of trypsin to the enzyme preincubated with S-adenosylmethionine results in a marked decrease in serine sulfhydrase activity. As shown in the table, trypsin and S-adenosylmethionine act not synergistically, whereas the combined treatment with both trypsin and S-adenosylmethionine produced a smaller increase in serine sulfhydrase activity than did treatment with trypsin or S-adenosylmethionine alone. It is undoupted that trypsin has different effects upon control enzyme and enzyme altered with S-adenosylmethionine or ethionine. However, the nature of the interrelationships among various actions of trypsin, ethionine and S-adenosylmethionine is unknown. It is now well established that administration of ethionine to rats leads to a rapid synthesis of S-adenosylethionine in the liver[11-14]. Both S-adenosylmethionine (SAM) and S-adenosylethionine (SAE) were found to increase hepatic cystathionine β-synthetase[4,6]. The present findings, coupled with the reports cited above, suggest that action of ethionine on serine sulfhydrase is mediated by S-adenosylethionine. It is obvious from the results of this study that trypsin and S-adenosylmethionine (as well as S-adenosylethionine) act in a different manner to activate rat liver serine sulfhydrase. The exact mechanism of interaction of trypsin and S-adenosylmethionine or S-adenosylethionine is not clear as yet. Based on the information derived from these experiments, it is postulated that serine sulfhydrase activated by SAM or SAE is more liable for proteolytic action of trypsin. These data support the conclusion that activation of serine sulfhydrase by S-adenosylmethionine or S-adenosylethionine is due to some modification of the enzyme structure.

Since trypsin has been shown to cause an increase in cystathionine β-synthetase activity[7], the findings presented in this study confirm the opinion that cystathionine β-synthetase and serine sulfhydrase activities are associated with the same protein.

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Changes of the prostaglandin F_{2a} metabolism in early human placenta[1]

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Summary. The quantitative metabolism of PgF_{2a} was studied in different ages of early human placentae in vitro. The 15-OH-Pg-dehydrogenase became minimal at about the 9th week.

In the last 10 years, it was proved that prostaglandins take an important part in regulating pregnancy. It was demonstrated by Karim and Devlin[3], Karim and Hillier[4], Jouvenaz et al.[5] and Keirse et al.[6] that the endogenous prostaglandins (E_2 and F_{2a}) significantly increase in the amniotic fluid from early pregnancy till term. According to Willmann et al.[7], the main site of synthesis is the decidua and myometrium. Metabolism mostly takes place in the placenta which is very active as regards 15-OH-prostaglandin-dehydrogenase, as well as prostaglandin Δ^{13} reductase enzymes[8,9]. Carminati et al.[10,11] studied the quantitative metabolism of the PgF_{2a} and E_1 at various stages of pregnancy in the rat. Results of these investigations showed that metabolism became maximal between days 9 and 12 of gestation.

In our own work we have studied 15-OH-prostaglandin-dehydrogenase (15-OH-PGDH) activity in early human placentae during the course of gestation.

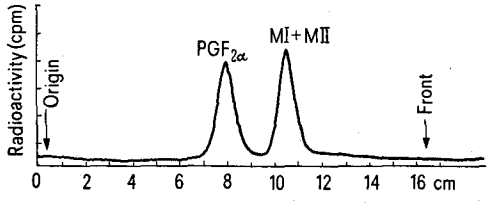

Fig. 1. Radiochromatogram demonstrating prostaglandin metabolism by homogenat of early human placenta. Solvent system, benzene:dioxan:acetic acid = 10:10:1; MI, 15-keto-PgF_{2a}; MII, 15-keto-13, 14-dihydro-PgF_{2a}.

Material and methods. 45 placenta tissues were obtained from interruption of pregnancies in healthy individuals. The length of pregnancy was established from the time which elapsed since the first day of final menstruation until the interruption. The placenta tissues were quickly separated and homogenized with 4 volumes of ice-cold Bücher medium[12] in a Potter-Elvehjem tissue grinder. The whole homogenates were centrifuged at 10,000 × g and 2 ml of supernatant incubated with 1.25 μCi H^3-PgF_{2a} (9.3 Ci/mMol, New England, Nuclear Corp.).

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2 The authors are indepted to Miss M. Pasztor, Mrs V. Palinkas and Miss G. Odrobina.

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The final concentration of the non-radioactive PgF_{2a} was 0.1 μMoles NAD was applied as a co-factor in 4 mMoles final concentration. The incubation period was 2.5 min at 37 °C, under aerobic conditions. The intact PgF_{2a} and the metabolites were dissociated by thin-layer chromatography, and Packard Radiochromatogram Scanner was applied to detect them (figure 1). The zones corresponding to PgF_{2a} and the metabolites were scarped and the radioactivity was measured with a Nuclear Chicaco Liquid Scintillation Spectrometer. The protein content of the incubated substance was determined according to Lowry et al.[13]. Metabolism of PgF_{2a} is expressed according to Carminati et al.[11] as pmoles of substrate metabolized h/mg protein.

