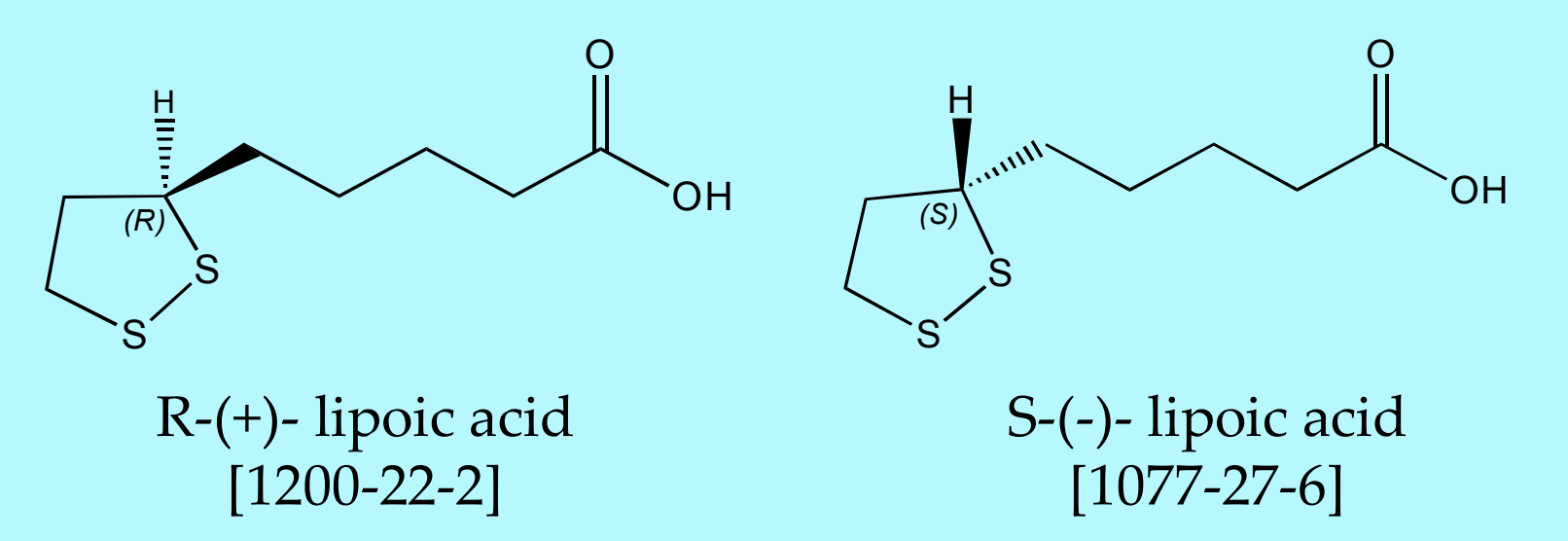


# A comparison of the pharmacokinetic profiles of lipoate enantiomers with the racemic mixture in healthy human subjects indicates possible stereoselective gut transport

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## Rationale

To test whether SLA positively or negatively alters gastrointestinal absorption and subsequent PK profiles, 600 mg of stabilized sodium salts of RLA, SLA and racemic-LA (rac-LA) were administered (P.O. dissolved in 200 mL water) in a classical three-period cross-over study undertaken with three healthy human subjects.

## Introduction

It is a well established principle of pharmacology that single enantiomers generally display different pharmacokinetic (PK) profiles due to differential absorption, transport, plasma protein binding affinity, metabolism, distribution and elimination relative to the racemate or to its antipode. Stereochemical binding preferences for a given enantiomer to an enzyme, receptor site, signaling molecule or target protein are documented, which may lead to differences in pharmacodynamics (PD) (1).

Lipoic acid (LA) has a single chiral center (at C6) and exists as two enantiomers, the naturally occurring R-lipoic acid (RLA) and S-Lipoic acid (SLA) but is generally administered as a racemic mixture (rac-LA) for pharmaceutical and nutraceutical applications. Stereochemical similarities and differences have been reported, suggesting the three forms of LA should be considered pharmacologically distinct. In vitro and animal models have indicated RLA is the eutomeric form but its application is limited by its inherent instability and propensity to form insoluble polymers (2, 3 and references therein).

Based on the condition of dose-concentration linearity, rat and human PK studies have indicated gut absorption of RLA is enhanced over rac-LA when administered as an oral solution of a RLA salt, evidenced by higher peak plasma concentrations (C<sub>max</sub>) and area-under-curve (AUC) values for RLA relative to equivalent doses of rac-LA (2 - 5).

