The case against controlled release lipoic acid:
A pharmacokinetic-mechanistic argument (part 1)

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Author's note: The following paper critically reviews claims that controlled release lipoic acid (CRLA) is the superior form of lipoic acid (LA) for nutritional and therapeutic uses. Although our position is forthright, our intention is to bring the relevant issues to the forefront of medical and scientific discussion and review. To date, CRLA has not been subjected to any challenges.

We were invited and subsequently submitted a preliminary study and basic review of current research on R-lipoic acid (RLA) dosage forms and pharmacokinetics [PK] (1). We have recently completed a 12 subject human study evaluating the basic pharmacokinetics of a high bioavailability, natural form of RLA [as RLA-sodium salt, NaRLA] (2). A comprehensive review of animal and human PK data published has also been recently completed (3). Additionally, we reviewed the biochemical and pharmacological issues related to LA stereochemistry and the differences between the three forms of LA [RLA, SLA and racemic-LA] (4). Thus, our current work and previous research positions us to critique the quick release LA (QRLA) versus CRLA issue (5-7).

Recently, sensationalized advertisements appeared claiming the therapeutic effectiveness of LA is limited due to the relatively short time period in which therapeutic plasma concentrations can be maintained. It is well established that oral doses of LA reach peak concentrations in the bloodstream very quickly, typically within 15-45 minutes. Years of clinical research indicate this is a fundamental physiological and metabolic property of LA, not a shortcoming. Unfortunately, these characteristics are being disingenuously exploited as rationale for the manufacture and use of CRLA products as nutritional supplements and as therapeutic agents for diabetics.

Companies advancing these claims have engineered aggressive marketing campaigns directed at physicians and alternative health care practitioners. Unfortunately, misunderstandings regarding the issues of dose, the mechanisms of action and the 'therapeutic window' for LA supplements are being promoted as valid scientific rationale for the use of CRLA. ***It is important to distinguish marketing literature from science.*** Thus, we intend to present the case that independent of advertising claims, CRLA or sustained release LA (SRLA) are simply marketing devices. Furthermore, the CRLA issue highlights the vast gap between basic and applied science, as well as a few of the many short comings of the US patent system.

Our findings and those of **ALL** the LA PK and clinical studies reviewed argue strongly against *any* advantage to CRLA over QRLA. Though CRLA products are not new, their PK parameters and metabolism have been studied far less than QRLA. Animal PK and human clinical testing with oral (QRLA), intravenous (IVLA) and intra-muscular LA (IMLA) extends back to 1955 (8). Clinical use of LA in humans began in Germany (9, 10), Italy (11), Japan (12-21) and the Soviet Union (22, 23) long before CRLA appeared on the market.

Extensive PK studies were done by Asta Medica, the Pharma division of DeGussa, from the mid 1980s to 2001 (these studies were continued by the successor companies Viatris and Meda Pharma GmbH & Co) using CRLA, IVLA, QRLA and the RLA-Tromethamine salt (Dexlipotam^{TM}). No discernable advantage could be shown for CRLA over QRLA, so the project was abandoned. A formidable body of data for QRLA has been accumulated which allows comparisons to be made with the limited claims for CRLA (24, 25) and SRLA (26). In addition to the PK studies, all clinical trials published to date have used standard QRLA forms and have also found QRLA to be both safe and efficacious (references below).

While the developers of CRLA claim to have spent millions of dollars and tested hundreds of formulations in development of their CRLA products, the results of their efforts have so far produced only two publications (24, 25)***. Unfortunately, these papers not only fail to demonstrate the superiority of CRLA, they do not provide data convincingly proving its therapeutic potential even matches that of QRLA.*** Unlike QRLA, the standard oral form of LA used clinically for over 50 years, no significant body of published research exists supporting the use of CRLA as a supplement or therapeutic agent including the CRLA publications! Thus, the burden of proof remains on those who wish to market it as a "superior form" of LA. In our opinion, the well known and proven efficacy of QRLA speaks for itself; the assumption that CRLA is somehow better or more efficacious "because it lasts longer" is simply made without valid scientific rationale. ***We present the argument that considering what is now known about the PK & metabolism of LA and the molecular mechanisms which underlie its efficacy, CRLA is less***

effective than standard or QRLA. ***While CRLA may still prove to have a benefit, we contend that so far it has not been demonstrated.***

