Cannabinoids as Therapeutics
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Endocannabinoids and regulation of fertility

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Introduction

The adverse effects of cannabinoids, and in particular of Δ^9-tetrahydrocannabinol (Δ^9-THC), on reproductive functions have been known for a long time [1, 2], and include retarded embryo development, fetal loss and pregnancy failure (recently reviewed in [3, 4]). Δ^9-THC has been reported to account for the majority of the reproductive hazards of marijuana use, in particular in males it leads to impotency by suppressing spermatogenesis, by reducing the weight of reproductive organs and by decreasing the plasma concentration of circulating hormones like testosterone. In females, Δ^9-THC inhibits ovulation by prolonging the estrous cycle and decreasing the proestrous surge of luteinizing hormone. In addition, exposure to natural cannabis extracts during pregnancy has been correlated with embryotoxicity and specific teratological malformations in rats, hamsters and rabbits. Also the major endocannabinoid anandamide (*N*-arachidonoylethanolamine, AEA) has been shown to impair pregnancy and embryo development in mice [3], suggesting that endocannabinoids might regulate fertility in mammals. Consistently, down-regulation of AEA levels in mouse uterus has been associated with increased uterine receptivity, which instead decreased when AEA was up-regulated [5]. The levels of uterine AEA fluctuate with changes in the pregnancy status, which is important because successful implantation is the result of an intimate cross-talk between the active blastocyst and the receptive uterus [5]. AEA might be critical in regulating the so-called window of implantation through synchronization of trophoblast differentiation and uterine preparation to the receptive state. This hypothesis is consistent with the observation that low levels of cannabinoid agonists exhibit accelerated trophoblast differentiation and outgrowth, while higher doses inhibit trophoblast differentiation [6]. In the same context, the higher level of AEA in the nonreceptive uterus correlates well with the embryotoxic effect of the nonreceptive uterine environment, as well as with the *in vitro* observation that AEA inhibits embryo development and zona-hatching of blastocysts [5]. In the mouse, mRNAs of AEA-binding CB_1 and CB_2 receptors are expressed in the preimplantation embryos, and the levels of CB_1 receptors are much higher than those found in brain [3]. Activation of blastocyst CB_1 receptor is detrimental for mouse preimplantation and development [5, 6], but