Endocrine Journal 2016, **63** (10), 937-938

THE JAPAN ENDOCRINE SOCIETY *SINCE 1925*

Letter to the Editor

L-carnitine supplementation for the management of fatigue in patients with hypothyroidism on levothyroxine treatment

Dear Editor,

We have read with interest the nice article by An *et al.* [1], and thank them for having cited some papers of our team, but not one [2]. That paper [2] not only mentions the wide range of patients who may benefit of L-carnitine supplementation, but also underscores that on some thyroid hormone targets L-carnitine acts as an antagonist, while on others as an agonist. We would like to discuss some aspects that were missed there [1].

We start with somewhat minor comments. First, we continue to confirm that L-carnitine has minimal, if any, side-effects. Second, the formulation of L-carnitine we use (one ampoule of 1 mg given twice a day) is more practical than the one used by An *et al.* (3 tablets of 0.33 g twice a day for a total of 1,980 mg/d) [1].

Concerning the relevant comments, we think that the setting or framework for this study is the symptomatology of hypothyroidism which persists despite adequate daily doses of L-T4, and that concerns approximately 10% of hypothyroid patients, especially those with no remnant thyroid tissue (*i.e.*, post-radioiodine, post-thyroidectomy hypothyroidism) [3]. This residual symptomatology consists essentially in physical and/or mental fatigue, and can be addressed by adding L-T3 to L-T4 [3].

Within the limits of words and references permitted by the journal and not to give complete details that would preclude publication of a full paper, we would like to give some information in support of the An and colleagues' article [1]. We have a number of hypothyroid patients who have taken 2 g/d L-carnitine even for longer than 12 weeks, and we confirm the benefit in terms of physical and mental fatigue. The benefit is observed particularly in premenopausal women with postoperative hypothyroidism. Thus, it is not surprising for us that women and postoperative hypothyroidism accounted for 100% and approximately two-thirds of the subgroup that improved, but approximately 75% and 40% of the subgroup who did not (table 3 of ref. 1).

A mechanistic explanation for the efficacy of L-carnitine we wish to offer has to do with previous research on the modulation of L-carnitine on glucocorticoid action [4]. L-carnitine promotes nuclear translocation of glucocorticoid receptor-α (GRα), an important activating step of the glucocorticoid signalling. After nuclear translocation, homodimers of the activated GRα modulate the transcription of many responsive genes by binding to specific DNA-associated glucocorticoid-responsive elements (GREs) in the promoters of these genes. Similarly to glucocorticoids, L-carnitine suppressed the release of tested cytokines (tumor necrosis factor-α [TNFα] and interleukin-12 release by the tested cells (human primary monocytes) [4]. The glucocorticoid-mimetic activity of L-carnitine, resulting from stimulated transcriptional activity of GRα, would have not been predicted by the inhibiting effect of L-carnitine on glucorticoid entry into cells [4]. Now, considering that (i) cytokines are pathogenetically involved in fatigue and other neuropsychological disorders, (ii) GRα-mediated action of glucococorticoids results in "energizing" effects [5], and (iii) glucocorticoids extert a well-known inhibition of TSH secretion, it cannot be coincidental that the improved subgroup had an almost 3-fold lower concentration of TSH compared to the non-improved subgroup [1].

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Submitted Aug. 2, 2016; Accepted Aug. 12, 2016 as EJ16-0374
Released online in J-STAGE as advance publication Aug. 30, 2016

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