CRLA: What Are the Claims? Advocates of CRLA claim that LA has limited efficacy *in vivo,* due to its short plasma half-life. By coating the LA particles using standard CR technology, they claim to have increased the T_{max} (time to maximum plasma concentration) and the area under the curve (AUC; a measure of relative bioavailability, which reflects the change in concentration over time). In a ***single pilot trial*** using CRLA, Evans et al correlated this apparent increase in T_{max} to three different markers used in assessing the extent of diabetes-related damage and changes in glycemic control in humans; fructosamine, glycosylated hemoglobin (HbA1c) and C-peptide (24). To date, this is one of only two known reports asserting improved efficacy of CRLA compared with QRLA in humans. ***Unfortunately, the questionable methodology, anomalous data and incongruent conclusions preclude any significance asserted to the author's findings.*** Thus, little can be concluded from the reported data which would support ***any*** claim of CRLA superiority over standard or QRLA preparations.

Evans et al in reviewing 4 different clinical trials utilizing intravenous LA (IVLA) concluded that IVLA was effective for treatment of diabetic neuropathy, but that (oral) QRLA was only "marginally effective." The authors further suggested the limited efficacy was due to the short plasma half-life ($T_{1/2}$). The author's final conclusion was that IVLA is effective because it reaches higher levels and maintains it for a longer duration (24). While IVLA reaches higher plasma levels, the second half of the conclusion is either a misunderstanding or a blatant misrepresentation of the data, since it has been demonstrated that the plasma half-life of LA is independent of the route of administration since the IV and per oral (PO) elimination half-lives are essentially the same (27-29). Therefore, contrary to the contentions of Evans et al, the observed differences in IVLA and QRLA (and thus CRLA) efficacy will be related to the maximum plasma concentration (C_{max}) reached and the area under the curve (AUC) not the mean residence time (MRT), $T_{1/2}$ or T_{max} in plasma.

Clinical Evidence Proves QRLA is Effective. Contrary to the claims of Evans et al, there were several concurrent and subsequent human pilot and clinical trials showing that oral RLA (30) or QRLA products or combination therapy with IVLA & QRLA have therapeutic efficacy in patients with diabetes and diabetic neuropathy, (31-50) migraine, (51) multiple sclerosis, (52) peripheral artery disease (53) and burning mouth disease (54-56). QRLA (600 mg) reduces plasma F2-isoprostanes (a marker of oxidative stress) in healthy subjects (57). QRLA (600 mg) improved the antioxidant status of plasma (measured by cyclic voltammetry) in healthy volunteers and had an even greater effect in diabetic subjects (58). The studies proving QRLA has therapeutic efficacy did nothing to dissuade the advocates of CRLA from their original contentions or to alter their aggressive marketing campaign.

Is CRLA Novel? Despite numerous companies claiming to present the first or only CRLA product, several patents had already been granted for similar LA products. In 1992, Asta Medica was granted U.S. patent 5,084,481 which consisted of LA mixed with a variety of conventional carriers and auxiliaries that affect the rate of disintegration, dissolution and bioavailability of the active substances. U.S. Patent 5,693,664 is a patent for RLA including controlled release and pH protected dosage forms. Interestingly, these CRLA products were ***not*** further developed, marketed or distributed to any significant degree, due to the low C_{max} values achievable and limited efficacy of CRLA products compared to IVLA or QRLA.

In the CRLA patents (6,191,162; 6,197,340; 6,572,888 and 7,118,762) the efficacy claim is made for CRLA products lowering fasting blood sugar and reports a clinical trial in humans. Such evidence of clinical efficacy for an over-the-counter product would be monumental.

However, the conspicuous absence of the most critical data proving that fasting glucose was lowered in the CRLA published human trial is suspicious (24). **The data reported in the patent does not concur with the data in the published PK (clinical trial) paper and nothing in the paper supports the claims of the patents**. U.S. Patent 6,348,490 is another CRLA formulation which was

granted at a later date. Thus it is clear, at least to the US Patent Office, that CRLA is NOT owned exclusively by any one company. Considering the relatively large number of CRLA patented formulations and the overlapping time course of their granting by the US Patent office, clearly the current purveyors of CRLA are NOT (as they claim) the "first and only" patented LA or CRLA formula.

