Nicotinamide administration alters the activities of hepatic microsomal mixed function oxidases[1]

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Summary. Systemic action of nicotinamide significantly alters the activities of hepatic drug metabolizing enzymes. Male rats injected with nicotinamide have reduced levels of cytochrome P450, demethylases and aniline hydroxylase. The changes appear to be sex-dependent since in the case of female rats activities of p-nitroanisole-o-demethylase and aniline hydroxylase are enhanced whereas cytochrome P450 content remains unaltered.

The activities of microsomal drug-metabolizing enzymes are known to be altered by changes in nutritional status such as vitamin deficiency[3,4]. Ingestion of excess vitamins also affects the activity of liver microsomal monooxygenases[5]. It appears from the literature that not much attention has been given to the effect of nicotinic acid or its derivatives on hepatic drug metabolism. In this report evidence has been presented that the administration of nicotinamide leads to significant changes in the activities of liver microsomal drug-metabolizing enzymes.

Materials and methods. Wistar rats (150–200 g) were injected i.p. with nicotinamide in physiological saline at a dose of 1 g/kg b.wt and sacrificed after 24 h. Animals were fed ad libitum with Hind Lever Laboratory Chow and they had free access to water. Liver microsomes prepared by the established procedure of Ichi and Yago[6] were used for the assay of enzymes. NADPH cytochrome C reductase was assayed by the spectrophotometric method of Christensen and Wissing[7]. The radiometric method of DePierre et al.[8] was followed for the assay of aryl hydrocarbon hydroxylase. Aniline hydroxylase was assayed by the method of Imai et al.[9]. The procedures of Patel and Pawar[10] and Kato and Gillette[11] were employed with slight modification for the assays of aminopyrine-N-demethylase and p-nitroanisole-O-demethylase respectively. Formaldehyde was estimated by the method of Nash[12]. All incubations for enzyme assays were performed aerobically at 37 °C with saturating concentrations of cofactors and substrates, and were linear with respect to incubation time and enzyme concentration. Protein was estimated by the method of Lowry et al.[13]. Cytochrome P 450 was assayed by the method of Omura and Sato[14] using a Gilford spectrophotometer.

Results and discussion. The pharmacodynamic effect of nicotinamide on liver microsomal mixed function oxidases has received little attention. The results presented in the table reveal that nicotinamide injection significantly alters rat liver monooxygenase activities. A marked elevation in the activities of hydroxylases is noted in the livers of nicotinamide-treated female rats. In treated male rats, the activity of aryl hydrocarbon hydroxylase was similarly increased, whereas the aniline hydroxylase and the demethylase activities were reduced. In female rats, aminopyrine-N-demethylase activity was reduced (but it was statistically insignificant), whereas the activity of p-nitroanisole-O-demethylase was enhanced. The activity of hepatic NADPH cytochrome C reductase was decreased in male rats while it increased in females. Level of cytochrome P450 was decreased in the livers of nicotinamide-treated male rats alone. Sex is known to influence drug metabolism[11]. Likewise the effect of nicotinamide seems to be influenced by sex and in fact the changes observed in males are nearly opposite to those in females. No toxicity was observed in animals treated with nicotinamide. Animals were all healthy and active and no mortality was observed during the course of nicotinamide treatment.

Many investigators use nicotinamide in the assay of microsomal monooxygenases to prevent the degradation of NADPH. But no adverse effect of nicotinamide in vitro on the enzyme activity has been reported. Hence the action of nictonamide on microsomal drug metabolizing enzymes seems to be effective systemically. The ability of nicotinamide to alter the hepatic metabolism of drugs can be conceived to have significance in modulating the effects of many xenobiotics including carcinogens. The mechanism of nicotinamide mediated change in hepatic mixed function oxidases is under investigation.

Effect of nicotinamide treatment on liver microsomal mixed function oxidase activities in male and female rats

Enzyme assayed	Male rats Control	Nicotinamide treated	Female rats Control	Nicotinamide treated
Cytochrome P450	0.716±0.054	0.493±0.032****	0.455±0.034	0.458±0.019
Aniline hydroxylase	2.15±0.10	1.60±0.11*	1.21±0.09	1.85±0.11*
Aminopyrine N-demethylase	11.85±0.86	7.15±0.58**	10.80±1.10	7.60±2.88
p-Nitroanisole-O-demethylase	4.93±0.30	2.59±0.50***	1.01±0.16	2.56±0.57****
NADPH cytochrome-C reductase	55.29±3.01	46.33±1.04****	53.66±1.50	64.14±2.73*
Aryl hydrocarbon hydroxylase	6070.00±989.00	12351.00±1646***	8048.00±1133	12264.00±973***

The enzyme activity is expressed as nmoles of product formed/15 min/mg protein except NADPH cytochrome-C reductase and aryl hydrocarbon hydroxylase activities which are expressed as nmoles of cytochrome-C reduced/min/mg protein and DPM/mg protein/15 min respectively. Cytochrome P450 level is expressed as nmoles/mg protein. The values denote mean±SE of 10 separate observations. * $p \leqslant 0.01$; ** $p \leqslant 0.001$; *** $p \leqslant 0.05$; **** $p \leqslant 0.02$.

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