J. Nutr. Sci. Vitaminol., **26**, 113–117, 1980

ANTAGONISM OF L(−)PANTOTHENIC ACID ON LIPID METABOLISM IN ANIMALS

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(Received December 14, 1979)

Summary The inhibition rate of L(−)pantothenate as an antagonist of D(+)pantothenate was discussed from the viewpoint of growth and lipid metabolism. The growth rate of mice given pantothenate-deficient diets containing L(−)pantothenate (300 mg per 100 g diet) was markedly decreased, and such pantothenate-deficient symptoms as "spectacle eyes" appeared. However, it was recovered by the simultaneous addition of D(+)pantothenate. This result suggests that L(−)pantothenate is an antagonist of D(+)pantothenate. The same phenomenon was observed in a rat experiment. The growth of rats given L(−)pantothenate was extremely poor but recovered by the simultaneous addition of D(+)pantothenate. Its complete recovery was seen when the ratio of L(−)pantothenate to D(+)pantothenate reached 100 : 1. The same tendencies were observed in the liver levels of total lipid, total cholesterol and triglyceride, and also in the lipoperoxide values. This experiment suggests that the inhibition rate of L(−)pantothenate to D(+)pantothenate in animals is similar to that of DL-ω-methyl pantothenate.

Keywords L(−)pantothenic acid, D(+)pantothenic acid, ω-methyl pantothenic acid, antagonist, pantothenic acid deficiency, cholesterol, growth inhibition, lipoperoxide, liver lipid

In the 1940's, there were reports regarding experiments with microorganisms (*1*), chicks (*2, 3*) and rats (*3, 4*) that D(+)pantothenate (PaA) was biologically active, while L(−)PaA was completely inactive, and the racemic compound DL-PaA had half the biological activity of D(+)PaA. Later, these studies were supported by many researchers. Sarett and Barboriak (*5*) found that L(−)PaA had no apparent biological activity when fed with equal amounts of D(+)PaA, however, a large excess of L(−)PaA relative to D(+)PaA inhibited the growth of rats. They also observed that the addition of L(−)PaA to the diets of PaA-deficient rats aggravated the signs of deficiency and led to more rapid death. On the contrary, L(−)pantothenyl alcohol did not inhibit utilization of D(+)PaA. In the

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former report, we showed in mice and rats that the inhibition rate of DL-ω-methyl pantothenate, a PaA derivative, to D(+)PaA was about 100 to 1 (*6*). In the present study, we discuss the inhibition rate of L(−)PaA as an antagonist of D(+)PaA from the viewpoint of growth and lipid metabolism.

Mice

Male ICR mice (Japan Clea Inc., Tokyo) weighing about 32 g were divided into three groups of eight animals and kept individually in screen-bottom cages. The first group was given PaA-deficient basal diet, the second PaA-deficient diet containing 12.4 mg of D(+)PaA per 100 g diet and the third PaA-deficient diet containing 300 mg of L(−)PaA per 100 g diet. L(−)Calcium pantothenate used in this study had a specific rotation of −27.3°C. The growth rate of the first group was reduced relative to the second group. In the presence of L(−)PaA, the growth rate was markedly decreased, the growth stopped at 35 days and such PaA-deficient symptoms as "spectacle eyes" appeared. However, the growth of the animals recovered rapidly by the addition of D(+)PaA at 50 days old (Fig. 1). These results show that L(−)PaA is an antagonist of D(+)PaA.

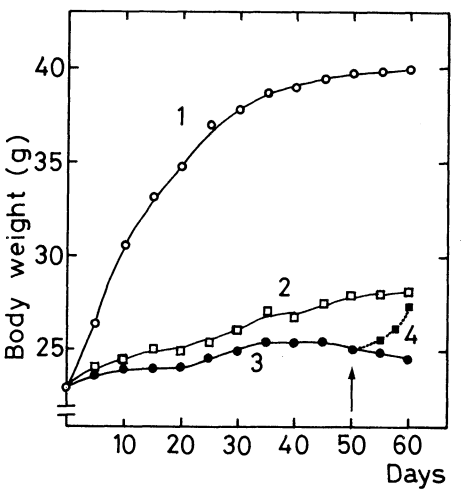

Fig. 1. Effect of D(+)- and L(−)pantothenate on the growth of mice. Male weaning mice received pantothenate-deficient diet (curve 2), D(+)pantothenate-supplemented diet (12.4 mg/100 g diet, curve 1), L(−)pantothenate-supplemented diet (300 mg/100 g diet, curve 3) and L(−)pantothenate-supplemented diet containing D(+)pantothenate (arrow, 12.4 mg/100 g diet) after receiving L(−)pantothenate-supplemented diet for 7 weeks (curve 4). Each plot represents mean values for eight animals in each group.

