Cannabis, cannabinoids and reproduction

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Abstract

In most countries Cannabis is the most widely used illegal drug. Its use during pregnancy in developed nations is estimated to be approximately 10%. Recent evidence suggests that the endogenous cannabinoid system, now consisting of two receptors and multiple endocannabinoid ligands, may also play an important role in the maintenance and regulation of early pregnancy and fertility. The purpose of this review is therefore twofold, to examine the impact that cannabis use may have on fertility and reproduction, and to review the potential role of the endocannabinoid system in hormonal regulation, embryo implantation and maintenance of pregnancy.
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1. Introduction

Marijuana is the most widely used illegal drug in many countries including New Zealand and USA [1]. One of the major concerns of habitual marijuana smoking or exposure to cannabinoid derivatives is their potential to produce adverse effects on reproductive functions. Recent years have seen an explosion in research concerning cannabis and cannabinoids. Two cannabinoid receptors that respond to Δ^9-tetrahydrocannabinol (THC), the major psychoactive component in marijuana [2] have been identified and cloned. These receptors, called CB1 and CB2, belong to the superfamily of G-protein coupled receptors [3,4]. Their signal transduction and localisation is the subject of extensive study [5]. CB1 receptors are distributed extensively in neural tissues [3], where their distribution has been well characterised in rat [6] and human brain [7]. In addition, CB1 has been localised to ovary, uterine endometrium, testis, vas deferens, urinary bladder, and other peripheral endocrine and neurological tissues [8,9]. CB2 receptors, in contrast, have a fairly limited distribution, being found predominantly in immune cells [4].

In 1992 a brain constituent that binds to and activates the CB1 receptor was isolated and identified as anandamide (arachidonyl ethanolamine, AEA) [10]. Three other endogenous agonists have been identified, 2-arachidonyl glycerol (2AG) [11], 2-arachidonyl glyceryl ether (noladin ether) [12] and O-arachidonyl ethanolamide (virodhamine) [13]. All these compounds exhibit various degrees of affinity and efficacy at CB1 and CB2.

The endogenous cannabinoids (endocannabinoids) have been implicated in a wide array of physiological and pathological processes [14–17]. Recently much work has focused on the synthesis and metabolism of the endocannabinoids [18,19]. Biochemical studies have revealed that both AEA and 2AG are released from neuronal membrane phospholipids through the action of different enzymic activities [20]. AEA is thought to be released by the cleavage of the phospholipid precursor N-archidonyl-phosphatidyl ethanolamine (NAPE) in a process catalysed by phospholipase D [21]. 2AG, however, is released through several pathways including phospholipase C-dependent and independent routes [22]. Both compounds have been proposed to be carried into cells by specific carriers [23,24], although these remain uncloned. Once inside the cells, endocannabinoids can be metabolised by multiple pathways. The best-characterised pathway is the breakdown of endocannabinoids to arachidonic acid by the enzyme fatty

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acid amide hydrolase (FAAH). FAAH is an integral membrane protein that was originally identified as the degrading enzyme of the sleep-inducing factor oleamide [25]. In addition to this well studied hydrolytic metabolism, recent studies have indicated that endocannabinoids also undergo oxidative metabolism by a number of fatty acid oxygenases, including the cyclooxygenases [26,27], lipoxygenases [18,28] and cytochrome P450s [29,30].

Modulation of the cannabinoid system can therefore be achieved through a wide range of potential targets including cannabinoid receptors, endocannabinoid synthesis and metabolism pathways. This review will focus on the range of studies that have investigated the role of cannabis and cannabinoids in reproductive function. Early studies focussed upon the impact of recreational use of cannabis during pregnancy, with corresponding animal studies. More recently, the role of endocannabinoids, their receptors and their metabolising enzymes has been implicated in the physiology and pathophysiology of pregnancy.

