

Ornithine ketoglutarate

If you have noticed that you do not have as much vim and vigor as you did ten or twenty years ago ... or that your muscles are not quite as buff as they used to be ... you are in good company. As we age, we all naturally lose muscle mass, strength, energy, and vigor—in varying degrees. This aging-related muscle deterioration is called Sarcopenia, and in its severe form results in disabling frailty and weakness, along with a significant increased risk of illness and death. The problem is this ‘frailty of aging syndrome’ is becoming a problem of epidemic proportions as the population grows older and lives longer.

Staying active and strong

We all know the importance of staying active and exercising, and numerous studies have shown that active people are indeed healthier. But as we get older, it takes more and more effort to get the results we want ... because our body and muscles just do not respond to exercise the way they did when we were younger. Exercise can be frustrating and discouraging because the results are so slow in coming. But it is important to keep it up!

Although no one cause has been found for Sarcopenia, one recent scientific conference focusing on research and treatments for the syndrome concluded that the only effective intervention was regular physical exercise that includes weight training. However, the researchers stressed the point that even people who are active, and maintain their fitness level, are not immune to developing Sarcopenia.

For years scientists have searched for a compound that could safely promote muscle growth and muscle health. Countless products have been sold to help people get more results from their exercise, both for body builders and people just interested in getting the most from their physical activity. Unfortunately, these products have been more hype than science.

Not surprisingly, most of these products have had little or no testing in humans to even show they are beneficial. This is in spite of the fact that scientists have been vigorously researching the causes and potential treatments of age-related muscle deterioration.

In fact, there is a special amino acid complex composed of Ornithine (an amino acid) and Ketoglutaric Acid (a natural energy-producing compound) that shows tremendous promise as a stimulator of muscle health, energy, and vitality. This compound is called Ornithine Ketoglutarate, or OKG.

OKG has a successful track record in Europe for helping severely traumatized patients like burn victims. Over several decades of research and clinical use, OKG has been used to limit the protein breakdown and muscle loss that results from trauma. Numerous studies have examined both the use of OKG in trauma victims and the elderly, and have attempted to understand how this amino acid compound stimulates protein synthesis in tissues and muscles.

Additionally, research has shown that OKG is also useful for supporting cardiovascular health and immune function. OKG is quickly emerging from a pharmaceutical for severely ill burn victims to a powerful amino acid supplement for all of us interested in promoting our health, strength, and vigor. Despite the need for a safe nutritional product to help people interested in getting the most from their exercise—and to help those of us determined to prevent the devastating consequences of age-related muscle deterioration.

From burns to bodybuilders

Severe burns are some of the most serious and difficult injuries to treat. Along with the threat of infection, one of the biggest problems facing burn victims is the inevitable catabolic state that follows severe burns. A catabolic state causes a breakdown of tissue and muscle proteins, and this is the opposite of the anabolic state, which

promotes protein synthesis in our body. Numerous treatments have been tried to reverse the catabolic state that plagues burn victims and contributes to tissue breakdown and infection.

One of the most effective compounds scientists and doctors have utilized is OKG. This safe compound composed of natural ingredients has been shown to significantly promote protein synthesis and healing in burn victims.

Although OKG has been safely used for burn victims in Europe for more than 20 years, it has remained an orphan drug (a drug used to treat or prevent rare diseases) in the rest of the world. Even though it is a very effective and safe compound for stimulating protein synthesis in the body and muscles, OKG has received little clinical interest outside its use for burn victims.

Because OKG is known to stimulate muscle health and growth, it is not surprising that it has been popular among bodybuilders. Numerous products containing OKG appeared on the market about a decade ago, but most of them have disappeared from store shelves because they contained an inferior calcium or magnesium OKG salt—not the pure OKG used in all the impressive research. Also, most OKG products did not contain the proper dosage that has been shown to be effective, but instead contained a small, ineffective amount. Only recently has real pharmaceutical-grade OKG become available in an effective dosage.

