

I Want To Know!

R(+)-lipoic acid or

R Dihydrolipoic Acid

## Which is the Real Anti-Aging Energy Supplement?

**Q** You've done a great job of informing us about the benefits of R(+)-lipoic acid. But I now see that some companies are selling R-dihydrolipoic acid (R-DHLA) pills (see Figure 1). Isn't R-dihydrolipoic acid the more powerful antioxidant? In fact, don't most of R(+)-lipoic acid's benefits come from being converted into R-DHLA in the body? Wouldn't it be better just to take R-DHLA directly?

**A** After a careful review of the evidence, we have concluded that the answer is *no*. **R(+)-lipoic acid** is by far the more evidence-backed supplement, and many of its key benefits - on cellular homeostasis, mitochondrial function, and perhaps aging itself - cannot be gained from substituting preformed R-DHLA in its place.

R-DHLA is undeniably an extremely potent antioxidant - and in terms of sheer antioxidant potential, it is an even more powerful antioxidant than **R(+)-lipoic acid** itself. But that doesn't necessarily mean that it's the better supplement to take. To use an analogy, there's a lot more energy packed into nuclear fuel rods than into a similar amount of gasoline - but that doesn't mean that you should try to run your car on it.

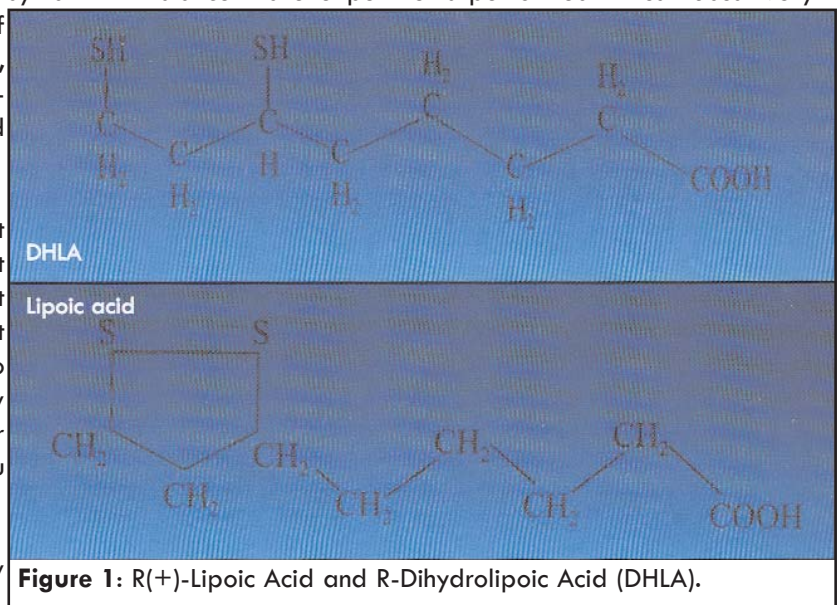
There are hundreds of animal studies, and many

randomized, double-blind, placebo-controlled human trials documenting the benefits of **R(+)-lipoic acid**, although many of these studies have been hampered by the presence of the unphysiological S(-)-lipoic acid isomer which takes up 50% of regular "lipoic acid" or "alpha-lipoic acid" supplements - see "Your Two-Faced Lipoic Acid" in *Advances* 2(1). It has now been used for two decades in Europe as a treatment for diabetic nerve damage, and its efficacy has been confirmed by a massive "meta-analysis" study (which pools together the result of all available valid studies on a subject to see what the total sum of the science says).<sup>1</sup> Researchers are also discovering new benefits to lipoic acid, such as its use in **burning mouth syndrome**.<sup>2</sup>

**R(+)-lipoic acid** is by far the more evidence-backed supplement

The most exciting research on **R(+)-lipoic acid** has been a series of groundbreaking animal studies<sup>3,4,5,6,7,8,9,10,11</sup> which have shown that supplementing the diet with **R(+)-lipoic acid** - especially when combined with **acetyl-L-carnitine (ALCAR)** - **dramatically rejuvenates the aging body**, restoring youthful activity levels, cognitive performance, and heart function. It also makes the "fires of life" in the cellular "power plants" (**mitochondria**) burn more brightly and efficiently, thereby relieving age-related oxidative stress. Preliminary human trials have provided evidence that these phenomena translate up into the human case.<sup>12,13,14,15</sup>