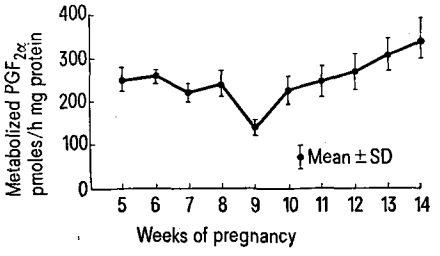

Fig. 2. Quantitative metabolism of PgF_{2a} by human placenta during early pregnancy.

Results and discussion. The 15-OH-PGDH activity of the placenta shows a declining tendency from the 5 week of pregnancy till the 9 week when a minimum can be observed, then they rise gradually as pregnancy advances (figure 2). Placental prostaglandin metabolism per mg protein was significantly lower on week 9 of gestation ($p < 0.01$ for week 9 then all other weeks).

The experimental results reported here demonstrate that there is an important relationship between the stage of pregnancy and the metabolism of PgF_{2a} in early human placenta. That the placenta could be a rich source of 15-OH-PGDH was demonstrated by Jarabak[8], and partial purifications of this enzyme from term placental tissue have been reported by Schlegel et al.[14]. It can be suggested that the high enzyme activities in the placenta is part of a mechanism by which the fetus is protected against potentially harmful effects of high concentrations of prostaglandins. The results of our studies may indicate that decrease of 15-OH-PGDH activity can result in the rise in the endogenous prostaglandin level, which makes a spontaneous contraction of the uterus possible. The highest probability of this is in the first trimester about the 9 week of the pregnancy.

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Isotope effect studies on the dehydrogenation of Δ^1-tetrahydrocannabinol in the rat

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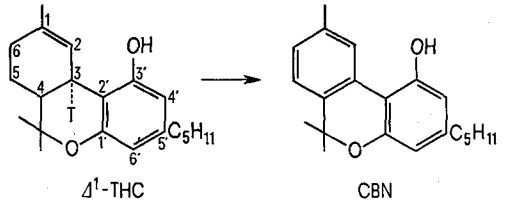
Summary. Isotope effect studies on the metabolic dehydrogenation of Δ^1-tetrahydrocannabinol in rats are described and it is shown that this process is confined to a very short period following i.v. administration. The implications of this finding are discussed.

Although the pharmacological potency of Cannabis sativa can be attributed mainly to its Δ^1-tetrahydrocannabinol (Δ^1-THC) content[4], recent work does indicate that other cannabinoids such as cannabinol (CBN) can modify the effects of this active constituent[5]. Thus, observations that CBN accelerates clearance of Δ^1-THC from the blood[6] and is also a rapidly formed metabolite of Δ^1-THC[7], suggests that the metabolic production of CBN may be involved with processes important to cannabis intoxication.



Since blood levels of metabolically produced CBN[6] are of little help in following its actual production it was decided to monitor the metabolism of Δ^1-THC by utilisation of the isotope effect. If tritium is substituted for the C(3) proton (figure 1) and this proton is involved in this metabolic process (as it appears likely), the reaction rate will be slower[8]. Thus in a mixture of the substituted and unsubstituted compound, a change in relative concentration can provide evidence of reaction involving the hydrogen isotope; and the rate of change can provide a concentration-independent measure of the nature and discrimination of this particular process.

Untritiated Δ^1-THC was labelled with ^{14}C in the aromatic ring so that relative concentrations of the tritiated and untritiated species could be conveniently monitored by the ratio of the tritium and ^{14}C-activities.

Materials and methods. A mixture of these labelled compounds[9], unlabelled Δ^1-THC and unlabelled CBN were purified twice using preparative thin layer chromatography[10,11]. 3 studies were conducted. The first involved administration of a mixture of the 2 labelled Δ^1-THC species, the second involved administration of the 2 labelled Δ^1-THC species and unlabelled CBN, and the third involved administration of the labelled Δ^1-THC mixture to rats which had been pretreated twice daily for 5 administrations of unlabelled Δ^1-THC. The cannabinoids were administered to rats[12] in propylene glycol[13] as described previously[7]. The Δ^1-THC mixture was isolated from the blood[7] after further unlabelled Δ^1-THC had been added, and purified using thin layer chromatography[10]. Activies were determined by scintillation counting and the ratios were calculated[14] as $I = \frac{^3H \text{ cpm}}{^{14}C \text{ cpm}}$ and errors from counting are quoted as 1σ. Pure labelled compounds were periodically subjected to the experimental work-up during the course of these experiments, to confirm that