Rats

In preliminary experiments on the influence of cholesterol on the growth inhibition by L(−)PaA, we observed that in the presence of 1% cholesterol and 300 mg of L(−)PaA all the animals died within 6 days. Male weaning rats of Wister strain were separated into five groups of eight animals each. All were housed in individual screen-bottom cages and given five kinds of experimental diets all containing 1% cholesterol, as shown in Table 1. After previous maintenance with PaA-deficient diet for 10 days, the rats of five groups were given the experimental diets for five days. The growth of the L(−)PaA group was extremely poor, but recovered by the simultaneous addition of D(+)PaA. Almost complete recovery of the growth rate was seen when the ratio of L(−)PaA and D(+)PaA reached 100 : 1. As shown in Table 2, the levels of total lipid, total cholesterol and triglyceride in the liver of PaA-deficient rats showed a tendency to decrease. In the L(−)PaA group, the concentrations of these lipids were significantly lower than those of the animals fed the pantothenate-supplemented diet. Though no recovery of the liver lipid levels was seen in rats given diets containing L(−)PaA and D(+)PaA at the ratio of 300 : 1, almost complete recovery was obtained at the ratio of 100 : 1. This experiment suggests that the inhibition rate of L(−)PaA in animals is similar to that of DL-ω-methyl PaA (*6*). The same finding was obtained in the liver TBA value (Fig. 2) which is recognized as being a reflection of lipoperoxide level (*7*). The liver TBA value was elevated in the PaA-deficient group and further elevated by the addition of L(−)PaA. However, the elevation could be suppressed by the simultaneous addition of D(+)PaA. In analogy with the results in liver lipid levels, the elevation of liver TBA value produced by the addition of L(−)PaA was

Table 1. Composition of experimental diets. L-PaA, L(−)pantothenate; D-PaA, D(+)pantothenate.

Component	Diet (g/100 g diet)				
	Sufficient	Deficient	Deficient +L-PaA	Deficient +L-PaA +D-PaA (300 : 1)	Deficient +L-PaA +D-PaA (100 : 1)
Vitamin-free casein	20	20	20	20	20
Glucose	64.5	64.5	64.5	64.5	64.5
Soybean oil	6	6	6	6	6
Salt mixture	6	6	6	6	6
PaA-free vitamin mixture	—	2	2	2	2
Cholesterol	1	1	1	1	1
Cholic acid	0.5	0.5	0.5	0.5	0.5
L-PaA	—	—	0.3	0.3	0.3
D-PaA	0.01	—	—	0.001	0.003

Table 2. Effect of L-pantothenate on liver lipid in cholesterol-fed rats.

Diet	Total lipid	Total cholesterol (mg/g tissue)	Triglyceride	Phospholipid
Sufficient	69.2±9.5	10.1±1.4	20.3±3.6	21.2±3.0
Deficient	55.7±11.4	8.6±1.2	14.7±8.1	21.1±3.2
Deficient +L-PaA	56.1±8.5*	5.0±1.6**	13.6±3.9*	22.6±1.2
Deficient +L-PaA, +D-PaA (300:1)	45.7±7.0*	5.1±1.0*	14.9±1.7	18.6±4.8
Deficient +L-PaA, +D-PaA (100:1)	54.2±10.1	9.0±2.3	17.8±1.0	17.3±0.3

Values represent means±SD. * $p<0.05$, ** $p<0.01$ (compared with sufficient group).

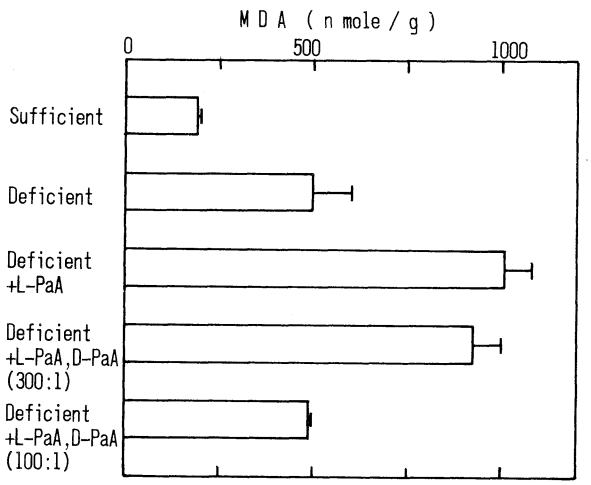

Fig. 2. Effect of L(−)pantothenate on liver TBA values in cholesterol-fed rats. The vertical bar shows the standard error of mean value. MDA, malon dialdehyde.

considerably suppressed at the ratio of 100:1 [L(−)PaA:D(+)PaA]. The findings from these experiments suggest that L(−)PaA is useful for the study of PaA deficiency in animals.

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