By contrast, we know almost nothing about what **supplemental R-DHLA does to the body**. Nearly all of the studies being cited to hype the alleged benefits of R-DHLA supplementation - their relative efficacy against **superoxide** and **peroxyl** reactive oxygen species,<sup>16</sup> repairing damage to the antioxidant enzyme **alpha-1 antiprotease**,<sup>17</sup> the reduction of **coenzyme Q<sub>10</sub>**,<sup>18</sup> or protecting cortical neurons saturated with iron solution,<sup>19</sup> for instance - are experiments performed in *test tubes*. Very



**Figure 1:** R(+)-Lipoic Acid and R-Dihydrolipoic Acid (DHLA).

few R-DHLA studies have even been performed in *organs*, removed from their owners and kept functioning in vats,<sup>20,21,22,23</sup> and only a tiny number<sup>24,25,26</sup> could be identified that have been carried out in living animals - and those animal studies have been carried out by *injecting* animals with R-DHLA. This doesn't tell us much about whether preformed R-DHLA will do much of anything when swallowed in a pill or liquid.

Moreover, none of the animal studies tell us anything about the real, long-term benefits of the regular use of R-DHLA. They have all been one-shot deals, in which R-DHLA has been injected on a single occasion, just before the animals were shot full of toxic chemicals or had a blood vessel choked off. After an extensive literature search, **we could not identify even one study to document benefits from taking R-DHLA orally, as a supplement**, in any living thing - human or otherwise. To date there have been no human trials on R-DHLA in any form whatsoever.

### Where is the Evidence?

Companies pushing R-DHLA supplementation are trading on the appealing idea that, since many of the benefits of **R(+)-lipoic acid** come from its conversion into R-DHLA, it makes more sense to take R-DHLA directly, which would make it immediately useable, in case the body fails to convert **R(+)-lipoic acid** into its more powerful antioxidant form. While this is a reasonable-sounding *assumption*, it is just that - an assumption, not a research finding. We don't know if oral R-DHLA is even absorbed from the stomach, let alone whether it reaches your cells, or exerts any actual benefits once it gets there.

In any case, the notion of inadequate formation of R-DHLA from **R(+)-lipoic acid** isn't backed by the scientific evidence. Studies show that there is no problem in converting **R(+)-lipoic acid** to R-DHLA. Cells readily take

up **R(+)-lipoic acid**, electrically "reduce" it to R-DHLA, and then release the surplus R-DHLA back into the surrounding fluid (see **Figure 2**), while keeping R-DHLA levels within the cell elevated for up to 24 hours.<sup>27,28</sup>

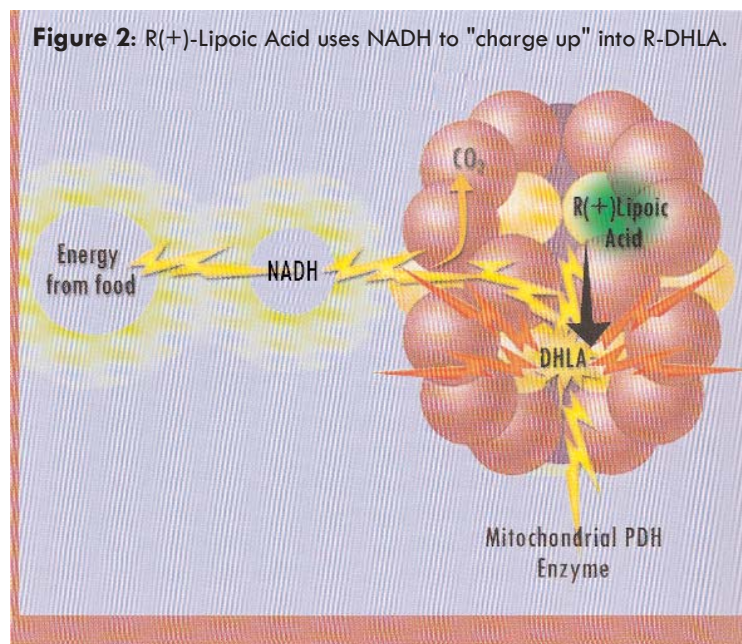
Even the studies on *injected* R-DHLA don't support its superiority to **R(+)-lipoic acid**, although some of them initially seem to. In one study,<sup>25</sup> for instance, laboratory animals were given a single under-the-skin injection of either R-DHLA or **R(+)-lipoic acid**, administered one half an hour before a simulated stroke. The R-DHLA injection reduced the amount of brain tissue destroyed in the process, while a similar one-time lipoic acid injection had no beneficial effect. So it initially looked as if R-DHLA had an edge over **R(+)-lipoic acid** - at least, when the two substances were injected, and at least in this model of stroke.

