safety of use by pregnant or breastfeeding women is not established, as full data are not available for these conditions.

Binding heavy metals

Lipoic acid is able to cross the blood-brain barrier and to bind heavy metals. It is a sulphur-containing molecule, which readily binds to (or chelates) mercury and other metals. For this reason, it has been suggested as a medium for removing mercury or other toxic metals from the brain. In the blood, other sulphur-containing supplements such as MSM (methylsulfonylmethane) also bind mercury and other heavy metals, transferring them safely into the urine for excretion. However, unlike alpha-lipoic acid, MSM does not cross the blood-brain barrier. Lipoic acid can act to prevent and treat the effects of heavy metal poisoning.[978] Free metal ions, such as copper and iron, induce oxidation

by catalysing reactions that produce free radicals. Both alpha-lipoic acid and its reduced form, DHLA, can bind metal ions, preventing the reactions that generate free radicals.[979] Alpha-lipoic acid can act as an indirect antioxidant, by inhibiting enzymes involved in oxidation and by binding to metal atoms.[980]

Alpha-lipoic acid forms stable complexes with copper, manganese and zinc.[981] In animal studies, alpha-lipoic acid has been found to provide protection from the poisonous metallic element, arsenic.[982] Alpha-lipoic

acid forms a complex with arsenic, preventing its absorption from the gut, and, if the arsenic has been absorbed, stopping it from interacting with enzymes.[987,983,984] Alpha-lipoic acid may also reduce cadmium damage to the liver,[985] and can bind mercury, to remove it from the kidney.[986] Alpha-lipoic acid can bind low levels of metal ions, removing them from the body and preventing damaging oxidation. However, in the presence of free copper and iron, which may occur in cancer cells, alphalipoic acid can generate free radicals.[c] In cancer, this interaction of alphalipoic acid with metal irons may be a primary source of free radical generation, leading to cell death.

An outstanding antioxidant

Alpha-lipoic acid is a powerful antioxidant.[987,988,989] It is particularly valuable, since it is available for use inside the cells, as well as in the surrounding tissue. Free alpha-lipoic acid enters cells rapidly, where it is reduced to DHLA, using electrons derived from metabolism.[990] This reduced form then acts as an antioxidant, preventing oxidative damage.[991] Since alpha-lipoic acid is soluble in both water and fat, it may have an exceptionally widespread distribution in the tissues of the body. Most other antioxidants are primarily soluble in water (like vitamin C) or lipid (like vitamin E). By contrast, alpha-lipoic acid can act as an antioxidant in water- and lipid-based body compartments.

Alpha-lipoic acid is a potent quencher of free radicals. When the reduced form, dihydrolipoic acid (DHLA), neutralizes a free radical, it is oxidized to form alpha-lipoic acid. Once this has happened, the alphalipoic acid is regenerated, being reduced back to DHLA by the cell's metabolism. DHLA is one of the most powerful free radical scavengers

[c] Sulphur containing organic molecules (RSH) like lipoic acid can react with copper or iron to form thiol radicals: RSH + Fe^{3+} □ ¨RS• + Fe^{2+} + H^{+} and RSH + Cu^{2+} □ ¨RS• + Cu^{+} + H^{+}.

available to the cell and can regenerate a number of other antioxidants, including glutathione, coenzyme Q10, and vitamins C and E.[992,993,994] In some conditions, such as stroke or coronary thrombosis, body tissues may be deprived of oxygen for a period. When the blood supply is restored, a burst of free radicals can damage the tissues. Alpha-lipoic acid may prevent such reperfusion injuries,[995,996,997,998,999,1000] and increase the rate at which cells can repair oxidative damage.[1001] Although this process has been observed in test tube and animal studies, it remains to be fully confirmed in clinical trials.

The reduced form of alpha-lipoic acid increases levels of an

important cellular antioxidant, glutathione, which is synthesized using a sulphur-containing amino acid, called cysteine. DHLA increases the uptake of cysteine into the cell, leading to greater glutathione synthesis. Although increases in intracellular DHLA following supplementation with alpha-lipoic acid may be short-lived, DHLA may improve intracellular antioxidant capacity by inducing glutathione synthesis.[967]

A genetic regulator

Alpha-lipoic acid is an anti-inflammatory agent and acts on mechanisms that control cell growth. Increasingly, inflammation is recognised as a factor in many diseases. A nuclear factor, known as NF-êB,[d] is an important protein in regulating genes that are involved in inflammation and diseases, such as atherosclerosis, cancer and diabetes.[974]
In particular, NF-êB regulates cell proliferation, transformation and tumour development.[1002] It does this by altering the way genes are expressed in inflamed cells.[e] When added to cells in culture, alpha-lipoic acid inhibits the activation of NF-êB.[1003] The reduced form, DHLA, inhibits the activity of other transcription factors.[1004]