2. Cannabis and pregnancy: human studies

As with research on all drugs of abuse, studies into the influence of cannabis use during human pregnancy have been fraught with contradictions and controversies. Because ethical considerations prohibit controlled human experiments in this area, clinical research has been limited to epidemiologic and retrospective studies, case reports and small studies of volunteers. Clearly regulations prohibit the administration of drugs to women who may become pregnant, thus studies are confounded by issues in reporting and confirming drug use; concurrent use of other drugs; as well as non-standardised drug intake between users (different quantities of intake at different times during pregnancy). Estimates of cannabis use by pregnant women vary between 10–20% [31–33]. Few studies have been conclusive regarding the effects of cannabis use during pregnancy. However, cannabis use has been correlated with low birth weight [33,34], prematurity [35], intrauterine growth retardation, presence of congenital abnormalities, perinatal death and delayed time to commencement of respiration [36]. Lifestyle and concomitant risk status is an important issue in interpreting prenatal marijuana outcomes. For example, in women with low-risk lifestyles, no evidence of increased meconium staining was noted among newborns of heavy marijuana users [37]. This observation contrasts with the first but not the second of two reports by Greenland and associates [38,39]. One of the primary differences between the two Greenland studies was the generally higher standard of living and health among the sample in the later report [38].

3. Cannabis and pregnancy: animal studies

A study utilising pregnant rats [40] bears directly upon the critical role that lifestyle may have in interacting with the teratogenic effects of cannabis. Briefly, different groups of pregnant rats were exposed to marijuana smoke while receiving diets varying in protein content. Pregnancies were markedly compromised when marijuana smoke was combined with a low-protein diet, conversely, if marijuana smoke was coupled with a high-protein diet some risks associated with the cannabis exposure were attenuated.

Animal studies have suggested that exposure to THC in utero can result in long-term changes. Several early studies reported embyrotoxicity, foetal toxicity, and specific teratological malformations in rats, guinea pigs, hamsters and rabbits associated with exposure to cannabis extracts during pregnancy [41–45]. In general, the dosage of cannabinoids resulting in frank teratology was well beyond the range used by humans. Other studies with synthetic THC failed to produce specific congenital malformations even at high doses. However, some investigators have reported an increase in embryotoxicity and foetal toxicity at pharmacologically relevant concentrations [44–49]. Studies have demonstrated that in Rhesus monkeys THC exposure during early pregnancy produced miscarriage [50]. These were associated with a rapid decrease in chorionic gonadotropin and a subsequent fall in progesterone concentrations to non-detectable levels. When rhesus monkeys were exposed chronically to THC over a 5-year period, increased reproductive loss was observed; this loss consisted of more than just increased miscarriage, but also increased resorptions, abortions, foetal deaths, stillbirths and neonatal deaths [51]. In mice THC increased the incidence of intrauterine deaths and reduced foetal weight [48]. In addition exposed male mouse foetuses had significantly reduced testosterone concentrations and reduced testis weight [52]. Exposure to THC shortly before or after birth may also result in impaired reproductive behaviour in mice when they reach adulthood: one study showed that females were slower to show sexual receptivity and males were slower to mount under these conditions [53].

4. Hormone levels and fertility: human studies

Many studies have examined hormone levels following acute marijuana exposure. Studies have shown the development of tolerance such that chronic female and male cannabis users show normal hormone levels [54]. Thus the development of tolerance must be considered as a variable in reproductive studies and may help to explain some of the conflicting data in human and laboratory animal studies.

THC and other cannabinoids have no direct estrogenic activity [55]. Yet marijuana smoke does interact with estrogen receptors [56]. The estrogenic effect is caused by phytoestrogens present in the herb, such as apigenin, an estrogenic flavonoid, which apparently retains its pharmacological activity in marijuana smoke [56]. The fact that cannabis contains more than cannabinoids is often overlooked. Marijuana contains dozens of terpenoids, which are volatilised and inhaled, cross the blood-brain barrier, and modulate the effects of THC [9].

Acute administration of THC suppresses the secretion of luteinizing hormone (LH) in humans. The stage of the menstrual cycle appears to dictate a woman's LH response to marijuana smoking. Exposure to marijuana during the luteal phase produces a 30% suppression of plasma LH levels within an hour of smoking when compared to placebo-smoking control subjects [57]. However, there were no changes in plasma LH levels following marijuana smoking by women in their follicular phase of the cycle [57], or in postmenopausal women [58]. Interestingly, there was a significant increase in plasma LH levels when women smoked marijuana during the periovulatory phase [59]. Disruption of the menstrual cycle by THC has also been reported, in one study of 26 women who reported using marijuana at least four times per week, users had a shorter menstrual cycle and a shorter luteal phase [60]. In a study of 13 pregnant women who used marijuana during pregnancy, no significant changes were observed in the circulating levels of maternal placental lactogen, progesterone, estradiol and estiol, human gonadotropin or pregnancy specific beta-1-glycoprotein [61]. However, low subject number and highly variable use within the drug using group, make it difficult to extrapolate these findings to a wider population.