How does OKG work?

After scientists discovered that OKG had unique and remarkable anabolic effects and promoted muscle health, they did research into how it works. One of the amazing discoveries was that while OKG strongly promoted protein synthesis and prevented tissue and muscle breakdown, the two components that make up the OKG molecule—ornithine and ketoglutaric acid—had much less effect when taken individually. Instead, the specific combination of ornithine and

ketoglutaric acid together was required. After OKG is consumed it is rapidly metabolized, and these metabolites seem to mediate much of OKG's benefits. Among the metabolites are arginine and glutamine. Both of these amino acids are considered 'non-essential,' meaning they can be made in the body. However, scientists have known for some time that during periods of stress and injury, or as a result of aging, these non-essential amino acids should be supplied in the diet. In fact, for optimal health we really should consider these amino acids to be essential dietary components.

Glutamine is essential for muscle health

Glutamine itself has been used for many of the same indications as OKG, and is considered essential for muscle health, although it is not considered an essential dietary component. Glutamine is an important link between the metabolism of carbohydrate and protein, a component of the important antioxidant glutathione, and improves the utilization of protein by the body.

Unfortunately, glutamine supplements have not proven very effective at significantly raising glutamine levels in the body. Because of this, many researchers have tried using precursors of glutamine like arginine and arginine ketoglutaric acid. These compounds also seem to be of little benefit for raising glutamine. OKG, however, has been shown to be very effective at raising glutamine levels in the body, working even better than taking glutamine itself. OKG also increases the levels of the anabolic amino acids ornithine and arginine, as well as proline, an amino acid vital for the production of collagen and connective tissue. It is this specific combination of metabolites produced from OKG in the body that are the key to its far reaching effects.

Beyond its metabolites, OKG also helps support our most important protein building hormones, including growth hormone, insulin-like growth factor, and insulin. It has been documented that trauma, stress, and aging cause a dramatic decrease in the level and function

of these important hormones. Among OKG's effects in the body is the ability to simultaneously increase all these important anabolic hormones. This, combined with OKG's metabolism in the body to amino acids required for these hormones to promote health, makes OKG a dietary supplement with profound beneficial effects.

More than muscle

While the metabolites formed from OKG play an important role in muscle health, they have many other functions in our body. So it was not surprising that OKG would be found to have a myriad of beneficial effects beyond its ability to stimulate protein synthesis. One of the important findings was that OKG improved immune function. While it is thought that glutamine production from OKG is involved in this immune stimulation, it is also now known that much of this immune enhancement is from the promotion of nitric oxide synthesis. Again, as in the case of glutamine, where OKG worked better than any of its components or metabolites, OKG stimulates immune function and nitric oxide production more effectively than other precursors. Amazingly, OKG worked even better than the amino acid arginine, which many people have used to enhance immune function and nitric oxide production. OKG is well documented to enhance immune function in severely injured people, and likely is a very effective immune stimulator for the elderly or anyone under stress.

While nitric oxide is important for immune function, it is best known as a promoter of circulation and cardiovascular health. OKG has not received much attention in this role. This is in spite of the fact that it works better than arginine, and arginine is routinely recommended to help promote nitric oxide production. Many years ago, OKG was found to be effective in the treatment of oxygen deprivation to the brain and stroke, showing it could preserve and improve brain function. More research is needed to demonstrate OKG's potential cardiovascular benefits, which most likely are numerous.

OKG offers support to the elderly recovering from acute illnesses

The elderly often have difficulty recuperating, healing, and regaining their strength after an illness. This all adds up to a lengthy recovery and high health care costs ... not to mention a diminishing of the patient's quality of life. In one groundbreaking study, doctors administered a dose of OKG daily with lunch for two months to a group of patients recovering from an acute illness. The group given OKG showed significant improvements in appetite, body weight, and independence. Additionally, they showed a dramatic improvement in their quality of life, along with a large decrease in their cost of medical care. This study was done in France, and the authors concluded that the almost 40% reduction in medical costs in the OKG group made the use of OKG supplements for people convalescing from acute illness very cost effective.

