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Apoptosis induced by the esters of picolinic acid with alkyl groups in HL-60 cells

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Abstract

We have previously found that picolinic acid and its related compounds can induce apoptosis in human promyelocytic leukemia (HL-60) cells, but not at <2 mM concentration. In the present study, we examined whether different esters of picolinic acid with alkyl groups and those with cholesterol can induce apoptosis. We found that the esters of picolinic acid with octyl, decyl, dodecyl, and hexadecyl groups induced apoptosis in HL-60 cells most effectively in a chain length-dependent manner. Particularly, dodecyl picolinate induced apoptosis even at over 0.01 mM concentration. On the other hand, cholesteryl picolinate did not induce apoptosis. In addition, we examined the effect of vitamin E as an antioxidant on apoptosis induced by picolinic acid or various esters of picolinic acid in HL-60 cells. We found that percent of sub-G1 peak was more effectively decreased by pre-treatment with vitamin E. Cumulatively, our results suggest that the apoptosis induced by esterification of the carboxyl group of picolinic acid with various alkyl groups is more effective.

Keywords : picolinic acid, niacin, apoptosis, flow cytometry, HL-60

I Introduction

Nicotinic acid, nicotinamide and nicotinamide riboside, namely niacin, are water-soluble vitamins that are converted to NAD *in vivo*. NAD is an important coenzyme in the oxidation- reduction reactions and is also a substrate for ADP-ribosylation enzymes, sirtuin and so on[1-3]. Therefore, further investigations of newer biological functions of niacin and NAD are extremely important and interesting.

We have previously investigated various physiological and pharmacological functions of niacin and its related compounds in diverse organisms. In our previous study, we examined whether niacin-related compounds possessed apoptosis-inducing activities and found that particularly, picolinic acid, dipicolinic acid, and isonicotinamide induced apoptosis in in human promyelocytic leukemia (HL-60) cells[4, 5] and human erythroleukemia (K562) cells[6] via the caspase pathway. However, in human quiescent normal lymphocytes, these compounds did not induce apoptosis under the same conditions[6]. On the other hand, nicotinic acid and nicotinamide did not induce apoptosis.

Picolinic acid, a structural isomer of nicotinic acid, is synthesized from tryptophan in a side pathway of NAD biosynthesis in animals, and it exists in various organisms and foods as a natural component. Moreover, picolinic acid has been reported to exhibit a growth-stimulating effect in rats[7] and may also improve the immune system by activating murine macrophage[8]. Interestingly, picolinic acid, which has several positive effects on normal cells and individuals, induces apoptosis in tumor cells. Therefore, we investigated whether different picolinic acid-related compounds show apoptosis-inducing activities. In addition, fusaric acid, picolinaldehyde, nicotinaldehyde, 2-aminopyridine, and 3-aminopyridine induced apoptosis in HL-60 cells[9]. These results suggest that pyridine-substituted groups and the consequent change in the resonant structure may play an important role in the induction of apoptosis. Interestingly, fusaric acid, which is 5-n-butyl-2-picolinic acid, induced

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