In males, cannabis smoking decreases serum LH when compared to hormone levels in non-smoking controls [62,63] or pre-smoking baseline levels [64]. Chronic marijuana use is associated with decreased plasma testosterone levels [62]. However, other studies have failed to reproduce these findings [64–66]. The differing results of these reports may in part be due to study design. The study by Kolodney did not control for the ingestion of other pharmacological agents, such as narcotics and alcohol, whereas the inpatient design of the study by Mendelson prevented this potential artefact. Reduced sperm counts in males have been more consistently seen [62,67].

5. Hormone levels and fertility: animal studies

Distribution studies have indicated significant accumulation of labelled THC in rat testes [68] and also in the ovaries and mammary glands of female mice [69]. In both male and female rats THC can suppress reproductive hormones and behaviour [53]. Studies have consistently shown that injections of THC result in rapid, dose-dependent suppression of serum LH [70].

Results have been similar in rats and in rhesus monkeys. THC has been shown to block the oestrous preovulatory LH surge in gonadally intact animals [71] and to produce dose-related inhibition of pulsatile LH release in ovariectomised rats and monkeys [72,73]. Because of its potent antigonadotropic activity, THC inhibits ovulation [74,75]. Ovulation and LH release could be induced by exogenous gonadotropins or gonadotropin-releasing hormone, even in the presence of high concentrations of THC, suggesting that these effects occur at the hypothalamic level [72–74,76]. Indeed, direct intracerebroventricular administration of THC produced decreased plasma LH levels and increased hypothalamic levels of gonadotropin releasing hormone (GnRH) [77], suggesting that decreased release of GnRH into the pituitary portal vasculature is responsible for the suppressed levels of LH that follow THC exposure. However, cannabinoids do not directly block the basal GnRH secretion from hypothalmi in vitro [78], rather they may produce this effect through modulation of neuronal systems known to inhibit GnRH. Several systems have been implicated. Increase in hypothalamic norepinephrine and dopamine activity, concomitant with decreased LH release have been reported in THC treated rats [79]. More recently, corticotropin releasing hormone and $5HT_{1a}$ receptors have been implicated in studies of ovariectomised rats [70,80].

Cannabinoids have a primarily inhibitory effect on prolactin release in female animals. Acute cannabinoid exposure inhibits basal prolactin release in monkeys [81] and rats [82] and blocks the prolactin surge which occurs on the afternoon of proestrus [83] or in response to suckling [84] in rats. The hypothalamic tuberoinfundibular dopamine system is predominately responsible for the regulation of prolactin release from the anterior pituitary gland. Acute cannabinoid exposure significantly increases the activity of this neuronal system and increases dopamine release, resulting in decreased prolactin secretion from the pituitary [85,86]. In some studies, however, prolactin response to THC is biphasic (early stimulation followed by suppression), and no changes are seen in serum levels of follicle stimulating hormone [87].

Male gonadal functioning has shown fairly consistent alterations in animal investigations. Smith et al. [88] found a significant decrease in serum testosterone concentration following acute doses of THC in rhesus monkeys. Acute and chronic doses of THC cause significant depression of testosterone formation by rat testis microsomes [89,90], and decrease testicular weight [90]. It was suggested that reduced testosterone synthesis

may be the result of THC's effects on the hypothalamo-hypophyseal area—THC reduces gonadotropin levels, causing a reduced interstitital cell microsomal cytochrome P-450 content needed for the synthesis of testosterone [90]. Treatment of THC-treated rats with gonadotropins was able to restore normal testicular weight, microsomal P-450 activity, and gamma-glutamyl transpeptidase activity. In vitro studies have shown that cannabinoids inhibit protein and nucleic acid synthesis and glucose metabolism in the rat testes [91,92]. This reduction in testosterone levels may explain the behavioural studies demonstrating that THC reduces copulatory behaviour in male rats [93,94].