The scientists then reasoned that the apparent ineffectiveness of **R(+)-lipoic acid** might simply be as a result of the *timing* of the injection. Giving the animals injections of preformed R-DHLA would raise levels of R-DHLA suddenly, whereas it would take a while for **R(+)-lipoic acid** to be taken up by the brain's neurons and converted into R-DHLA. So they performed another set of experiments in which they injected the same amount of **R(+)-lipoic acid** under the animals' skins at one, two, four, and six hours before the "stroke" instead of just 30 minutes. The result: **R(+)-lipoic acid was as effective at reducing brain damage as preformed R-DHLA**, so long as it was given an hour or two before the induction of the "stroke."<sup>26</sup> Again, however, unless you're planning on taking up "mainlining" your supplements any time soon, and expect to get a 30 minute warning about the impending crisis, it's unlikely that any of this makes any *real-world* difference to your health. If you're taking **R(+)-lipoic acid** regularly, as a supplement, the timing difference of the two substances when given in the form of *injections* just doesn't apply.

Taking a step back: it's important to keep in mind that the main reason that we take supplements is not to use them to deal with short-term crises like the ones simulated in these experiments. We take them to support optimal health *today* - in our regular, day-to-day lives - and to avoid, postpone, or ameliorate *chronic* disease and the symptoms of aging. So, for instance, many people take **R(+)-lipoic acid** as a "drug" for the pain of diabetic neuropathy, or as a potential intervention against biological aging - precisely to avoid the kind of catastrophic endpoints of a bad lifestyle simulated in the experiments on R-DHLA discussed above.

While this is a reasonable-sounding assumption, it is just that - an assumption, not a research finding.

**Figure 2:** R(+)-Lipoic Acid uses NADH to "charge up" into R-DHLA.



### It's the Journey, Not the Destination

The exciting rejuvenating effects of **R(+)-lipoic acid** at the mitochondrial level are the results of moderate doses, taken orally, day in and day out. Again, *only R(+)-lipoic acid* - not R-DHLA - has been shown to exert the potent mitochondrial-rejuvenating functions for which it's known - and these results have been seen *in living organisms*, not test tubes. Here, another key difference between **R(+)-lipoic acid** and R-DHLA emerges, in the way that the body handles the two supplements and the resulting effects on cellular metabolism. For as research is beginning to show, the ability of **R(+)-lipoic acid** to rejuvenate mitochondrial function depends on the process by which the body converts **R(+)-lipoic acid** into R-DHLA, rather than the R-DHLA itself. In fact, based on what researchers now understand about the role of **R(+)-lipoic acid** in energy metabolism, **only R(+)-lipoic acid itself - and not preformed R-DHLA - will return mitochondria to youthful function, and possibly intervene in the aging process itself.**

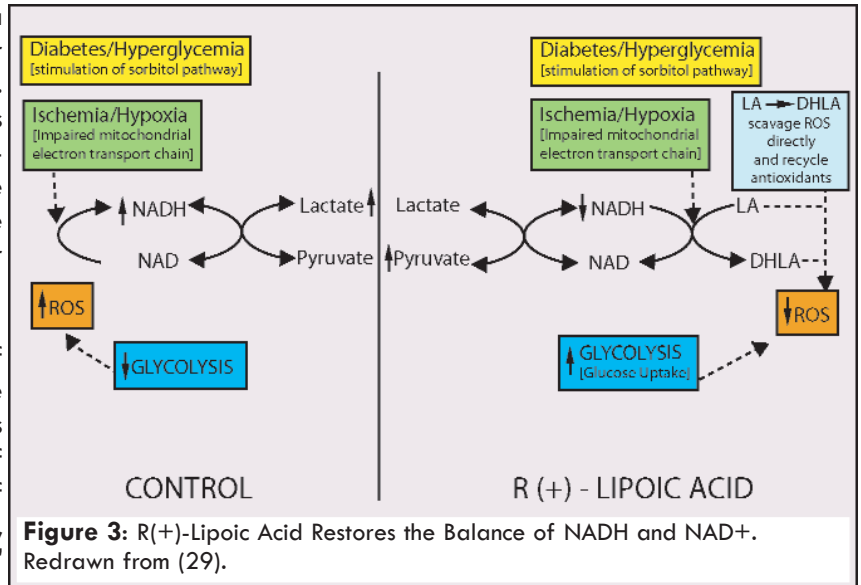
This conclusion ultimately derives from the recent discovery of the reason for the beneficial effects of lipoic acid in diabetic nerve dysfunction.<sup>29</sup> The pain relief delivered by the supplement can't be explained in terms of a simple antioxidant effect, and indeed, no other antioxidant has much impact on the disorder. Instead, Dr. Lester Packer and his colleagues presented evidence to suggest that the real benefit of lipoic acid in neuropathy comes from the ability of **R(+)-lipoic acid** to modulate the electrical state of the energy carrier **Nicotinamide Adenine Dinucleotide (NAD)**.<sup>29</sup>

