Role of mu opioid receptor in addiction and HIV

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Abstract

Until recently, the most common view was that drug addicts are weak or bad people, unwilling to control their behavior and gratifications. In fact, addiction is a chronic brain disease with genetic predisposing. Genetic factors influence the vulnerability to develop drug addiction, the progression from intermittent to regular drug use, the transition from abuse to addiction, and the propensity for repeated relapse after achievement of a drug-free state. It has been estimated that genetic contribution to addiction is 30-60%. There is no single gene that responsible for addiction. However, one of the genes that has received a lot of attention in addiction studies is OPRM1 gene which encodes the μ opioid receptor (MOR). In addition to the role of mu opioid receptor in addiction, there is a link between immunity and opioid drugs. The presence of MOR on monocytes has been demonstrated this. The interaction between mu opioid receptor and opioid administration has shown affecting antibodies production, natural killer activity, cytotoxicity, cytokine production, and phagocytosis. Besides, the ability of MOR activation to induce CCR5 expression suggests MOR agonists, such as morphine, may promote susceptibility to HIV-1 infection and disease progression associated with this infection. Perhaps this one of the reason why worldwide, injecting drug use is estimated to account for just less than one-third of new nfections outside sub-Saharan Africa Information about this is very important as a basic for addiction and HIV treatment in the future.

Key words : mu opioid receptor, Injecting Drug Users, HIV

Introduction

Worldwide, injecting drug use is estimated to account for just less than one-third of new infections outside sub-Saharan Africa (1). The transmission of HIV among injecting drug user (IDUs) due to sharing injecting equipments remains a major public health challenge in many countries (2). The most used drug for injection is opioid (3). Therefore, HIV-prevention programs for IDUs put emphasis on people actively injecting drugs, especially through needle exchange or opioid replacement.

Furthermore, IDUs may also play an important role in transmitting HIV infections to the general population especially through sexual risk behavior (4, 5). Alcohol abuse, methamphetamine and amphetamine use and other drugs were associated with risky sexual behavior (6).

Until recently, the most common view was that drug addicts are weak or bad people, unwilling to control their behavior and gratifications (7, 8). However, it has been shown that addiction is a chronic brain disease (7, 9). In one important study of more than 3,000 twin pairs, Tsuang and colleagues reported that both environmental and genetic factors influenced abuse and dependence for several types of drugs, with genetic factors accounting for over 50% of the variance for opiate abuse or dependence (10, 11). A family study found that the adjusted odds ratio for having the same drug disorder in adult first-degree relatives was over 7 for cocaine and over 10 for opioids, again indicating an involvement of genetic factors (12).

Genetic factors also influence the progression from intermittent to regular drug use and the transition from abuse to addiction, and the propensity for repeated relapse after achievement of a drug-free state (12). There is no single gene that responsible for addiction. However, a gene that has received a lot of attention in addiction studies is OPRM1 gene which encoding the μ opioid receptor (13) (14, 15). In addition to the role of mu opioid receptor in addiction, there is a link between immunity and opioid drugs (16, 17).The presence of MOR on monocytes has been demonstrated this (16, 17). The interaction between mu opioid receptor and opioid administration has shown affecting antibodies production, natural killer activity, cytotoxicity, cytokine production, and phagocytosis. Besides, the ability of MOR activation to induce CCR5 expression suggests MOR agonists, such as morphine, may promote susceptibility to HIV-1 infection and disease progression associated with this infection (18). Information about this is very important as a basic for addiction and HIV treatment in the future. In this paper, the role of mu opioid receptor in addiction and HIV and its interaction will be discussed

Role of mu opioid receptor in addiction

Opioid Receptor Gene (OPRM1) has been selected as a candidate for human genetic studies of the addictions for many reasons. The MOR is the molecular target of the active biotransformation products of heroin (6-monoacetylmorphine and morphine), as well as most opiate and opioid analgesic medications such as oxycodone, hydromorphone, and fentanyl, each of which has significant potential for addiction. Abuse of and addiction to these MOR-directed agents is increasingly recognized to constitute a major addiction problem. From our early work that led to the development of methadone maintenance treatment for heroin addiction in the 1960s, we know that μ-selective agonists with long-acting pharmacokinetics such as methadone and levo-α-acetylmethadol (LAAM) or partial agonists (buprenorphine) are the most effective treatments for this disorder (15).

Furthermore, studies of quantitative trait loci in mice identified a chromosomal region containing the μ opioid receptor gene as contributing to a substantial amount of the variance in analgesic and reward responses to morphine. Also, studies of mice with targeted deletion of the μ opioid receptor gene definitively established this receptor as essential for morphine analgesia, physical dependence, and reward as measured by antinociception, withdrawal, conditioned place preference, and self-administration studies. Chronic morphine administration or heroin self-administration alters naloxone efficacy measured using 5'-*O*-(3-[^{35}S]thio)triphosphate ([^{35}S]GTPγS) binding in several brain regions by increasing MOR binding and decreasing MOR-activated G proteins (15).

Common genetic variations among individuals, including in OPRM1, involve single nucleotide polymorphisms (SNPs), in which a single nucleotide of the genome is altered. SNPs occur every 100–300 base pairs and account for approximately 90% of human genetic variation. The nature of the change produced by the SNP greatly depends on which nucleotide is being altered and where this change occurs in the gene. For instance, synonymous SNPs will alter the nucleotide without changing the resulting amino acid (also called a "silent mutation"). Non-synonymous SNPs are produced when the nucleotide substitution alters the resulting amino acid. Additionally, these alterations can occur in promotor, exonic, or intergenic regions and, consequently, may differentially affect transcription, processing, stability, translation, folding, transportation, and ultimately, function of the corresponding gene product (19).