Acute treatments with cannabinoids can decrease the fertilising capacity of sea urchin sperm [95]. In rodent studies, high THC doses caused a modest increase in abnormally formed sperm. Moreover, long-term cannabinoid exposure in male mice disrupted spermatogenesis and induced aberrations in sperm morphology [96]. The presence of cannabinoid receptors in sperm [97] suggests the possibility of a natural role for cannabinoids in modulating sperm function during fertilisation. However, it remains to be determined whether smoked marijuana or oral THC at doses achieved during recreational or medical use has a clinically significant effect on the fertilising capacity of human sperm.

6. The endocannabinoid system in pregnancy & reproduction

Following the discovery of the endocannabinoids and cannabinoid receptors, research has focused on whether this system may be involved in the physiological regulation of pregnancy. Most studies examining the expression and role of cannabinoid receptors in the reproductive system have been carried out in the mouse. Das and associates [98] used Northern blot hybridisation and reverse transcriptase-polymerase chain reaction (RT-PCR) to demonstrate that CB1 but not CB2 mRNA is expressed in the mouse uterus. Both CB1 and CB2 mRNA have been identified in mouse preimplantation embryos [99]. A recent study has shown that sex steroids control the expression of the CB1 gene in the anterior pituitary gland of both male and female rats, leading to the speculation that such a regulatory mechanism might be operational also in the reproductive organs [100]. Paria et al. [101] utilised cannabinoid receptor mutant mice to further investigate the role of CB1 and CB2 in preimplantation embryo development and in implantation. They found that the embryos recovered from $CB1^{-/-}/CB2^{-/-}$ mice were asynchronous with normal development. For example, on the fourth day following fertilisation, about 98% of wild-type embryos were blastocysts, whereas only about 61% of the double-knockout embryos were at the blastocyst

stage (most of the mutant embryos were at the morula stage). Nevertheless, retarded embryo development had modest, if any, adverse effects on implantation. The mutant embryos were resistant to the effects of anandamide, and double-knockout mice were resistant to THC-induced implantation failure [101].

FAAH mRNA is also expressed in mouse preimplantation and implanted embryos [102], and uterine luminal and glandular epithelial cells [102]. Furthermore, FAAH protein expression and activity was recently localised to these regions of mouse endometrial epithelium [103]. FAAH expression was demonstrated to fall from days 0 to 5.5 of pregnancy [103]. Maccarrone and colleagues [103] present two lines of evidence to suggest that FAAH modulation in the early stages of pregnancy are hormonally regulated and independent of the presence of embryos in the uterus. Firstly, pseudopregnant mice undergo down regulation of FAAH expression and activity in the uterus; secondly, ovariectomised animals demonstrate less regulation of FAAH with pregnancy, however the down regulation is increased when these animals are treated with estrogen.

Until recently little information was available on cannabinoid receptor and FAAH distribution in human reproductive tissues and gestational tissues. RT-PCR studies have suggested that both CB1 and CB2 receptors are localised to the human myometrium [104]. This method has also been used to demonstrate that human placenta expresses mRNA for both types of cannabinoid receptors [31], however it was unclear whether this study included placental membranes (amnion, chorio-decidua) or utilised solely placental villous tissue. Recently, we identified CB1 immunoreactive labelling in most major cell types throughout all layers of the human placental membranes, as well as in the placental villous [128], suggesting that both cannabis and endocannabinoids could have an impact directly on placental tissues. Likewise FAAH activity has been demonstrated in human uterine epithelial cells [103], and in the epithelial layer and decidual layer of the human placenta [128]. Human reproductive fluids, such as seminal plasma, mid-cycle oviductal fluid, follicular fluid and amniotic fluid have been reported to contain anandamide in the low nanomolar range [105].

Anandamide levels in the mouse uterus have been demonstrated to be inversely related to uterine receptivity for implantation; upregulation is correlated with uterine refractoriness to blastocyst implantation [106]. Furthermore, anandamide levels are highest in inter-implantation sites and lowest at sites of implantation [107]. The low levels of anandamide at the implantation sites correlated with high levels of both COX2 and FAAH levels in these regions [108], suggesting that one or both of these metabolising enzymes may control the levels of anandamide. These studies correlate with the determination of blastocyst sensitivity to anandamide