To understand the importance of this action of **R(+)-lipoic acid**, let's look at what happens in the cell when the balance of NAD's two energy states are upset in vulnerable cell types such as those of the nervous system and the cells of the retina of the eye. When exposed to high levels of glucose, these cells are not able to properly "discharge" the electron-carrying (NADH) form of this energy-shuttling molecule down to its free form (NAD+). For complex metabolic reasons - some of which were not to come to light until long after Dr. Packer's team presented their evidence<sup>30,31,32</sup> - the resulting shift in the balance of NAD+ to NADH wreaks metabolic havoc in the cell.<sup>33,34</sup>

On the one hand, the cell is denied access to the free NAD+ that it needs for a variety of essential cellular functions, including the proper uptake and utilization of glucose and protein for fuel. On the other hand, the excess NADH leads to free radical damage through two distinct mechanisms. First, excess NADH creates "**reductive stress**," breaking down the cell's bound-up stores of reactive iron, intensifying the toxicity of *existing* free radicals though

deadly "**Fenton reactions**." Even more dangerously, excess NADH also increases the *creation* of free radicals in the mitochondria, as the "power plants" become literally "backed up" with excessive electrons and begin to "fumble" them out of their normal, carefully-controlled path down the energy-production chain (a lot like the famous "I Love Lucy" factory scene). When electrons are "fumbled," they react with oxygen in the mitochondria, generating **superoxide radicals**.<sup>33,34</sup>

**R(+)-lipoic acid** resolves this metabolic crisis by helping to restore the balance of the two forms of NAD. As we discuss in "Your Two-Faced Lipoic Acid" (Advances 2(1)), the mitochondrial enzyme complex **pyruvate dehydrogenase (PDH)** uses excess electrons donated by NADH to "power up" **R(+)-lipoic acid** into R-DHLA, as part of its role in energy production (see **Figure 2**). When you take **R(+)-lipoic acid** as a supplement, you give the body more **R(+)-lipoic acid** than is necessary for the immediate needs of the mitochondrial energy-production machinery. When the surplus **R(+)-lipoic acid** is "upgraded" to R-DHLA, therefore, the extra R-DHLA is simply released - first into the cell and then into the surrounding fluid<sup>27,28</sup> - making R-DHLA available systemically. More importantly, the



metabolic balance of the diabetic neuron or retinal cell is restored. Having freed itself of its extra electrons, NADH is recycled back into its free form, NAD+, making it available to meet the cell's metabolic needs. At the same time, the relentless, radical-generating oversteering of the mitochondria is relaxed (see **Figure 3**).<sup>28,35</sup>

### NAD, Mitochondria, R(+)-lipoic acid, and Aging

This has been great news for diabetics suffering from nerve damage who have often achieved great relief through this safe, orthomolecular compound instead of relying on toxic drugs. **R(+)-lipoic acid** supplementation also reduces the mitochondrial production of free radicals in normally-aging organisms.<sup>10,36,37</sup> As we discussed in "Your Two-Faced Lipoic

Acid" (*Advances* 2(1)), most of the free radicals that ravage their way through your cells don't come from toxic chemicals in your environment, but are actually produced by your own cellular "power plants" as a kind of cellular "pollution."<sup>38</sup>

This means that the body's cellular energy factories are the site of an ongoing "reactor leak," exposing them to the biggest load of free radical marauders in the body.