In human populations, a commonly investigated SNP (rs1799971) occurs in exon 1 of the μ-opioid receptor gene (OPRM1), in which an adenine to guanine substitution (A118G) exchanges an asparagine for an aspartic acid at a putative N glycosylation site (N40D). It is common in persons of European (15–30%) and Asian ancestry (40–50%), with lower prevalence in African American and Hispanic populations (1–3%). The A118G SNP has been implicated in a wide variety of disorders, such as drug addiction and stress responsivity, and in treatment responses, including dependence and pain reduction; however, the mechanisms that mediate these alterations have not been determined (19).

Role of mu opioid receptor in HIV

The presence of mRNA for the μ-opioid receptor has been found in human T- and B-cell lines, CD41 T cells, monocytes, macrophages, and granulocytes (17). In rat, the sequence for the μ-opioid receptor of the peritoneal macrophages is essentially identical to the brain μ-opioid receptor (20). In addition, research has shown that opioid administration affects both innate and adaptative immunity, such as antibodies production, natural killer activity, cytotoxicity, cytokine production, chimiotaxism, and phagocytosis (16, 17).

In the progression of HIV-1, there are two chemokine receptors that play crucial roles. Those receptors are CCR5 and CXCR4. CXCR4 participates in T cell-tropic HIV-1 infection, while CCR5 participates in monocyte/macrophage-tropic HIV-1 infection. The spikes projecting from the surface of HIV-1 particles are composed of the envelope glycoprotein (Env), whose function is to promote HIV entry by a process of direct fusion between the virion membrane and the plasma membrane of the target cell. In their function as HIV coreceptors, CCR5 and CXCR4 physically associate with CD4-activated gp120. The functional envelope glycoprotein on the surface of the HIV particle or infected cells is organized as a trimer of three gp120-gp41 heterodimers. The HIV fusion reaction is initiated by sequential receptor binding of gp120, first to CD4 and then to a specific chemokine receptor, generally CCR5 or CXCR4 (21).

The influence of opioids on the expression of chemokine receptors has been studied in both leukocytes and neuronal cell populations. Recent results show that

administration of morphine to the human astrocytoma cell line U87 resulted in the elevation of CXCR2 transcript levels. These studies also showed that CCR5 and CCR3 transcript levels are increased with morphine administration, as determined by RT-PCR, in normal human astrocytes. A more recent study using a human brain derived astrocytoma/glioblastoma cell line termed U373 showed marked increases in CCR3 and CCR5 expression following morphine treatment. The ability of MOR activation to induce CCR5 expression suggests MOR agonists, such as morphine, may promote susceptibility to HIV-1 infection and disease progression associated with this infection (18).

Further understanding of the function and expression of these co-receptors is of interest because of their role in inflammatory diseases, as well as their participation in infection by HIV-1. Moreover, other chemokine receptors are known to participate in the progression of disease following HIV-1 infection. Most notably, CCR2 is a critical chemokine receptor involved in the traffic of HIV-infected monocytes across the blood – brain barrier during the development of HIV encephalitis (18).

Propposed model to explain the regulation of CCR5 and CXCR4 gene expression by kappa opioid receptor (KOR). The kappa opioid receptor agonist U50, 488H selectively binds to the KOR triggering an intricate signaling cascade. Part of this mechanism includes transcriptional activation of the interferon gamma (IFN-γ) gene as illustrated. Secretion of the interferon gamma protein results in binding to IFN-γ receptors (potentially in an autocrine manner). Activated interferon gamma receptor allows for active JAK formation and phosphorylation of the IFN-γ receptor itself. This provides a docking site for STAT proteins to bind and be phosphorylated by JAK. Once STAT1 is phosphorylated, STAT1 can homodimerize to itself (or heterodimerize to other STAT family members) and with dimerization, the protein complex translocates into the nucleus and binds to STAT elements, thus regulating transcription of target genes. One gene that is activated by the interferon gamma depended STAT1 activation is IRF1. IRF1 and IRF2 bind an identical IRF element (IRFE). IRF1 is able to trigger production of IRF2, which functions as a transcriptional repressor for IRF1 as well as several other genes. Since IRFE's have been found in the promoter of CXCR4 and CCR5, it is possible that IRF1 is bound constitutively and with U50,488H mediated up-regulation of IRF2, IRF2 replaces IRF1 on the IRFE within the promoters of CXCR4 and CCR5. The end

result of this transcriptional mechanism is dramatically decreased levels of CXCR4 and CCR5 mRNA transcription (22)

Quite the opposite, Chang et al (2007) showed that in individuals infected with HIV-1, the MOR is up-regulated, possibly by circulating HIV-1 proteins such as gp120, and HIV-1 proteins may play a significant role in modulating the response to bacterial infection in opioid-using HIV-infected individuals (23).

Conclussion

Mu opioid receptor has a role in addiction and HIV and there is an interaction between mu opioid receptor and chemokine receptor. The treatment for comorbidity of HIV and drug addiction should be conducted together to increase the successful of the treatment program.

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