levels. Blastocysts exposed in culture to low levels (7 nM) of anandamide exhibit accelerated activity and trophoblast outgrowth, with an observed inhibition of differentiation at higher doses (28 nM) [109]. Liu et al. [110] showed that low level of anandamide (14 nM) can significantly promote blastocyst attachment and out-growth whereas high level (56 nM) anandamide delays attachment and inhibits outgrowth of blastocysts. It was suggested that different culture conditions result in these discrepancies. Furthermore, anandamide and THC induce inhibition of embryo development and zona-hatching of blastocysts [99,106,111–113] most likely through a CB1 mediated pathway [111]. Thus it is not surprising that increased cannabinoid levels may inter-fere with the implantation process. Infusion of the synthetic cannabinoid CP55,940 via miniosmotic pumps during the preimplantation period prevents implanta-tion in a CB1 receptor mediated mechanism [111], however infused THC does not produce this effect, except when administered with a cytochrome p450 inhibitor. This resulted in equivalent plasma levels, but an accumulation of THC in the uterus, suggesting that local metabolism of THC may protect against the deleterious effects of THC. When administered chroni-cally anandamide prolongs the duration of pregnancy and increases the rate of still birth in rats [114], furthermore the postnatal development of the hypotha-lamic pituitary axis in the offspring of animals who receive anandamide during the pregnancy is temporarily inhibited particularly in males [115].

As was described for THC, anandamide decreases serum LH and prolactin levels in rats of both sexes [116]. The effects are assumed to be due to hypothalamic regulatory centres, however, recently the CB1 receptor was identified in the anterior pituitary itself [117,118] and receptor levels were demonstrated to be regulated by sex steroids [100] allowing for the potential of a direct action. Intriguingly, hypothalamic levels of anandamide peak immediately before the onset of puberty in female rats, suggesting modulation of endocannabinoids and potentially FAAH in times of hormonal regulation aside from pregnancy [119].

In, perhaps, the most compelling study correlating the endocannabinoid system with pregnancy outcome, Maccarrone et al. [120] reported the association between decreased levels of FAAH in maternal lymphocytes and early pregnancy loss in humans. This study also showed a clear regulation of FAAH expression and activity during the first trimester of normal pregnancy, with levels and activity peaking at 9–10 weeks, prior to dropping again by 12 weeks. No such increase was observed in the women who consequently miscarried. It was further shown that lymphocyte FAAH was stimulated by progesterone and Th2-type cytokines [121], which favour human fertility [122,123]. Moreover, the addition of AEA to human lymphocytes in vitro

inhibited the release of leukaemia inhibiting factor [121], which is critical for implantation, and maintenance of the foetus in humans [124]. More recently, Maccarrone et al. [125] demonstrated low levels of FAAH in lymphocytes of in vitro fertilisation-embryo transfer patients who failed to achieve an ongoing pregnancy than in those who become pregnant, and this was paralleled by a significant increase in blood AEA. Interestingly, non-pregnant controls had the same FAAH activity and content as the subjects with normal gestation, suggesting that a down-regulation of FAAH occurred in lymphocytes of patients who failed to achieve pregnancy. Taken together these findings indicate that an active FAAH in maternal lymphocytes is needed for successful pregnancy, hence suggesting that the high levels of AEA that might follow the defective expression of FAAH could adversely affect gestation in humans, as has been demonstrated by the animal studies described above. Indeed, approximately fourfold higher levels of blood AEA were observed in women experien-cing miscarriage than in women with normal gestation (M. Maccarrone, V. Di Marzo, pers. comm.). Consistent with this proposal, defective leptin signalling, which causes sterility in leptin-deficient ob/ob mice [126] has been recently associated with elevated levels of hypotha-lamic endocannabinoids in the same animals [127], whereas leptin treatment which restores fertility, reduces hypothalmic endocannabinoids.

In conclusion, recent studies have demonstrated that the endocannabinoid system is tightly modulated in gonadal tissues and during pregnancy. Marijuana, THC, and other exogenous cannabinoids exert potent effects on this homeostasis. Furthermore these substances are modulated by and involved in the anterior pituitary and hypothalamic control of hormones and sex steroids. Thus these substances have the potential to have powerful effects on the reproductive health of females and males. Further studies into the roles of endocanna-binoids in human hormone regulation and pregnancy will point towards the contribution of these compounds in normal and pathophysiology. Current understanding suggests that they may be critical in the areas of embryo implantation and miscarriage. For the time being it is clear that cannabis-based substances are contra-indicated during pregnancy, as are compounds that might interact with endocannabinoid synthesis and metabolism.

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