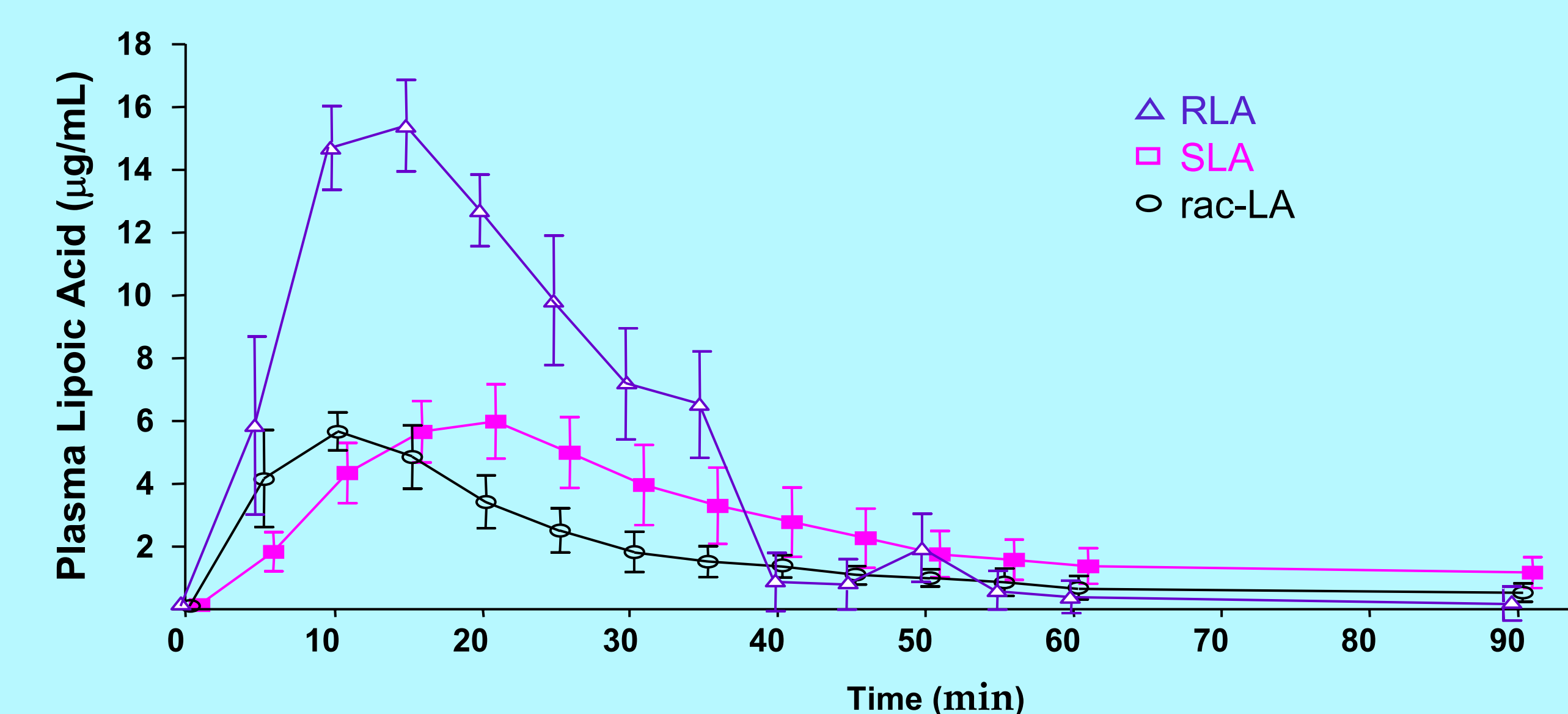
The PK of rac-LA has been extensively studied and reported by several groups. Enantioselective analysis revealed higher plasma levels of RLA when rac-LA is administered, suggesting possible stereospecific PD. The enantioselective PK of orally administered rac-LA indicates the peripheral bioavailability of RLA is greater by a factor of ~1.6 -2:1 over SLA (4-6, 8-10). It has been suggested this is due to a hepatic stereoselective first pass mechanism leading to higher concentrations of SLA transported into hepatocytes. Alternative explanations are also possible, such as stereoselective uptake of RLA from the gut and/or stereoselective renal elimination of SLA.

## Materials and methods

Whole blood was collected in Li or Na-heparinate tubes. Total plasma LA was separated from protein by vortexing samples with mobile phase at 37 deg C, followed by cooling and centrifugation (2, 7). Standard curves were generated from spiking known concentrations of RLA reference standards dissolved in ethanol and diluted in phosphate-buffered saline (PBS) into each individual's baseline plasma to account for inter-individual differences in protein binding and to prevent denaturing of plasma proteins. Total plasma RLA, SLA and rac-LA content were determined by the percent recovery using high-performance liquid chromatography (electrochemical/coulometric detection; HPLC/ECD) (2, 3, 8).

## Conclusions

The poor physical stability and absorption of free acid preparations of RLA limits its potential pharmaceutical and nutraceutical applications. These limitations are overcome by administering RLA in the form of a salt. The human C<sub>max</sub> and AUC values of RLA are significantly greater than either rac-LA or SLA when administered as oral solutions of the sodium salts. The fast T<sub>1/2</sub> and T<sub>max</sub> values of RLA indicate a possible stereoselective transport mechanism, benefited when SLA is absent. Both RLA and SLA, as the single enantiomers are absorbed more rapidly and to a greater extent, resulting in higher C<sub>max</sub> and PK values relative to enantiomeric components of the racemic mixture, indicating competition for the transporter. The diminished peak plasma concentration of rac-LA dosages compared with RLA and SLA also suggests the presence of SLA, even in the racemate, may limit the overall bioavailability of either of the LA enantiomers. Based on PK values previously reported for 600 mg of the therapeutically effective rac-LA, it should be possible to achieve similar PK profiles with 150 mg of the natural and eutomeric form, RLA when administered in the form of an aqueous solution of NaRLA.



	Subject 1	Subject 2	Subject 3	Mean values
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### RLA

C <sub>max</sub>	18	12.9	16.1	15.7 ug/mL
T <sub>max</sub>	15	15	10	13.3 min
AUC	8.47	6.27	5.85	6.86 ug*hr/mL
t <sub>1/2</sub>	16.6	15.7	5.2	12.5 min

### SLA

C <sub>max</sub>	6.0	5.0	8.3	6.4 ug/mL
T <sub>max</sub>	15	20	20	18.3 min
AUC	2.26	4.59	4.84	3.89 ug*hr/mL
t <sub>1/2</sub>	18.7	48.7	19.2	28.9 min

### rac-LA

C <sub>max</sub>	7.1	5.1	6.9	6.37 ug/mL
T <sub>max</sub>	5	15	10	10.0 min
AUC	1.82	3.10	3.16	2.69 ug*hr/mL
t <sub>1/2</sub>	12.1	22.2	27.9	20.7 Min

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## For further information

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