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REVIEW

Dual action microbicides: reappraisal of their roles in contraceptive research

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Dr Syed N Kabir obtained his MSc and PhD degrees in Physiology from Calcutta University, Kolkata, India. He is currently the Head of the Department of Reproductive Biology Research, Indian Institute of Chemical Biology, Kolkata and was honoured with the prestigious Federation of Obstetrics and Gynecological Society of India (FOGSI) award in Reproductive Endocrinology in 2007. Current areas of interests include reproductive endocrinology and development of spermicidal contraceptive modalities with anti-HIV hallmark. He has filed a US patent for a pharmaceutical composition having virucidal and spermicidal activity and he and his group are looking forward to exploring the future promise of this molecule as a dual action microbicide.

Abstract Of the variety of contraceptive options available for women, very few provide dual protection against sexually transmitted diseases. Due to increased incidence of human immunodeficiency virus type 1 (HIV-1), genital herpes, hepatitis B and human papilloma virus, development of novel contraceptive strategies that incorporate antiviral activity has become the top priority in contraceptive research. Topical microbicides are now considered to be the last ray of hope, as they would ideally provide protection against unwanted pregnancy, proper lubrication during sexual activity, and preclude the vaginal/rectal transmission of sexually transmitted diseases. A large number of vaginal microbicides are in the preclinical or clinical stages of evaluation for their safety, efficacy and acceptability. However, a major bottleneck in the development of novel mechanism-based dual microbicides has been their detergent-like effects, along with debilitating action on the vaginal microflora. Hence the search is still on for the ideal dual microbicide/s that may obliterate these disadvantages and provide an invincible shield to women in their crusade against unintended pregnancy as well as sexually transmitted diseases. The present review highlights the current scenario towards the development of novel contraceptive strategies to counteract the rampant spread of sexually transmitted diseases, with special reference to HIV/AIDS.

KEYWORDS: contraception, dual action microbicides, fertility control, HIV/AIDS, spermicide

Introduction

The worldwide human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) epidemic has spurred a great deal of interest in the area of vaginal microbicide and rectal microbicide development to restrain the inexorable increase in viral mucosal transmission (D'Cruz and Uckun, 2004). This, combined with the rapid augmentation in population, is a perilous alliance that has stretched nature's bounty to the limit. Topical microbicides, self-administrable prophylactic agents applied to the vagina or rectum in various formulations, currently hold great promise to prevent the relentless spread of sexually transmitted infections (STI). They may or may

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not possess contraceptive properties. However, if the candidate microbicide does possess contraceptive properties, then an inevitable combination arises that can combat the twin problems of population explosion and STI transmission effectively.

Global snapshot of HIV/AIDS epidemic

According to the current Joint United Nations Programme on HIV/AIDS (UNIAIDS) 2007 estimate, 33.2 million people were globally infected with HIV/AIDS with nearly 2.5 million new infections being added each year to the global HIV burden (UNAIDS, WHO, 2007). More than half of all the HIV/AIDS infected people comprise women, and this proportion has been increasing since the mid-1990s (Centers for Disease Control and Prevention, 2004; UNAIDS, 2005). HIV is among the leading causes of death worldwide and the number one cause of death in sub-Saharan Africa. Gender inequalities in socio-economic status and access to prevention and care services exacerbate women's vulnerability to HIV. Sexual violence may also increase women's risk, and women, especially young women, are biologically more susceptible to HIV infection than men (UNAIDS, 2008). Thus, the global HIV pandemic has a deep multi-sectarian impact on the economic development of nations. Initial reporting of AIDS identified cases among men who have sex with men (MSM), eventually heralding this epidemic as a sexually transmitted disease (STD). While additional cases were identified among injection-drug users, blood transfusion recipients, haemophiliacs receiving blood products, and subsequently in infants through perinatal transmission from mother to infant, the epidemic has remained predominantly sexually transmitted. Approximately 85% of all worldwide adolescent and adult HIV-1 cases have been acquired through heterosexual transmission (Newman, 2004).

