Structure-dependent effects of pyridine derivatives on mechanisms of intestinal fatty acid uptake: regulation of nicotinic acid receptor and fatty acid transporter expression

Pyridines are widely distributed in foods. Nicotinic acid (NA), a carboxylated pyridine derivative, inhibits lipolysis in adipocytes by activation of the orphan NA receptor (HM74A) and is applied to treat hyperlipidemia. However, knowledge on the impact of pyridine derivatives on intestinal lipid metabolism is scarce. This study was performed to identify the structural determinants of pyridines for their effects on fatty acid uptake in enterocyte-like Caco-2 cells and to elucidate the mechanisms of action. The impact of 17 pyridine derivatives on fatty acid uptake was tested. Multiple regression analysis revealed the presence of a methyl group to be the structural determinant at 0.1 mM, whereas at 1 mM, the presence of a carboxylic group and the N-methylation presented further structural characteristics to affect the fatty acid uptake. NA, showing a stimulating effect on FA uptake, and N-methyl-4-phenylpyridinium (MPP), inhibiting FA uptake, were selected for mechanistic studies. Gene expression of the fatty acid transporters CD36, FATP2 and FATP4, and the lipid metabolism regulating transcription factors peroxisome proliferator-activated receptor (PPAR) alpha and PPARgamma was up-regulated upon NA treatment. Caco-2 cells were demonstrated to express the low-affinity NA receptor HM74 of
which the gene expression was up-regulated upon NA treatment. We hypothesize that the
NA-induced fatty acid uptake might result from NA receptor activation and related intracellular
signaling cascades. In contrast, MPP increased transepithelial electrical resistance. We therefore
conclude that NA and MPP, both sharing the pyridine motif core, exhibit their contrary effects on
intestinal FA uptake by activation of different mechanisms.

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