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Journal

Nature medicine, 10(1)

ISSN

1078-8956

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Publication Date

2004

DOI

10.1038/nm0104-19

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Peer reviewed

THC: moderation during implantation

Daniele Piomelli

Endogenous marijuana-like compounds regulate implantation during pregnancy by activating cannabinoid receptors on the embryo's surface. A new study explores the dynamics of this process and renews concerns about marijuana use in pregnant women.

Women who smoke marijuana have several good reasons to quit if they plan to get pregnant: maternal marijuana use has been associated with lower infant weight at birth¹, as well as subtle cognitive deficits in childhood and adolescence². Studies in animals support these findings. The active constituent of marijuana, Δ^9 -tetrahydrocannabinol (THC), binds to most nerve cells and some immune cells. Prenatal exposure of rats and mice to chemicals that engage these receptors reduces birth weight and impairs exploratory behavior and memory in offspring^{3,4}.

Adding new grounds for concern, experiments in mice now unveil how cannabinoid signaling intricately regulates embryo implantation, the sequence of events leading to the adhesion of the embryo to the uterine wall⁵. The new study, by Dey and colleagues, appears in a recent issue of the *Proceedings of the National Academy of Sciences*.

A mammalian embryo can successfully implant in the uterus only after it has become a blastocyst. This consists of a small cluster of cells called the inner cell mass, which eventually develops into the fetus, and a thin layer of outer cells called trophoblast, which gives rise to the placenta (Fig. 1 and 2). When cells in the trophoblast become ready to implant, their metabolic rate increases and they develop a repertoire of surface molecules that allows them to adhere to the uterine epithelium. But for this interaction to occur, the uterus must first mature to a receptive state.

The process of synchronization between blastocyst and uterus involves a complex network of membrane-associated molecules and soluble signals, including steroid hormones, growth factors and lipid mediators. In a series of landmark studies, Dey and colleagues have established that cannabinoid receptors and their endoge-

Deborah Maizels

Figure 1 Cannabinoid control of mouse embryo implantation. (a) At low concentrations, the endogenous cannabinoid anandamide may activate cannabinoid receptors (CB₁) on the surface of trophoblast cells, stimulating ERK and facilitating implantation. (b) At higher concentrations, anandamide may engage a second CB₁-dependent pathway, which may inhibit the activity of voltage-operated N-type calcium channels, reduce calcium entry and halt implantation.

nous activator, anandamide⁶, are integral components of this network^{5,7,8}.

Before it becomes receptive, the uterus contains exceedingly high levels of anandamide—higher, in fact, than anywhere else in the body⁷. As the tissue progresses into receptivity, anandamide concentrations drop, suggesting that a lower cannabinoid tone creates a friendlier environment for implantation. In keeping with this idea, activation of cannabinoid receptors on the trophoblast inhibits blastocyst development and implantation⁸.

This simple scenario does not explain all the available data, however. If the only role of the endogenous cannabinoid system were to prevent implantation, mutant mice that do not express cannabinoid receptors should be more fertile than wild-type animals. Yet the opposite is true: mutant animals actually have 40% fewer pregnancies than do wild-type ones. Another inconsistency is that anandamide improves implantation when administered at very low doses, lower than those needed to impair it. How can these seemingly opposite effects be explained?

Dey and coworkers addressed this ques-

tion using either freshly isolated mouse blastocysts or, when they needed larger quantities of tissue, trophoblast cells in culture⁵. The researchers found that anandamide activates cannabinoid receptors in the trophoblast to initiate two distinct signaling cascades in a dose-dependent manner. At a low concentration (7 nM), anandamide stimulated the extracellular signal-regulated protein kinase (ERK); at a higher concentration (28 nM), anandamide reduced calcium entry by closing voltage-operated N-type calcium channels. These events had opposite functional consequences, such that blastocysts treated with 7 nM anandamide became competent for implantation, whereas those treated with 28 nM anandamide did not. Thus, the uterus may be able to titrate its anandamide production to either promote or arrest embryo implantation (Fig. 1).

