Enhancement of antipyrine clearance and induction of antipyrine 4-hydroxylation by 3-methylcholanthrene in rats

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Antipyrine is frequently used as a model substrate to assess the capacity for hepatic drug metabolism *in vivo* in humans and animals. Using this substrate (50 mg/kg, i.v.) in rats we observed that 3-methylcholanthrene (3-MC) (20 mg/kg, i.p.), given 48 and 24 h beforehand, enhanced antipyrine clearance, measured by GLC (Prescott, Adjepon-Yamoah & Roberts, 1973), from 6.6 ± 0.3 to 15.4 ± 1.6 ml min^{-1} kg^{-1} ($P < 0.001$, $n = 6$). Antipyrine 4-hydroxylation by 9000 *g* liver supernatant, determined according to Tabarelli & Uehleke (1977) was induced to 139% of control values ($P < 0.05$, $n = 6$). This reaction was inhibited 50% by α-naphthoflavone (0.1 mM), an inhibitor of cytochrome P_1-450, in 3-MC treated animals but not in controls. Conversely SKF-525A (0.5 mM) inhibited the reaction by 77% in controls but only by 42% in 3-MC treated rats. This indicates that antipyrine 4-hydroxylation is, in part, catalysed by cytochrome P_1-450.

The effect of 3-MC on antipyrine metabolism *in vivo* was further studied by determining antipyrine metabolites in urine. After administering antipyrine (50 mg/kg i.p., containing 60 μCi/kg of [^{14}C]-methyl antipyrine), urine was collected for 24 hours. After incubation for 20 h with β-glucuronidase arylsulphatase (10.000 U), metabolites were extracted at pH 1 and 7 with chloroform:methanol (9:1) and separated by two dimensional thin-layer chromatography. The radioactive zones were scraped off and counted. Total urine [^{14}C] accounted for 75–85% of the dose. In addition to the known metabolites: 4-hydroxy-, 3-hydroxymethyl and 3-carboxy antipyrine, three as yet unidentified metabolites were detected (I, II and III) (Figure 1). Pretreatment with 3-MC increased the amounts of 4-hydroxy antipyrine and compounds I and II, indicating that their formation is enhanced. Excretion of 3-hydroxymethyl antipyrine was diminished to about the same extent as antipyrine clearance was increased, indicating that the 3-hydroxylation was not influenced. Comparison with phenobarbitone, which also induced antipyrine metabolic clearance, revealed that this compound does not change the amounts of antipyrine metabolites in the urine and, thus, induces all metabolic pathways to the same extent.

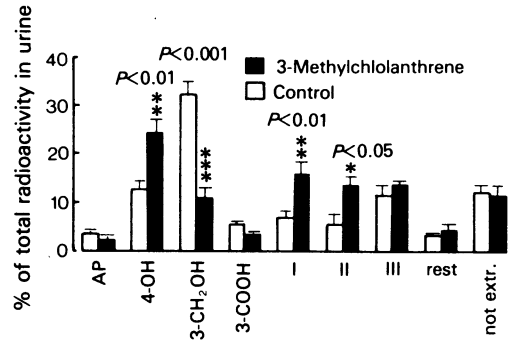

Figure 1 Antipyrine metabolites in hydrolysed 24 h urine after administration of ([^{14}C-methyl)antipyrine to 3-MC treated and control rats.

References

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