An overwhelming body of research exists to document that it's the free radicals churned out every day from the mitochondria

that drive the aging process.<sup>38</sup> (The real question today is exactly what *links* mitochondrial free radicals to the physical decay, functional loss, and accelerating risk of disease and death that we recognize as biological aging.<sup>39,40,41,42,43</sup>) Unfortunately, conventional antioxidants do nothing to affect this process: they can't effectively concentrate at the mitochondrial level, are not in a position to be "recycled" to their active forms when they do get there (making any radical-quenching effect a one-off deal), and can only quench free radicals *after* they've been formed. As a result, it's almost impossible for the common antioxidant supplements to intercept free radicals being produced by the mitochondria before they tear a piece out of the "power plant" itself. So **conventional antioxidants do little or nothing at the vulnerable "ground zero" of the aging process.**<sup>44,45</sup> Similarly, while your body produces antioxidant enzymes that can partially protect the *rest* of the cell from free radical damage, these enzymes are much less able to effectively protect the mitochondria from their own toxic wastes.<sup>44,45</sup>

This explains why supplementation with conventional antioxidants - including alpha-tocopherol, vitamin C, beta-carotene, polyphenols, melatonin, synthetic "radioprotectant" drugs, and many others - has often been shown to increase average lifespan (primarily in animals in stressful lab conditions or life-shortening congenic mutations), while having consistently failed to extend *maximum* lifespan (the seemingly "built-in" limit to lifespan that reflects the fundamental processes of aging, as opposed to particular diseases).<sup>46,47,48,49</sup> However much they may relieve some of the "oxidative stress" of excess free radical levels in the cells and throughout the body, common antioxidant supplements fail to address the ultimate cause of increased oxidative stress and biological decay: mitochondrial free radical production.

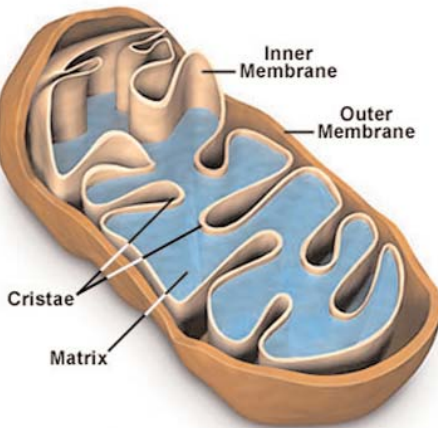
This is what makes **R(+)-lipoic acid** so exciting as a supplement. **R(+)-lipoic acid** takes some of the surplus electrons from NADH that would otherwise be force-fed into the mitochondria, and uses them instead to "power up" into R-DHLA. Since some of these excess electrons would otherwise spin out of control to form superoxide radicals, **R(+)-lipoic acid goes beyond just mopping up some of the cellular havoc wrought by these radicals and instead actually reduces the production of free radicals by the mitochondria in the first place.**<sup>10,36,37</sup>

Granted our understanding of the role of mitochondrial free radicals in the aging process, the potential impact of such an effect on the aging body is profound. But of course, we don't have to just guess about the impact of reduced free radical production at the mitochondrial level resulting from **R(+)-lipoic acid** supplementation. Extensive work by Drs. Tory Hagen and Bruce Ames has shown that supplementing the diet with **R(+)-lipoic acid** - especially as a "cocktail" with **acetyl-L-carnitine (ALCAR)** - results in a **R(+)-lipoic acid** takes some sweeping improvement in the health of old organisms that can only be described as a *rejuvenation* of youthful functionality at every level, from the mitochondria, to the cell, to the organ, to the tissue, and the organism as a whole.