Diabetes

Because of the involvement of glucose in the development and possible treatment of cancer, we need to describe the action of alphalipoic acid on blood glucose. In Germany, high intakes of alpha-lipoic acid have been used in the treatment of diabetes mellitus since the 1960's.[988,1005] Supplements may lower blood glucose levels in diabetics and

[d] Pronounced N-F-Kappa-B.
[e] NF-êB is a transcription factor that binds to DNA and alters the rate of expression of certain growth related genes. DHLA inhibits the transcription factor AP-1, by decreasing the expression of the proto-oncogene, c-fos.

subjects with impaired glucose tolerance. Diabetics using alpha-lipoic acid may be able to reduce their dependence on insulin or other treatments; they should therefore monitor their blood glucose levels. People with diabetes also suffer an increased risk of cataracts. In rats, Ralpha-lipoic acid is more effective than the synthetic RS form for preventing cataracts.[1006]

There is evidence that high dose alpha-lipoic acid increases sensitivity to insulin. This has implications for the uptake of vitamin C by tumours, using insulin dependent glucose transporters. Researchers gave intravenous doses of alpha-lipoic acid (600mg and 1,000mg) to patients with type 2 diabetes, and found insulin sensitivity increased (by 27% and 51%, respectively).[1007,1008] In a second study, 20 type 2 diabetics were

given twice-daily oral doses of 600mg alpha-lipoic acid for four weeks, whereupon their measures of glucose metabolism improved.[1009] In a further study, 72 type 2 diabetics were given doses of 600 mg/day, 1,200 mg/day or 1,800 mg/day for four weeks. The results showed that oral alpha-lipoic acid increased insulin sensitivity by 25%.[975] Type 2 diabetics given injections of alpha-lipoic acid were reported to show a substantial improvement in glucose uptake.[1008,1010]

These studies were performed using synthetic alpha-lipoic acid; it is possible that R-alpha-lipoic acid is more effective for improving insulin resistance.[1011,1012] In addition, alpha-lipoic acid itself may stimulate glucose uptake by muscle cells, in a similar way to insulin.[1012]
People with either type 1 or 2 diabetes experience high levels of oxidative stress. This may be the principle cause of associated vascular and neurological complications. In one experiment, 33 diabetic patients took alpha-lipoic acid (600 mg/day) for at least three months. The researchers found the supplemented patients had lower levels of oxidised lipid in their blood than 74 controls.[1013] This finding has been confirmed in a trial with 10 diabetic subjects.[1014]

Cancer

Alpha-lipoic acid is a powerful antioxidant and may be an effective anti-cancer agent.[1015] Its antioxidant action indicates its potential in cancer prevention. In this book, however, we are primarily concerned with its use as a cancer treatment. Much research in this area has focussed on its use in combination with conventional treatments.

Preventing side effects of chemotherapy

The platinum-based chemotherapy drug, oxaliplatin, has a side effect of damaging peripheral sensory nerves. This acute but transient neuropathy can appear during the first few treatments, in 85% to 95% of patients receiving the drug.[1016] With continued doses, nerve damage accumulates in about 10-20% of patients, limiting the dose that can be given. Alpha-lipoic acid relieves nerve damage in diabetics,[1017] and can help prevent this restrictive side effect of oxaliplatin.[1018] Intravenous alpha-lipoic acid, 600 mg once a week for three to five weeks, followed by thrice-daily oral doses of 600 mg, prevented the damage in eight out of 15 patients (53%).

Alpha-lipoic acid protects against nerve damage in patients given the anticancer drugs cisplatin and docetaxel.[1019] Cisplatin is a platinumbased
therapeutic agent, with a side effect of kidney damage. Alpha-lipoic

acid protects rats against cisplatin-induced oxidative damage to their kidneys.[1020] Use of alpha-lipoic acid also produced a synergistic increase in survival in experimental mice, undergoing doxorubicin therapy against leukaemia.[1021] At a low concentrations (1 µM/L), alpha-lipoic acid acted as a cancer growth factor, while at higher concentrations (100 µM/L) it acted as an antiproliferation agent. This concentration-dependent response is analogous to the effects of the related antioxidant, vitamin C. Cells from a disease[f] that causes increased sensitivity to radiation and oxidative stress were also found to benefit from alpha-lipoic acid.[1022] Since both radiation therapy and most forms of chemotherapy depend on inducing oxidative stress, the role of alpha-lipoic acid as an agent for reducing side effects is easily understood.