Use it or lose it

Decades of research have shown that when it comes to amino acid or protein supplements, OKG is the heavyweight champion. With benefits for both young and old, and the ability to help us support and maintain our muscles, brain, cardiovascular system, and immune system, no other amino acid complex comes close. *But to benefit from OKG you must obtain the real, pharmaceutical grade product—and use it correctly.*

Real OKG is used as a powder that is added to water or juice. In order to maximize your benefits, a minimum of 5 grams should be taken once daily with a meal. Elderly individuals and people convalescing from illness will get better results taking 10 grams with a meal once daily. No side effects have been found in studies using up to 30 grams daily. If you are interested in using OKG to maximize the results of your exercise program, take 5-10 grams of OKG with a meal immediately after exercise.

While OKG is just the support your muscles need for optimal health,

it is still important to exercise. Most scientists and doctors agree that regular exercise (and preferably weight training) can slow down age-related muscle loss. Unfortunately, as mentioned earlier, even the physically fit can succumb to the devastating consequences of Sarcopenia. However, it seems clear that OKG, especially when combined with regular exercise, is exactly what your body needs to fight off one of the most feared consequences of aging; becoming weak and frail.

Ornithine α -ketoglutarate (OKG) is a salt formed of 2 molecules of ornithine and 1 α -ketoglutarate. Its administration improves nutritional status in chronically malnourished (e.g., elderly) and acutely malnourished patients (especially burn and trauma patients). There is evidence that OKG activity is not the simple addition of the effects of ornithine (Orn) and α -ketoglutarate (α KG), because the presence of both moieties is required to induce the generation of key metabolites such as glutamine, proline, and arginine (Arg), whereas this does not occur when one or the other is given separately. This observation is related to the fact that the main feature of Orn at the whole-body level is to be metabolized through the Orn aminotransferase-dependent pathway, whereas the simultaneous administration of Orn and α KG saturates this pathway, diverting Orn toward metabolism into Arg. For years, OKG activity has been associated with its ability to induce the secretion of anabolic hormones, such as insulin and growth hormone, and to increase glutamine and polyamine synthesis. Recent studies using chemical inhibitors of nitric oxide synthase (NOS) suggest that nitric oxide derived from Arg could be partly involved in OKG activity. The use of genetically modified animals (i.e., knockout for NOS expression) is required to confirm this hypothesis.

The claim that ornithine (Orn) is a precursor of arginine (Arg) and that ornithine α -ketoglutarate-mediated actions could be linked to its ability to generate Arg is hardly an impressive statement, because any biochemistry textbook indicates that Orn generates Arg in 3 steps

through the Krebs-Henseleit cycle. However, this complete pathway is almost entirely limited to the liver, and at the whole-body level, Orn is mainly driven through the ornithine aminotransferase (OAT, EC 2.6.1.13)–controlled pathway. In addition, there is evidence that OAT naturally works mainly in the ornithine →glutamate direction, because OAT-deficient patients (i.e., patients with gyrate atrophy) have high blood ornithine levels. The ability of ingested Orn to generate Arg is therefore very limited at the whole-body level. The situation is quite different when the α-ketoglutarate salt of Orn (i.e., ornithine α-ketoglutarate; OKG) is administered. The purpose of this review is to demonstrate that OKG is a precursor of Arg, and that the latter amino acid could be involved [through production of nitric oxide (NO)] in OKG-mediated effects.

Ornithine α-ketoglutarate: an old friend

The concept of OKG was proposed in the 1960s by Robert Molimard with the aim of reducing hyperammonemia in end-stage liver failure at a time when it was believed that ammonia was the determinant of hepatic encephalopathy. Indeed, this therapy was very successful in normalizing ammonia levels, but unfortunately had no effect on coma status. However, through a fortunate coincidence, OKG therapy improved the nutritional status of these patients. It was therefore applied in various malnutrition situations, including burn injury and postoperative stress.