Is LA an antioxidant in vivo? LA is generally categorized as a both a water and fat soluble antioxidant with the ability of recycling oxidized CoQ10, Vitamin E and Vitamin C to their reduced (active) forms (89). LA is rapidly absorbed from the gut and appears in the plasma with peak concentrations (C_{max}) typically appearing 15-45 minutes after ingestion. Of equal importance is the observation that oral and IVLA is cleared from the plasma within 2 hours, with plasma LA levels returning to baseline. This observation has been incorrectly equated to elimination from the body by the advocates of CRLA. A recent study revealed that only 12.4 % of LA and its total metabolites were found in the 24 hr urine after oral dosing of QRLA (59). Previous studies found that <1% of the total oral LA dose is un-metabolized LA (17, 60, 61). Therefore, it is incorrect to equate plasma clearance with body clearance. Rapid plasma clearance is a well known pharmacokinetic property of LA which is being falsely exploited as "negative" and is being used as a rationale for the marketing of CRLA products. Current scientific research into the molecular mechanisms of how LA works *in vivo* suggests that this rapid plasma clearance is fundamentally related to its safety and therapeutic action (3, 6, 62).

LA induces a beneficial stress response: Evidence indicates the *in vivo* mechanisms of action of LA involve activation of the natural environmental stress response systems which up-regulate the so-called 'early response genes', thus activating Phase II detoxification enzymes via Nr-f2 and the antioxidant response element (ARE) (63). Activation of these genetic systems is nature's way of making the body more adaptable to stress and environmental insults. One physiological result of Nr-f2 and ARE activation is a significant increase of endogenous antioxidants (vitamin C, vitamin E, GSH, etc.) and antioxidant enzyme systems (64, 86) Despite its abbreviated half-life, this is how LA is able to affect the redox status of the cell, not by acting as a direct scavenger of free radicals. The theory that LA acts as a direct scavenger of free radicals, or that it acts directly as an 'antioxidant' in the cell has been disregarded as a valid theory by most LA experts several years ago (6) and yet is still being advanced by the advocates of CRLA. To date there is lack of evidence that LA acts this way *in vivo* and a large body of research demonstrating the 'stress-response' theory of action for therapeutic LA. Thus, the misguided or ill-conceived basis for suggesting increased efficacy of CRLA products due to their increased "free-radical scavenging" or "antioxidant properties" due to an increased MRT forms an erroneous rationale.

LA up-regulates the early response genes by inducing a mild "hormetic" or "redox stress" which paradoxically confers protection against oxidative stress but requires a threshold concentration to initiate the therapeutic response. The activation of PI3-K & MAP kinases (65, 66) and up-regulation of Nr-f2 (63) heme oxygenase [HO-1] (66-68) and heat shock proteins [HSPs] (69-70) indicate the mechanism of action of LA involves induction of a stress response that resets the cell's homeostatic mechanisms that become disrupted; for example, during age-related diseases and diabetes. The typical range of concentrations required to induce the hormetic, Phase II (therapeutic) response is 10-20 μg/mL (~50-100 μM) and can be achieved with multiple oral doses of typical or QRLA preparations (e.g. Na-RLA) (2, 60, 71). Like the name "early response" implies, activation requires only short time periods of 15 minutes-1 hr, which coincides closely with the plasma time course of both IVLA & QRLA products (68). If this theory is correct, and all of the existing evidence indicates it is, then high concentrations, rapid plasma clearance and metabolism of LA are essential for both the safety and the efficacy *in vivo* (1, 2*)*. It further suggests that CRLA preparations require more toxicity data due to their increased plasma MRT before being considered safe. Furthermore, it is not valid to utilize QRLA safety or efficacy data to claim CRLA is safe and effective (88).

Reaching an effective concentration is critical to the therapeutic action of LA: The purveyors of CRLA or SRLA promote the sale of their products by creating and marketing the false assumption that LA functions *in vivo* like it does *in vitro*, (i.e. by scavenging free radicals). Unfortunately, sales representatives for certain CRLA products have recently been claiming that since LA has a short

half-life, the only way to effectively "antagonize free radicals which are produced continuously" is to increase the MRT in plasma. This is a gross misunderstanding of the *in vivo* mechanisms of action of LA and may be dangerous because the increase in MRT may inhibit beneficial oxidative signals. While free radicals have been erroneously demonized, it is well established that normal cellular signal transduction is, in part, mediated by free radicals (73-77).

As discussed above, recent evidence indicates scavenging free radicals is NOT the way LA functions. Many of the papers cited both by scientists and supplement companies attempting to explain the "mechanisms of action" of LA have been extrapolated from high concentration (100-1000 μg/mL (~500-5000 μM) *in vitro* experiments maintained for up to 72 hours. Concentrations above 50 μg/mL (250 μM) cannot be achieved by oral or IV dosing of humans and even CRLA is only maintained (at low concentrations; 1.79 μg/mL, ~8.7 μM) for 6 hours. Therefore, extrapolation of *in vitro* results to humans must be done with extreme caution. It would be more relevant if cell biologists used concentrations and time courses achievable *in vivo* in their cell culture studies, rather than splashing mega-concentrations of LA on to cultured cells and then making an attempt to utilize the data to explain *in vivo* effects (6).

