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Influence of vitamin B_{12} status and different folic acid dietary levels on the methylation cycle during growth and aging in rats

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Elevated folic acid (FA) intakes create analogous conditions to those of metabolic folate deficiency[1]. In a similar way, vitamin B_{12} status influences the physiological response to different FA doses in the organism[2]. In previous studies, we have demonstrated that FA deficiency compromises methionine metabolism, whereas supplementation does not show additional positive effect compared to control diet in growing animals[3]. However, there is no information on the FA supplementation effect on the methionine cycle in vitamin B_{12} deficiency in two critical physiological states such as growth and aging.

The methionine/methylation metabolism during growth and aging was determined to evaluate the global effect of different levels of dietary FA and vitamin B_{12}.

Male Sprague–Dawley rats (6 weeks, *n* 50, and 20-month-old, *n* 35) were assigned into four groups at three levels of folic acid both in the absence of vitamin B_{12} for 30 d: [C_B/C_F (50 μg vitamin B_{12}; 2 mg FA), D_B/D_F (0 μg vitamin B_{12}; 0 mg FA), D_B/C_F (0 μg vitamin B_{12}; 2 mg FA) and D_B/S_F (0 μg vitamin B_{12}; 8 mg FA)]. Manipulation of the animals was performed following European Union Normative (2003/65/CE). Student's *t* test was used to evaluate the differences in the same group between the two populations (*$P<0.05$, **$P<0.01$ and $P<0.001$).

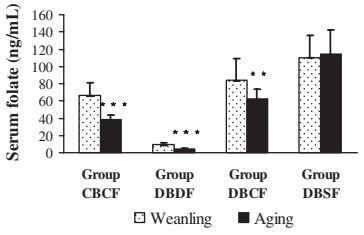

Fig. 1. Serum folate.

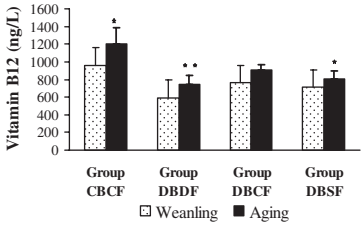

Fig. 2. Serum vitamin B_{12}.

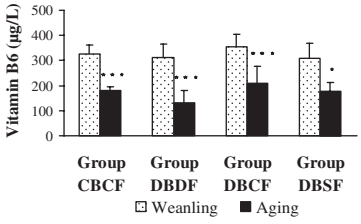

Fig. 3. Serum vitamin B_6.

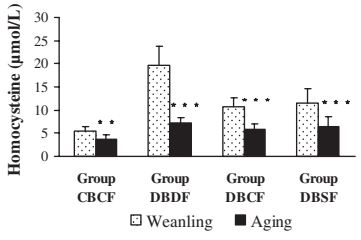

Fig. 4. Serum homocysteine.

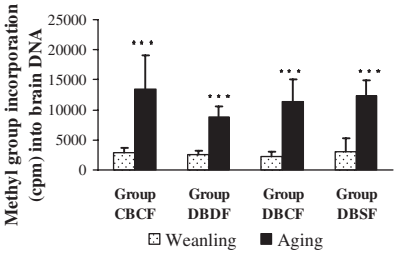

Fig. 5. DNA methylation in brain.

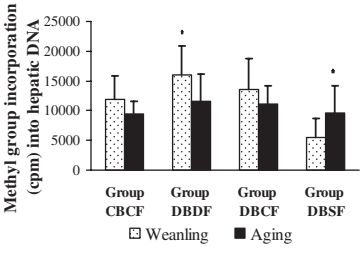

Fig. 6. DNA methylation in liver.

Serum homocysteine, vitamin B_6 and FA concentrations were lower in aging *v.* weanling rats (Figs. 1, 3 and 4, respectively), but serum vitamin B_{12} values were higher (Fig. 2). However, aging seemed not to affect the folate liver stores (data not shown). Only during growth, both vitamins deficiency induced a hepatic DNA hypomethylation that was reverted when rats were FA supplemented (Fig. 5).

There were some parameters of methionine cycle in weanling rats and none in aging rats that recovered similar values to controls when rats deficient in vitamin B_{12} were supplemented with FA. Therefore, FA supplementation should also be accompanied by the same nutritional action for vitamin B_{12} in order to solve these alterations in this vitamin B_{12} deficient group.

1. Troen AM, Mitchell B, Sorensen B *et al.* (2006) *J Nutr* **136**, 189–94.
2. Morris MS, Jacques PF, Rosenberg IH *et al.* (2007) *Am J Clin Nutr* **85**, 193–200.
3. Partearroyo T, Ubeda N, Alonso-Aperte E *et al.* (2010) *Ann Nutr Metab* **56**, 143–151.