Ornithine α-ketoglutarate in chronic and acute malnutrition

Following the pioneering studies mentioned above, many studies confirmed that OKG administration regulates nutritional and immunological status and improves wound healing in chronically malnourished (e.g., elderly patients and infants receiving long-term parenteral nutrition) and acutely malnourished patients [e.g., burn, trauma, and postoperative patients]. Numerous experimental studies confirm the beneficial effects of OKG therapy, with particular emphasis on immunological status, protein turnover, and gut structure and function.

Ornithine α -ketoglutarate: more than the simple addition of Orn and α KG

As mentioned in the introduction, Orn at the whole-body level does not contribute substantially to Arg synthesis. Results from studies using different approaches support this idea.

First, classical studies measuring the effect of single amino acids on growth in rats indicate that Orn does not mimic Arg effects.

Second, in one study in rats, i.v. administration of ^{14}C -ornithine produced trace amounts of ^{14}C -arginine in the plasma but not in the kidney, liver, intestinal mucosa, or muscle. In another study using the same methodologies, ^{14}C -ornithine was administered enterally. After 60 min, detectable amounts of ^{14}C -arginine were found in the liver but not in the intestinal mucosa, kidney, or muscle. Whatever the route of administration of ^{14}C -ornithine, the main metabolite produced was ^{14}C -glutamate, confirming that the OAT-mediated pathway is the main Orn metabolic pathway at the whole-body level.

Third, when Orn hydrochloride was administered as a bolus to healthy subjects, there was a large increase in plasma glutamate (GLU; +65%, $P < 0.001$), peaking at 30–90 min; significant levels persisted until 150 min after Orn loading. It should be noted that administration of α KG as a bolus produced similar GLU patterns. Conversely, Arg levels increased modestly (+20%, not significant) after Orn loading and decreased after α KG loading.

Fourth, it is clear from demonstrations using stable isotopes that the predominant direction of carbon flux in burn patients is from Orn to GLU, with little flux in the opposite direction.

Fifth, in healthy fasting subjects, the flux of Orn to citrulline represents $2.5 \pm 0.5 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ compared to $6.5 \pm 0.7 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for Orn oxidation (presumably through GLU transamination followed by α KG oxidation, the difference being even more important in fed subjects: 3.7 ± 0.8 vs. $14.4 \pm 1.7 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, respectively). Hence, it appears that at the whole body level, the Orn \rightarrow GLU pathway contributes up to 80–90% of the metabolism of

Orn. This estimate fits very well with the fact that treating mice with gabaculine (an irreversible inhibitor of OAT) inhibits oxidation of Orn by 85%. In addition, conversion of Orn to citrulline represents only 6% of whole-body Orn flux in healthy subjects. However, it is worth noting that other calculations indicate that the contribution of oxidation to total Orn flux is ~50% in healthy subjects and burn patients.

The earliest firm evidence that OKG metabolic behavior is different from that of its components comes from a study conducted with healthy subjects. On 3 separate occasions, subjects received 10 g OKG, 6.4 g Orn, or 3.6 g α KG (i.e., the amounts of Orn and α KG contained in 10 g OKG). Under these conditions, the peak plasma GLU level was lower after OKG loading than after α KG or Orn loading alone, whereas Arg levels increased dramatically (+40%, $P < 0.05$), peaking at 30 to 90 min after OKG loading but not after Orn or α KG loading (see above). Furthermore, there was a very significant relation between the increase in plasma Orn concentration and the plasma Arg concentration at 60 min after OKG loading ($r = 0.89$, $P < 0.02$). In fact, the same study showed that OKG stimulated insulin secretion, whereas Orn hydrochloride and Ca α KG did not.