To date, there is no solid evidence to support the theory that LA scavenges free radicals or functions directly as an antioxidant (free radical scavenger) *in vivo* or that this is related to the efficacy of LA. Further supporting this lack of evidence is the rapid metabolism and clearance of LA from the plasma. Though its therapeutic benefits are clearly seen many hours or days after a dose, there simply is not sufficient residence time in cells or plasma to expect that any therapeutic action is attributable to radical scavenging (6) or intact LA. The "antioxidant benefit" of LA is almost certainly attributable to its stimulation of Phase II and antioxidant response elements. ***Taken together, it is evident that rapid uptake and clearance of LA from the plasma is a beneficial attribute, not a shortcoming.***

The potential toxicity of CRLA products: QRLA is toxic in cats (above 13 mg/kg) though it is a safe and efficacious supplement for dogs up to 25 mg/kg (78). The difference in toxicities between the two species is because LA is sustained for significantly longer periods of time in the plasma of cats (79, 80). This is presumably due to lower rates of hepatic metabolism and excretion. Therefore, it must be questioned whether sustaining LA in plasma is beneficial or whether it may increase the toxicity of LA or be indicative of cirrhosis. When QRLA was administered to cirrhotic patients, the plasma half-life was increased compared to normal or hepatitis patients, indicating an inability to clear LA from the blood (23). Thus, decline in liver function can increase the mean residence time of LA in plasma. ***Rapid clearance and metabolic transformation of LA by hepatocytes seems to be necessary and fundamental to the mechanisms of action in the liver and to prevent tolerability and safety risks of LA, especially during long term therapy***. This may be also important for specific therapeutic effects, like the anti-inflammatory activity since liver physiology and metabolism affect many processes, and markers outside the liver (81).

The brief study [12 weeks] by Evans et al reported no toxicity and few adverse reactions (24). However, since this product has not been as widely tested as QRLA, more adverse reactions may occur when larger populations are tested for longer periods of time. Based on what is known about the biochemistry and metabolism of LA, it appears that the relatively low levels (1.79 μg/mL= 8.7 μM) of plasma LA achieved by CRLA products are unlikely to have **<u>any</u>** significant therapeutic effect. The ironic outcome for consumers of CRLA is that the levels achieved are also likely too low to produce any dangerous toxic effects. So the question remains, where's the advantage in using CRLA? Since the CRLA marketing literature recommends CRLA for "daily supplemental" use, while appealing to diabetics seeking better insulin and glucose control, ***long term testing (including measurement of individual time courses and plasma levels of LA and its metabolites) is essential to determine safety before these products can be considered as a medicine or suitable replacement for traditional preparations of QRLA****. The metabolite profile of CRLA may differ considerably from QRLA due to the increased MRT and exposure of active sites to lower concentrations of LA and metabolites. To date no metabolite testing has been done on CRLA products.*

In fact, ALL of the PK studies in animals and humans published since 1955 clearly indicate the MRT is NOT the critical determinant regarding the therapeutic efficacy of LA. It should also be pointed out that even if LA could be sustained *in vivo* long enough to mirror *in vitro* (antioxidant) effects, (impossible and likely undesirable) it would still be impossible to correlate these effects directly due to different metabolic fates. Even human cells in culture medium do NOT respond like cells *in vivo* (7).

The CRLA Marketing Subterfuge: Unexplained Anomalies in Published CRLA Research. The PK study of CRLA was financed and conducted by MRI, a supplement company with patents for CRLA products (24). The study compared 12 normal patients and 21 Type II diabetes patients and compared a 600 mg QRLA product to 900 mg and 1200 mg CRLA product for 12 weeks. Several questionable methods of analysis and data reporting were used in that manuscript which were unexplained. First, while several good HPLC methods were available to rapidly quantify racemic LA, the authors chose to use a specialized method designed to differentiate RLA and SLA stereoisomers which were not reported. The method is not commonly adapted for quantitation of total LA in plasma since it requires separate derivatization and standard curve generation for both RLA and SLA (validated reference standards for the single LA enantiomers were unavailable at the time of this study) and further steps to validate the calculations. Second, the C_{max} (6.68 μg/mL ± 3.70) for 600 mg QRLA used as a control in the Evans study are significantly higher (39%) than those published by the German group that developed the assay (82-84) upon administering 600 mg QRLA but provide no experimental or statistical details of the assay to explain these discrepancies. [As a side note, the wide range of PK values from various studies suggests that in the clinical trials where QRLA was ineffective, was at least in part due to non-bioequivalent dosage forms, inadequate plasma and tissue levels as a result of the wide inter-individual differences in absorption, abbreviated testing periods and/or poor patient selection criteria.] Third, the CRLA plasma PK data is presented in log-linear format. Presumably this was done intentionally to conceal the apparent differences in both C_{max} and AUC between the CRLA and QRLA products. The CRLA product produced an unremarkable C_{max} only 27% as high as the comparatively inexpensive QRLA. Further, the CRLA AUC was only 60% that of QRLA. The T_{max} was extended to 1.25 hours (versus 0.5 hours with QRLA) representing a 2.5 fold increase. ***This increase in T_{max} is meaningless without critical consideration of the shortcomings demonstrated by the CRLA C_{max} and AUC data.***