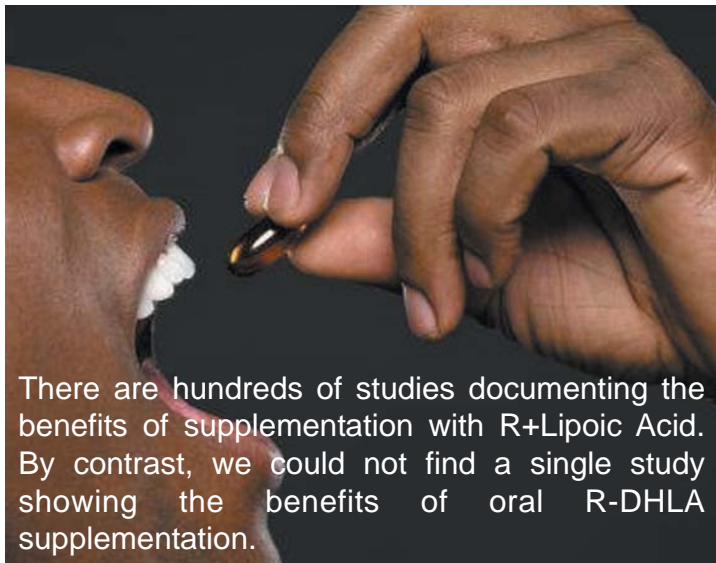
Because the "fires of life" in the cellular "power plants" of **R(+)-lipoic acid**/ALCAR-supplemented organisms burn more brightly and cleanly, their age-related energy crisis is alleviated, and oxidative stress is relieved. The extensively-documented result is that **those taking R(+)-lipoic acid plus ALCAR enjoy more youthful activity levels, restored cognitive performance, reduced molecular damage, and rejuvenated heart function.**<sup>3,4,5,6,7,8,9,10,11</sup> As Dr. Ames told *Discover* magazine, the aged animals given **R(+)-lipoic acid**/ALCAR-supplements by his lab are "doing the Macarena."<sup>50</sup> A press release from the Children's Hospital Oakland Research Institute where Dr. Ames works described the **R(+)-lipoic acid**/ALCAR cocktail as "A Veritable Fountain of Youth."<sup>51</sup> Furthermore, evidence from preliminary human trials<sup>12,13,14,15</sup> suggests that humans enjoy similar restorations of youthful energy and functionality.

There's also another way that **R(+)-lipoic acid**'s ability to modulate the NADH-to- NAD<sup>+</sup> balance might influence the aging process at the cellular level. A class of genes known as **sirtuins**, first identified in budding yeasts, have been shown to be crucial anti-aging genes in a wide range of organisms, apparently including humans.<sup>52,53,54,55,56,57</sup> Indeed, the activation of sirtuins may be responsible for the sweeping anti-aging effects of **calorie restriction**, which is

Mitochondria Structural Features



so far the only *proven* way to slow down biological aging in mammals (See "The Road to Aging is Paved with Calories," *The Holistic Lifestyle* 1(5), and "The Truth to the Fountain of Youth" in *Advances* 2(4)). To cut a long story short, **the availability of NAD<sup>+</sup> is essential to the anti-aging effects of sirtuins, while excessive NADH inhibits them.**<sup>58,59,60,61</sup> This opens up the possibility that **R(+)-lipoic acid's** ability to boost free NAD<sup>+</sup> while lowering NADH in the cell might thus facilitate the sirtuins'



There are hundreds of studies documenting the benefits of supplementation with R+Lipoic Acid. By contrast, we could not find a single study showing the benefits of oral R-DHLA supplementation.

youth-preserving activity, providing a second pathway whereby **R(+)-lipoic acid** could influence the aging process.

### The Magic is in the Mechanism

Of course, **none of these benefits accrue from taking preformed R-DHLA. R(+)-lipoic acid's** multiple beneficial effects - its ability to restore normal cellular function to nerves ravaged by diabetes, its capacity to reduce mitochondrial free radical production, and its potential to help keep anti-aging sirtuin genes activated - all rely on the fact that the mitochondrial PDH enzyme uses excess electrons from NADH in the *process of converting R(+)-lipoic acid* to R-DHLA. When R-DHLA is provided as a preformed supplement, there is no opportunity to take advantage of this biochemical process. The cell's NAD<sup>+</sup>-to-NADH ratio is left unaffected, and the multiple benefits of modulating this ratio cannot be reaped. You're left with a powerful antioxidant, but with no fundamental change in the basic metabolism of the cell. It's a clear case of "all hopped up - but nowhere to go."