Cancer killer

Like vitamins C and K, alpha-lipoic acid kills cancer cells preferentially, leaving healthy cells unharmed. Indeed, its antioxidant properties are beneficial to normal cells. Rather than damaging healthy tissues, as conventional chemotherapy does, alpha-lipoic acid may have general benefits for the health of cancer patients. Human tumour cell lines commit suicide following exposure to alpha-lipoic acid.[g] By contrast, healthy cells are inhibited from cell growth and division[1023] so they may be less affected by chemotherapy. Such properties indicate that alpha-

[f] Ataxia-telangiectasia.
[g] Cell lines subject to lipoic acid induced apoptosis include FaDu, Jurkat, and Ki-v-Rastransformed
Balb/c-3T3 murine mesenchymal cells.

lipoic acid could be beneficial in both the prevention and treatment of cancer.

Free radical generation

Alpha-lipoic acid exploits the distinct metabolism of cancer cells, to act as a highly selective anticancer agent. In healthy cells, alpha-lipoic acid
acts as a powerful antioxidant.[1024] In cancer cells, it acts as an oxidant, generating free radicals. For example, it has been shown to generate superoxide within human colon cancer cells, causing them to commit suicide. Application of a suitable antioxidant can prevent the cell dying by apoptosis.[1025] A similar induction of cell death in human leukaemic cells, but not in healthy white cells, has been described.[1026] These results indicate the potential for alpha-lipoic acid as an anticancer agent. Selective killing of cancer cells has been replicated by several laboratories. For example, Lester Packer, a leading alpha-lipoic acid researcher, reports that alpha-lipoic acid (100 µM/L) kills leukaemic cells but not normal white blood cells.[1027]

Synergy with vitamin C

Alpha-lipoic acid boosts the power of vitamin C to destroy cancer cells. Vitamin C might reduce alpha-lipoic acid radicals, generating a redox cycle, resulting in oxidation that damages the cancer cells.[h] Riordan has tested the potency of an ascorbate and alpha-lipoic acid mixture for killing cancer.[1028] The addition of alpha-lipoic acid greatly increased the anti-cancer effect: only about one eighth the amount of ascorbate was required when alpha-lipoic acid was included. The treatment was effective against both rapidly growing and non-proliferating cells. This combination may be more effective than existing drugs.

As with vitamin C, tumours may absorb more alpha-lipoic acid than expected, although the underlying mechanism remains to be established. If this is so, then alpha-lipoic acid may reach cytotoxic levels in cancer tissues at lower blood levels than predicted. Research data supports this suggestion. In cancer patients, alpha-lipoic acid is absorbed more quickly into red blood cells than in healthy patients,[1029] and thus may be more available to tissues. Breast tumour tissues have an increased uptake and binding of alpha-lipoic acid, compared to normal tissue.[1030] Cancer cells accumulate more alpha-lipoic acid in their mitochondria than do healthy cells.[1031] When rats are injected with alpha-lipoic acid, those

[h] The proposed reaction of organic sulphur radicals (RS•) with ascorbate (A) is $AH^- + RS\bullet \rightarrow RSH + \bullet A^-$.

with cancer accumulate more than healthy animals do; repeated injections have been shown to extend the sick rats' lifespan by 25%.[1032,1033]

Conclusions

Like vitamin C and some forms of vitamin K, alpha-lipoic acid can be a powerful, non-toxic anticancer supplement. Its antioxidant action suggests it could prevent cancer development. An equally exciting feature is its potential for use as an anticancer treatment.

The action of alpha-lipoic acid appears to be concentration dependent, as is that of vitamin C. Low levels act as an antioxidant in healthy and cancer cells, benefiting both. At higher concentrations, alphalipoic acid causes oxidation and cell death by apoptosis in cancer cells, though not in normal cells. The cancer killing action of alpha-lipoic acid, like that of vitamin C, may be related to the presence of free iron, or similar metals, in cancer cells. Redox cycling of alpha-lipoic acid may be the principle mechanism involved.

As with vitamin K, alpha-lipoic acid's anticancer action is greatly

increased by high levels of vitamin C. The combination of R-alpha-lipoic acid and vitamin C can be taken orally for long periods, providing sustained plasma levels. Tumours may accumulate high levels of these antioxidants, promoting redox cycling and destruction of cancer cells. This finding leads us to wonder whether non-toxic anticancer substances may be more frequent in the diet than previously realised.