One possible interpretation for the escalation of HIV prevalence in the women is the fact that the female genital mucosa is probably more sensitive to HIV and other STI due to substantial mucosal exposure to seminal fluids (European Study Group, 1992). Mucosal transmission serves as a primary port of entry for HIV-1 transmission and male to female transmission is more efficient than *vice versa* (Nicolosi et al., 1994). Despite the low risk of infections via mucosal entry through needle sharing, the threat of spread increases considerably due to severe compromise in membrane integrity. Cervico-vaginal epithelial disruption prior to or immediately after sexual contact, accompanied by genital inflammation or ulceration, creates a receptive milieu for subsequent entry of STI causing pathogens such as herpes simplex virus type 2 (HSV-2), *Treponema pallidum* and *Neisseria gonorrhoeae*.

Most STI are commonly asymptomatic, thereby underestimating individual exposure to STI. STI, especially genital ulcerative disease/genital herpes, predispose the risk of acquiring HIV infection by as much as eightfold by altering tissue integrity. Reports stating increased cervico-vaginal and plasma HIV loads in co-infected women with genital ulcers have confirmed that HSV-2 is a co-factor for HIV transmission (Kaul et al., 2007; LeGoff et al., 2007).

Brief overview of STI transmission

Mechanistic details behind STI transmission are still under scrutiny, with most of the helpful insights being supplied from advances gained in the HIV field. Pathogens need to surpass two major lines of defence for successful entry into genital mucosal epithelium (**Figure 1**). Firstly, the physicochemical barrier is very effective in reducing the HIV viral load, while the cell-mediated defence also hinders unrestricted access between the host and the pathogen.

The organization of genital mucosa comprises the physical barrier against pathogen infiltration, with vaginal and ectocervical mucosa unveiling a pluristratified squamous epithelium less susceptible to infection. Contrarily, the monostratified endo-cervical and rectal mucosa helps to induce membrane disruption, thus facilitating the infiltration of infectious agents. Microabrasions exacerbate such breaches, thus increasing the risk of infection. Despite reports suggesting in-vitro entry of HIV via transcytosis through the intact epithelial layer, the in-vivo mechanism is far from being clearly understood (Bomsel, 1997).

A chemical barrier in the form of low vaginal pH and oxidative radical-enriched cervical secretions constitutes a hostile environment for pathogen entry and survival (O'Connor et al., 1995). Once infiltration is successful, the cellular defence underlying the mucosal epithelia is provided by the dendritic cells (DC)/Langerhan's cells, macrophages and subsets of CD_4^+ lymphocytes, defensins and secretory leukocyte protease inhibitors (SLPI). Findings from the study of the non-human primate model (rhesus macaque) of HIV transmission have clearly elucidated that HIV can cross an intact mucosal barrier and can infect the target host cells (CD_4^+ T cells, macrophages, dendritic cells) resident in or around the mucosa. HIV infection of the target cells requires adhesion between the viral membrane and the cell membrane by chronological interaction of viral membrane glycoproteins (gp 120) with CD_4^+ T cell surface where one of two chemokine (CC) receptor molecules (CXCR4 or CCR5) serve as HIV co-receptors. In-vitro studies have revealed that expression of these CC receptors can make the otherwise immune CD_4^+ T cells susceptible to HIV infection (Alkhatib et al., 1996; Deng et al., 1996; Dragic et al., 1996). Macrophages, T cells and dendritic cells (DC) can be prolifically infected with HIV. While virus infection of a cell necessitates membrane fusion, DC enable HIV binding to their cell surface without being infected, and maintain or even amplify viral infectivity in T cell co-cultures. The ability of mature human DC to promote HIV infection of T cells, in the absence of infection, has been related to expression of the C-type lectin receptor, which is DC-specific intercellular adhesion molecule (ICAM)-grabbing non-integrin (DC-SIGN) (Geijtenbeek et al., 2000). DC-SIGN binds HIV via interaction with high mannose residues expressed on viral gp120, and can maintain HIV infectivity for up to 5 days on DC (Pohlmann et al., 2001). This local repertoire population of infected cells now produces progeny virions that are capable of persistent and target specific integration at specific points in the host system (Haase, 2005). Via the bloodstream, HIV gains entrance to the gut-associated lymphoid tissue (GALT), where full-blown replication occurs, thereby elucidating the premature depletion of CD_4^+ T lymphocytes