These data reinforce earlier pioneering work by Molimard et al. indicating that perfusion of OKG but not of Orn hydrochloride or Na α KG increases plasma Arg. Finally, in one rat model, OKG perfusion induced greater production of proline (Pro; a secondary product in the OAT-controlled pathway) than did Orn or α KG perfusion.

It is not known why OKG is a potent precursor of Arg at the whole-body level whereas Orn hydrochloride is not. Our hypothesis, first published in 1993 (and still prevalent, is based on the fact that the sequence of reactions is fully reversible (reactions 1 and 4 depend on the transaminases, and reactions 2 and 3 are chemically driven and work at equilibrium). It is therefore likely that by increasing GLU formation, the administration of α KG together with Orn displaces the equilibrium to the left, diverting Orn metabolism to Arg, Pro, and

polyamine synthesis. The fact that OKG but not Orn increases Pro synthesis suggests that either reaction 2 or reaction 3 acts as the site of interaction between Orn and α KG.

This hypothesis predicts that the generation of Arg from OKG is dependent on the OKG administration rate. Faster OKG perfusion should lead to faster saturation of the Orn \leftrightarrow α KG pathway, thereby diverting more Orn toward Arg formation. This was tested in burn patients on d 7 post injury. Patients received 10 g of OKG, either as a bolus or mixed with enteral nutrition and infused over 21 h. The control group did not receive OKG. Enteral nutrition was the same (isocaloric and isonitrogenous) for the 3 groups. Analysis over the 7-h kinetic period clearly shows a greater increase in plasma Arg concentration after the bolus administration, compared with continuous perfusion of OKG.

The effects of OKG seem to be specific to the Orn- α KG combination:

- i)* Orn aspartate increased plasma GLU but not plasma Arg in patients with cirrhosis, compared with control patients;
- ii)* OKG improved nitrogen balance in rats with traumatic injuries, whereas Orn alone and α KG alone did not (22);
- iii)* Replacement of Orn by Arg (i.e., administration of Arg α KG) suppressed the effects of OKG on nutritional status in rats with burn injuries.

Mechanisms of action previously proposed for OKG

Orn and α KG are central to intermediary metabolism, and as such OKG is a potential precursor of several potential modulating agents. Hence, polyamines, branched-chain keto acids and glutamine (Gln) have all been suggested as being involved in OKG mechanisms of action, and they probably are, because OKG seems to have different mechanisms depending on the underlying pathology, or even different overlapping mechanisms in a given situation.

OKG also acts a potent stimulator of the secretion of anabolic hormones such as insulin, growth hormone, and IGF-1/Sm-C, and this effect has been implicated in OKG anabolic activity in infants receiving long-term total parenteral nutrition and trauma patients.

Until recent times (i.e., when NO was discovered), Arg generation was not really considered as a mechanism of OKG, and even recently only a limited role was attributed to Arg and NO in OKG mechanisms.

Ornithine α -ketoglutarate as an Arg and NO precursor: the new job

Nutritionists ignored what the pharmacologists were doing for far too long. It is to the credit of Jorge Albina and co-workers that they pointed out the role of NO in Arg-mediated effects on wound healing. It was then recognized that OKG action could be at least partly mediated through Arg, followed by NO generation.

In addition to the data presented above, several studies indicate that OKG increases Arg pools or counteracts the stress-induced decrease in Arg tissue pools, for example, in muscle in rats with tumors or after surgical removal of a tumor, or after burn injury; or in the intestine in rats treated with LPS or subjected to burn injury. In postoperative patients, parenteral OKG ($0.35 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ for 3 d) counteracts the stress-induced decrease in muscle Arg concentration. It is interesting to note that perfused Na α KG does not have this effect in the same model.

The intestine may play a major role in the ability of OKG to generate Arg, because OKG does not increase Arg pools in plasma or muscle after massive intestinal resection (i.e., 80%) in rats.

Again it is surprising that this feature of Arg was never specifically discussed until fairly recently.