The authors did not explain why CRLA produced a lower C_{max} than the QRLA product, though product literature asserts that CR products are designed to improve bioavailability. It must be considered that significantly higher plasma levels of LA could be reached by consuming 2-3 QRLA 600 mg capsules every 15 minutes, achieving a T_{max} comparable to IVLA. In other words the CRLA advocates are attempting to show that T_{max} is more relevant than C_{max} or the AUC, despite the fact that all the published PK data suggests otherwise. It remains to be demonstrated that low and sustained (1.79 μg/mL at C_{max}) plasma LA at has any beneficial or measurable effect or whether this can be compared with the immense body of QRLA or IVLA research. It is likely these low levels are continuously removed by hepatic extraction, thus limiting effective levels reaching the periphery (62).

While CRLA advocates have claimed superiority of their product over QRLA they have attached success of a clinical trial utilizing QRLA to help sell CRLA (88). This "sleight of hand" trick is an example of blatant deception and marketing subterfuge and questions the scientific integrity of companies making such claims.

CRLA is not proven safe or effective: The literature contains only two papers concerned with the clinical safety or efficacy of CRLA (24, 25) and a single paper promoting a chitosan-based LA for sustained/pulsed release (SRLA) that displays a bi-phasic rather than a continuous release profile (26). This bi-phasic profile is also shown in the plasma-time course of CRLA in a single volunteer and should not be interpreted as a beneficial or unique characteristic of the CRLA product (24). A bi-phasic PK profile has been reported with QRLA and in animal models and most likely represents uneven

disintegration, dissolution, distribution and subsequent redistribution of LA or impaired gastrointestinal emptying in diabetics (60, 85).

In the first paper advocating CRLA, Evans states, “If the limitations of oral (LA) therapy can be overcome, LA could emerge as a safe and effective adjunctive antidiabetic agent with insulin sensitizing activity” (25). As shown by the numerous references above, these apparent (only to the CRLA advocates) limitations have been surmounted by extensive testing from numerous research groups. In addition, it is now possible to achieve significantly higher (therapeutic) levels of the natural form of LA using either RLA tromethamine salt (30, 60) or RLA sodium salt (1, 2).

On the surface, CRLA looked like it could have some therapeutic efficacy not reported for QRLA due to the reported correlation between the increase in MRT and a reduction in fructosamine. Unfortunately, even this data is irrelevant since thiols in general and dihydrolipoic acid (DHLA) in particular, which is formed by the reduction of LA, interferes with the fructosamine assay, rendering the results meaningless (87).

Summary: All of the PK studies over the last 57 years provide irrefutable evidence that QRLA is safe and efficacious. Recent attempts to market CRLA as a superior form of LA are without technical merit. Based on what is known about the fundamental mechanisms of action of LA, *in vivo* it is doubtful that CRLA will ever be able to replace or compete favorably with QRLA. This position is further strengthened by the fact that to date there has been no positive correlation between the PK and pharmacodynamics (PD) of LA. This indicates that the beneficial effects of LA are induced **quickly**, do not depend on the MRT in plasma and require a threshold concentration not achievable with the current CRLA products.

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Heinz Ulrich, MD is considered to be one of the world’s leading experts on LA and its use in treatment of diabetic neuropathy and clinical medicine. Heinz re-initiated world interest in R-lipoic Acid (RLA) in the early 80’s after a 20 year hiatus. Heinz has 15 peer reviewed articles on LA, 44 patents, was the former Division Head of Medical & Scientific Department of Asta Medica (Frankfurt) and the organizer of two international conferences on LA. He began exploring the pharmacokinetics (PK) and pharmaco-dynamics (PD) of LA in 1984.

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