Creative, guanidinoacetate and homoarginine in statin-induced myopathy

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Abstract
Our study evaluated the effect of creatine and homoarginine in AGAT- and GAMT-deficient mice after simvastatin exposure. Balestrino and Adriano suggest that guanidinoacetate might explain the difference between AGAT- and GAMT-deficient mice in simvastatin-induced myopathy. We agree with Balestrino and Adriano that our data shows that (1) creatine possesses a protective potential to ameliorate statin-induced myopathy in humans and mice and (2) homoarginine did not reveal a beneficial effect in statin-induced myopathy. Third, we agree that guanidinoacetate can be phosphorylated and partially compensate for phosphocreatine. In our study, simvastatin-induced damage showed a trend to be less pronounced in GAMT-deficient mice compared with wildtype mice. Therefore, (phospo) guanidinoacetate cannot completely explain the milder phenotype of GAMT-deficient mice, but we agree that it might contribute to ameliorate statin-induced myopathy in GAMT-deficient mice compared with AGAT-deficient mice. Finally, we agree with Balestino and Adriano that AGAT metabolites should further be evaluated as potential treatments in statin-induced myopathy.

Dear editor,

We thank Drs. Balestrino and Adriano for their insightful comments on our publication about the effects of AGAT- and GAMT-deficiency in simvastatin-induced myopathy (Balestrino and Adriano 2020). Among all our findings, Balestrino and Adriano point out the increased vulnerability of simvastatin induced myopathy in AGAT-deficient (AGAT−/−) mice compared with wildtype and GAMT-deficient (GAMT−/−) mice (Sasani et al. 2020). AGAT−/− mice are devoid of creatine, homoarginine and guanidinoacetate—the only known products of the AGAT and GAMT pathway.

First, we have shown that creatine reduces simvastatin-induced muscle damage in creatine-deficient AGAT−/− mice. This finding in mice is in line with their and other previous work in patients (Balestrino and Adriano 2018; Shewmon and Craig 2010). In mice, we have shown that creatine-deficient AGAT−/− and GAMT−/− mice reveal a severe myopathy and reduced muscle strength (Nabuurs et al. 2013; Schmidt et al. 2004). Therefore, creatine possesses a protective potential to ameliorate statin-induced myopathy in humans and mice.

Second, homoarginine was studied in statin-induced myopathy, given that we were the first to show that AGAT is mandatory for homoarginine synthesis in mice and humans (Choe et al. 2013). However, our current experiments revealed that homoarginine supplementation in homoarginine-deficient AGAT−/− mice did not affect simvastatin-induced myopathy, which is in contrast to homoarginine’s
Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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