Because OKG perfusion (28 mg/min for 150 min) does not modify leg exchange of Arg in healthy subjects, it is likely that muscle Arg is

derived from Orn taken up by the muscle (Orn flux: 48 ± 6 vs. -1 ± 1 $\mu\text{mol}/\text{min}$ during infusion and basal level, respectively; $P < 0.001$).

Original data suggesting that Arg is involved in OKG-mediated effects are rather indirect: in OKG-treated rats with burn injuries, there was a correlation between muscle Arg content and thymus weight. More consistent are data from Robinson et al.: rats with tumors were fed OKG, Gln, or Arg for 14 d. Splenocytes and macrophages were then studied *in vitro*. Nitrite production in mitogen-activated splenocytes increased in rats fed an OKG-enriched diet but not in those fed a Gln- or Arg-enriched diet. Similarly, nitrite production in stimulated macrophages was higher in cells of rats treated with OKG compared with control and Arg treatment groups. These results are difficult to explain because the cells were incubated in a medium that did not contain OKG. It may be suggested that *in vivo* OKG treatment modifies the NO synthase (NOS): Arg balance by inhibiting arginase, and therefore later favoring the flux of Arg from the culture medium through NOS action. Indeed, recent studies strongly support the idea that the arginase: NOS balance is a key regulatory step in immune cell metabolism and function.

A further study on dexamethasone treatment in rats demonstrated that LPS-stimulated macrophages from rats treated with OKG *in vivo* stimulate NO⁻ production *in vitro* (1.77 ± 0.64 vs. 0.29 ± 0.28 $\mu\text{mol}/10^6$ cells in treatment and control groups, respectively; $P < 0.05$). Treatment with *S*-methylthiourea (SMT), a specific inhibitor of NOS II, abolished OKG-induced NO⁻ production. Recently, Moinard et al. conducted similar experiments in polymorphonuclear (PMN) cells of dexamethasone-treated rats. Treatment with OKG increased both the production of reactive oxygen species (evaluated by chemiluminescence, ferricytochrome C reduction, and flow cytometry and chemotaxis. Treatment with SMT in addition to OKG abolished the effect of the OKG on respiratory burst and PMN migration. An intriguing finding was that Arg treatment affected chemotaxis less than did OKG treatment, suggesting differences in intracellular channeling. This point deserves further study.

Finally, Schneid et al. recently addressed the involvement of the NOS pathway in OKG-mediated effects on insulin secretion. Pancreatic islets were isolated from Wistar rats and incubated in the presence of OKG. OKG stimulated insulin secretion in a dose-dependent manner, and this effect was inhibited when cells were incubated in the presence of L-nitroarginine-methylester (L-NAME), again suggesting the involvement of NO[•] in OKG-mediated activity.

In a further study, i.v. OKG (25 mg/kg) was administered with or without glucose (0.8 g/kg). OKG alone increased plasma insulin, and OKG with glucose increased glucose-induced insulin secretion. This latter effect was also demonstrated in vitro. In any case (i.e., in vivo or in vitro), L-NAME abolished the effects of OKG but did not affect basal insulin secretion or glucose-mediated insulin secretion.

However, reports by Moinard et al. and Schneid et al., could not credit NO[•] as the sole mediator responsible for OKG action

Conclusions

There is now firm evidence that OKG is a potent Arg precursor (which is not shown with Orn hydrochloride), and that some of these effects are mediated, at least in part, through NO[•] synthesis. These latter results were obtained using chemical inhibitors such as SMT and L-NAME. Whether or not these molecules are truly specific inhibitors of NOS remains a subject for discussions. Studies using genetically manipulated animal models should reinforce the results presented above. For example, Barbul's group, using inducible NOS knockout mice, elegantly demonstrated that Arg effects on wound healing are mediated by NO[•] production. Of major interest, the same group, using the same model, showed that the effects of Orn hydrochloride are not mediated through NO[•] production. This finding does not conflict with our results and hypothesis.