And even this benefit is questionable: as we've already discussed, there is as yet no evidence that there are any favorable effects to taking R-DHLA orally, or that it provides benefits in anything other than during extreme crisis. Is it absorbed when taken orally? Will it reach your cells? Does it do *anything at all*? We just don't know. It's even possible that R-DHLA may exert a negative influence, by exerting prooxidant activities because of interactions with cellular iron.<sup>62</sup>

### Expert Opinion Weighs In

It's revealing that, while many prominent researchers are calling for the replacement of racemic "lipoic acid" supplements with R(+)-lipoic acid (see the sidebar: What Researchers Are Saying), **not one lipoic acid expert has come forward to endorse the use of R-DHLA supplements.** In fact, some of the quotes that are being used by promoters of R-DHLA supplements to tout their supposed benefits are lifted flatly out of context.

### Researchers Are Saying

"We're finding - and others are, too - that the R(+)-form - the natural form - is much more powerful than the racemic mixture ... Hopefully ... companies are going to be producing on more of a clinical scale the R(+)-form of lipoic acid, because we're finding very significant effects using this, as opposed to the racemic mixture."  
Dr. Tory Hagen, in *Mitochondrial Decay in Aging*.

"The effect of the thioctic [that is, lipoic] acid R(+)-isomer on glucose transport was significantly more potent than that elicited by the S(-)-isomer the racemic mixture, or an unrelated antioxidating agent."  
Dr. Elizabeth Estrada and colleagues, in *Diabetes*.

"Lipoic acid sold in a health food store is a synthetic mixture, a racemic mixture. And R[+]- is the natural form and S[-]- is an unnatural one ... And in our hands R[+]- works and S[-]- doesn't."  
Dr. Bruce Ames, at the Strategies for Engineered Negligible Senescence conference.

"R[+]-LA [that is, R(+)-lipoic acid], and not a racemic mixture of R[+]-and S[-]- LA, should be considered a choice for therapeutic applications."  
Dr. Lester Packer and colleagues. in *Free Radical Biology and Medicine*.

"The S[-]-enantiomer ... part of the racemate, which is present as about a 50% impurity, needs to be eliminated."  
Dr. Guido Zimmer and colleagues, in *Methods in Enzymology*.

Take for example a paper which discusses study in which R-DHLA reversed oxidative damage to a protein called **alpha-1 antiprotease** by activating a regenerating enzyme known as **protein methionine sulfoxide reductase (PMSR)**.<sup>17</sup> The abstract of the article says that R-DHLA "may exert a curative effect in diseases accompanied by oxidative stress," and this quote is gleefully reproduced in promotional materials as if it were an endorsement of R-DHLA supplement use. But a reading of the complete scientific publication makes it painfully clear that the authors intended no such thing.

The first thing to realize about the PMSR study<sup>17</sup> is that, despite mentioning the possibility of an effect "in diseases," it was not performed in an *actual* disease state in any

living, breathing organism, but in a *test-tube*, using isolated proteins with added R-DHLA dissolved in the immersing fluid. In fact, the authors are careful to point out the limitations of a study carried out entirely under glass. This includes the fact that they were forced to use more R-DHLA in their test tubes than can actually be obtained in the body ("non-physiological concentrations"<sup>17</sup>), because such high concentrations were necessary "to allow measurement of the PMSR activity by the equipment"<sup>17</sup> - not because such concentrations had anything to do with the actual results of R-DHLA supplement use in a living body. As they say, "it would be interesting to determine at which concentration [R-]DHLA influences PMSR activity *in vivo* [ie, in the living organism, as opposed to in a test tube]". Of course, it's possible that no real-world concentration of R-DHLA would actually create these effects in your body.

In any case, the researchers are definitely *not* suggesting that preformed R-DHLA be used as a supplement. Instead, they explicitly state that R-DHLA's benefits should be gained by the use of *lipoic acid supplements*! In the full context of the article, they are careful to state that "Because the concentration of endogenous, unbound lipoic acid and DHLA are low, **therapeutic supplementation with lipoic acid is needed for activating PMSR**" as had been shown in the paper;<sup>17</sup> "When lipoic acid is therapeutically applied, its plasma concentration gradually increases and larger amounts of [R-]DHLA are formed [emphasis added]."<sup>17</sup>

Whatever the real-world effect of **R(+)-lipoic acid** on PMSR's protein-repair activity may be, we do know that the documented benefits of **R(+)-lipoic acid** come from a metabolic process which R-DHLA does not undergo. Therefore, these benefits cannot be gained when R-DHLA is taken as a preformed supplement.

From everything we know today, **R(+)-lipoic acid** - and not R-dihydrolipoic acid - is the anti-aging supplement of choice.

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