These results confirm and extend the regulatory function of the endogenous cannabinoid system in female fertility. At the same time, they raise two potentially serious public health issues. The first derives from clinical reports that link defects in anandamide breakdown to

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Figure 2 Cannabinoids at work. Red, CB₁; blue, nuclei. (a) dormant, and (b) activated blastocyst.

increased risk of spontaneous abortion⁹. These studies found that expression of fatty acid amide hydrolase, the enzyme that catalyzes the intracellular degradation of anandamide, was reduced in lymphocytes obtained from women who had had miscarriages, compared with those who had not. It is unclear, however, whether the mechanism underlying these miscarriages (which occurred mostly between seven and ten weeks of pregnancy) is related to the ability of anandamide to stop implantation (which occurs in humans six to seven days after egg fertilization).

The second issue stems from the fact that a large number of women of childbearing age—4.9%, according to a recent survey¹⁰—regularly smoke marijuana. How might this drug affect their fertility? If the same signaling system described in mice were present in humans, one might expect

fertility problems among heavy marijuana users. Although there is no clear indication at present that marijuana impairs fertility, this possibility should certainly be revisited in the light of the current animal data.

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HTLV-1 sweet-talks its way into cells

Julie Overbaugh

HTLV-1 infection poses a risk for leukemia and other ailments. Now the elusive cellular receptor for this pathogen has finally been identified, and it is the same receptor that allows glucose to enter cells.

The first infectious human retrovirus to be identified, before we even imagined the devastation of HIV, was human T-lymphotropic virus type 1 (HTLV-1)¹. HTLV-1 causes disease—mainly adult T-cell lymphoma or leukemia or HTLV-1-associated myelopathy—in only small fraction of infected individuals. The virus, however, cuts a wide swath, infecting about 10–20 million people worldwide by spreading from person to person through infected cells in semen, blood and breast milk. Despite years of effort, the identity of the receptor that facilitates the spread of HTLV-1 has remained elusive. In a recent issue of *Cell*, Manel *et al.* provide evidence that GLUT-1, a ubiquitous glucose transport protein, is a receptor for HTLV-1 (ref. 2).

Most retroviral receptors have been cloned by transferring a library of sequences from a cell line that is permissive for entry, and therefore expresses the receptor, into one that

is nonpermissive. A marked version of the virus can then be used to specifically select cells with the receptor gene from cells that acquired irrelevant cellular sequences. HTLV-1 infects most cell lines but is found primarily in lymphocytes, including lymphoma cells, in infected patients. The paucity of nonpermissive cell lines, as well as difficulties in making high titers of marked virus, has foiled attempts at conventional receptor cloning strategies. For these reasons, Manel *et al.* used a clever deductive approach that relied on several clues to identify a receptor candidate.

The first clue was that cells expressing the HTLV-1 envelope protein, which binds the receptor and initiates entry, showed perturbations in lactate and glucose metabolism—namely, delayed acidification of the cell culture medium. This observation implicated a receptor involved in lactate or glucose transport. Because many known retroviral receptor proteins are transporters³, a transport protein has always been a strong contender for the HTLV-1 receptor.

Another crucial clue came from HTLV-1 envelope binding studies, which suggested that the receptor was expressed very early

after lymphocyte activation, and that its temporal pattern of expression was distinct from that of many other activation markers^{4,5}. Together, these clues led the authors to GLUT-1, a member of a family of glucose transport proteins.

The tactic of finding a receptor to meet the authors' criteria, rather than letting the virus select the receptor in a functional screen, carries with it a considerable burden of proof. The authors used several lines of evidence to support their case. Binding studies demonstrated a direct interaction between the HTLV-1 envelope and GLUT-1, but not other related transport proteins. Downmodulating GLUT-1 led to reduced HTLV-1 binding and infection, whereas increasing GLUT-1 expression restored these outcomes. Finally, the authors provided data that GLUT-1 is a receptor for a related, relatively avirulent retrovirus, HTLV-2, fulfilling predictions from previous studies⁶. Collectively, the results provide a compelling case for GLUT-1 as an HTLV-1 receptor (Fig. 1). Left unresolved is whether GLUT-1 can render a normally nonpermissive cell susceptible to HTLV-1 infection, a challenging experiment given

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