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Chemosterilant action of trimethylphosphate in rodents

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Trimethylphosphate, the simplest tri-alkyl ester of phosphoric acid, produces marked antifertility effects in experimental male rodents (Jackson & Jones, 1968). The predominant effect is the "functional" sterilizing action involving spermatids from which intact, motile but incompetent sperm continue to be produced. Relatively high doses are required in the mouse (5×1 g/kg orally), whereas it is effective in the rat at one tenth of this level.

Trimethylphosphate is remarkable in that it possesses no anticholinesterase activity, is freely soluble and stable in water, is effective orally and has a high level of tolerance. Whereas 500 mg/kg orally render male rats sterile for the ensuing 3 weeks, five times this amount, although tolerable, completely disorganizes spermatogenesis without damaging tubular architecture. Such treated rats remain infertile for 20–25 weeks, apparently retaining sexual activity, though a proportion appear to be more permanently sterilized. Rats treated weekly at 5×100 mg/kg orally for over one year have remained sterile but recover fertility 3–5 weeks from terminating treatment. "Side-effects" so far observed are a sedative action and, towards one year of treatment, hind leg paresis, although five times this dose rate caused progressive loss in weight.

Using ^{32}P-trimethylphosphate the sole phosphorus-containing metabolite is dimethylphosphate (Jackson & Jones, 1968), which has no antifertility activity. With ^{14}C-trimethylphosphate, *S*-methyl cysteine was identified as a urinary metabolite, indicating that trimethylphosphate is involved, at least in its detoxification process, as an alkylating agent.

The antifertility action of trimethylphosphate is probably related to methyl alkylation. This would bring it into line with the methyl ester of methanesulphonic acid which also produces the "functional" type of sterility in rats and mice (Jackson, 1964). Like methyl methanesulphonate (Partington & Bateman, 1964), trimethylphosphate in sub-sterilizing doses induces so-called dominant lethal mutations.

Preliminary structure/activity studies have shown that tri-ethyl- and tri-*iso*-propyl-phosphates do not affect the fertility of male mice (5×1 g/kg orally). Both these esters together with tri-*n*-propyl- and tri-*n*-butyl-phosphates still have the capacity to alkylate, and like trimethylphosphate, the only metabolites in the rat were the di-alkylphosphates and corresponding *S*-alkyl cysteines. Whereas all these substances interact with cysteine *in vitro*, only trimethylphosphate reacts readily with glutathione. This might be pertinent to its biological activity.

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