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Δ^9-Tetrahydrocannabinol inhibits human sperm motility

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Marihuana can inhibit male reproduction in several animal species (Bloch et al 1978). Δ^9-Tetrahydrocannabinol (THC), the principal psychoactive constituent of marihuana, inhibits bull sperm motility (Shahar & Bino 1973).

There is no information about the effect of marihuana on the motility of ejaculated human sperms, although it is known to reduce serum testosterone levels (Kolodny et al 1974) and decrease sperm density in the ejaculate (Kolodny et al 1974: Hambree et al 1979). We now report the dose-response relationship between THC and human sperm motility.

Fresh human semen samples were collected either from volunteers or patients attending the seminology laboratory at our hospital. Only samples with sperm concentrations higher than 15×10^6 ml^{-1} and percentage of progressive forward moving sperms higher than 20% were used, because a preliminary study (Hong et al 1981) had shown that motility measurement in poor motility samples was less accurate.

The effect of THC on sperm motility was measured by dividing each semen sample into 100 μl aliquots which were then mixed with 50 μl THC solution of various concentrations. 100 μl of each mixture was pipetted into a small tube to the lower end of which a sheet of Nuclepore membrane, with many evenly distributed 5 μm capillary pores, had been bonded. This tube was then inserted into a glass bottle which contained phosphate buffer (Dulbecco A, pH 7·3, Oxoid Ltd). The proportion of sperms that move across the membrane into phosphate buffer during 2 h incubation at 37 °C is called trans-membrane migration ratio (TMMR) (Hong et al 1981).

Because THC is insoluble in water, we used an ethanol–Tween 80–phosphate buffer (Dulbecco A, pH 7·3) (5:1·5:93·5% v/v) as solvent.

To exclude interference from ethanol and Tween 80, we compared the effects of (i) phosphate buffer, (ii) 5% ethanol in phosphate buffer and (iii) 1·5% Tween 80 with 5% ethanol in phosphate buffer (TEB) on human sperm motility. Sperms varied considerably in their basal motility values and therefore a within-sample comparison was made to determine the effects, if any, of ethanol and Tween 80. Six samples were used and neither ethanol nor Tween 80 concentration significantly changed the motility (buffer alone TMMR = 32·7 (s.d. 15·9); ethanol + buffer 31·5 (s.d. 14·1); Tween 80 + ethanol + buffer (TEB) 30·7 (s.d. 13·6): n = 6 $P < 0.05$ paired t-test. Despite the large s.d. values, within-sample differences were ca 9–20%).

Fig. 1 shows the log concentration-response curve for THC and inhibition of human sperm motility. Five samples were used. The motility of sperms in semen-TEB mixture was used as control and those of semen-THC mixtures were expressed as percentage of control. The concentration of THC that decreased sperm motility to 50% of control was 0·65 mM.

Cannabinoids may reduce fertility by direct suppression of testicular tissues (Dalterio et al 1977), anti-androgenic effects (Purohit et al 1980), oestrogen-like effects (Rawitch 1977) or through inhibition of the hypothalamo-pituitary-gonadal axis (Symons et al 1976). It is unlikely that these mechanisms are responsible for the inhibition of sperm motility in the ejaculate.

THC has been reported to alter membrane stability in cultured T-lymphocytes (Desoize et al 1978). It also inhibits respiration and reduces the ATP content of bull sperm (Shahar & Bino 1973). Membrane-active drugs (Peterson & Freund 1975) and drugs that interfere with cellular metabolism (Tamblyn & First 1977) are known inhibitors of sperm motility. It is probable that THC inhibits sperm motility through these mechanisms.

THC is highly lipid-soluble and although its peak serum concentration was only about 0·2 mM after a single intravenous infusion of 5 mg THC in man (Garrett 1979), the tissue concentration may be much higher, especially after long-term use. Information concerning the concentration of THC in the semen of cannabis smokers is not available, but our observation suggests that marihuana may be a cause of infertility by reducing sperm motility.

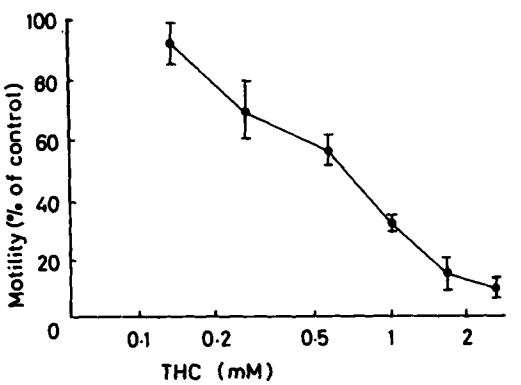

Fig. 1. Log concentration-response curve for the inhibition of human sperm motility by THC expressed as percentage of control values. THC was dissolved in TEB (Tween 80, ethanol and phosphate buffer). The motility of sperms in semen-TEB mixture was used as control. All points are mean ± s.e.m. of five samples.

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In vitro metabolism of zipeprol using hepatic preparations from rabbits

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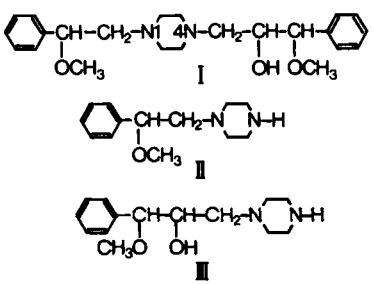
The fate of the antitussive agent zipeprol(I) in man has been studied extensively (Beckett & Achari 1977a, b, c). Its metabolism using 9000 *g* liver homogenates of rabbits fortified with cofactors is now reported.

After zipeprol had been incubated at pH 7·4 for 60 min, an ethereal extract of the alkaline (pH 12) incubation mixture showed four products on thin layer chromatography (silica gel 60; benzene-diethylamine–methanol (80:10:10)) in addition to the substrate (R_F 0·63). Products A(R_F 0·31) and B(R_F 0·22) corresponded with the reference compounds II and III, respectively; these products were examined by mass spectrometry as their NBD derivatives (see later).



I

II

III

The major metabolic product C(R_F 0·48) gave colour reactions similar to zipeprol with Dragendorff and iodoplatinate reagents. This metabolic product was scraped off the plate before spraying, extracted with ether and the concentrated ethereal extract was examined by direct inlet mass spectrometry using an AEI-MS 9 mass spectrometer operated at an ionization potential of 70 eV. The mass spectrum (Fig. 1) indicated that it was the *O*-demethylated product IV (Fig. 2). The spectrum displayed no molecular ion; the abundant ion at *m/z* 249 expelled a molecule of benzaldehyde via the four membered transition state (Fig. 2) to form *m/z* 143. The metastable ion at *m/z* 82·1 supported this direct fragmentation.

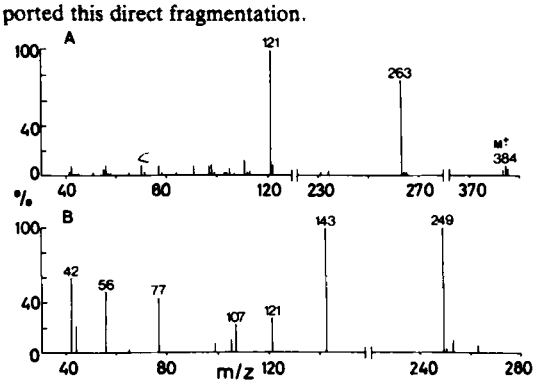


FIG. 1. Direct inlet mass spectra of (A) zipeprol(I) and (B) its metabolic product(IV).

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