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Immunotherapy in Opioid Use Disorders

Opioid Kullanım Bozukluklarında İmmünoterapi

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Abstract

Opioid use disorders are a deadly problem worldwide. Pharmacological therapies are effective for abstinence but remain inadequate in the treatment of addiction. Immunotherapy is a promising treatment modality in opioid use disorders. Immunotherapy aims to detect and capture substances by antibodies. Specific antibodies generated against substances bind a psychoactive substance and prevent them from passing through the blood/brain barrier. The psychoactive substance, which cannot pass through the blood brain barrier, will not be able to reveal both the euphoria effect and its side effects such as respiratory depression. Pre-clinical studies are partially sufficient in terms of effectiveness and reliability. However, long term high antibody levels could not be obtained in the blood following the vaccinations. The number of studies on opioid vaccines that have reached the clinical research level is very low. Thus, the effect of matter in the brain is prevented from occurring. Although effective results were obtained in preclinical studies, long-term high antibody levels could not be achieved in the blood. The number of studies that have reached the level of clinical research is insufficient. Efforts to increase the effectiveness of vaccines are ongoing. Although positive results are obtained in these studies, there are some difficulties vaccination studies. The financial burden of vaccine development, the use of multiple substances in opioid dependents, immune system suppression by the opioids, and changes in the degree of opioid purity are some of them. Despite all these difficulties, immunotherapy is the treatment that the researchers and patients expect with hope.

Keywords: Opioid addiction, morphine, heroin, vaccine, antibody, immunotherapy

Öz

Opioid kullanım bozuklukları dünya çapında ölümcül bir sorundur. Farmakolojik tedaviler yoksunluk için etkilidir, ancak bağımlılığın tedavisinde yetersiz kalmaktadır. İmmünoterapi, opioid kullanım bozukluklarında umut verici bir tedavi yöntemidir. İmmünoterapi, antikorlarla maddeleri tespit etmeyi ve yakalamayı amaçlamaktadır. Maddelere karşı üretilen spesifik antikorlar psikoaktif bir maddeye bağlanır ve kan / beyin bariyerinden geçmelerini önler. Kan beyin bariyerini geçemeyen psikoaktif madde hem öfori etkisini hem de solunum depresyonu gibi yan etkilerini ortaya koyamayacaktır. Klinik öncesi çalışmalar etkinlik ve güvenilirlik açısından kısmen yeterlidir. Bununla birlikte, aşıları takiben kanda uzun süreli yüksek antikor seviyeleri elde edilememiştir. Klinik araştırma düzeyine ulaşmış olan opioid aşıları ile ilgili çalışma sayısı çok düşüktür. Aşıların etkinliğini artırma çabaları devam etmektedir. Bu çalışmalarda olumlu sonuçlar alınmasına rağmen aşılama çalışmalarında bazı zorluklar bulunmaktadır. Aşı gelişiminin mali yükü, opioid bağımlılarında çoklu maddelerin kullanımı, opioidlerin bağışıklık sistemi baskılanması ve opioid saflık derecesindeki değişiklikler bunlardan bazılarıdır. Tüm bu zorluklara rağmen, immünoterapi araştırmacıların ve hastaların umutla bekledikleri tedavidir.

Anahtar sözcükler: opioid bağımlılığı, morfin, eroin, aşı, antikor, immünoterapi

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UNITED NATIONS OFFICE on drugs and crimes has reported that approximately 5.6% of the global population aged 15-64 years (275 million people) has used an illegal substance at least once in 2016 (2018). On the other hand, 31 million people using Other Psychoactive Substances (OPS) other than alcohol and tobacco have substance abuse disorder. Opioid related deaths make up 76 percent of deaths related to substance abuse disorders (WHO 2018). This rate shows that opioids are the most lethal substances among all substances. Opioids are not used only as psychoactive substances but also as painkillers. Use of prescribed opioid analgesics has increased more than two-fold between 2001-2013 worldwide (Berterame et al. 2016). Studies have shown abuse of opioid painkillers to be the strongest risk factor for initiating heroin abuse (Compton et al. 2016). All these data show that opioid dependence is an increasing problem worldwide.

Addictions involve a chronic and recurrent disease process (Xiaoshan et al. 2020). In addition to encountering many difficulties with the treatments currently used in addicitons, recurrence rates are also rather high (Campa et al. 2017). Increased recurrence rates mean use of opioids for a long time. Prolonged opioid use leads to physical, mental, social and cognitive functional disorders (WHO 2018). Impairments of executive functions like memory processing, impulse control and decision making are the most frequently seen functional cognitive disorders (Ornstein et al. 2000, Fernandez-Serrano et al. 2011). Although some studies show that functions are partially reversed after stopping opioid use, high doses and prolonged use lead to permanent cognitive and mental impairment (Fernandez-Serrano et al. 2011, Koparal et al. 2020). Immunotherapy is introduced as a new treatment option for addicitons in pre-clinical studies (Baruffaldi et al. 2018).

Opioids have rather important functions on numerous body functions like processing and controlling harmful emotional inputs, homeostasis of hormones, analgesia and immune system. Endogenous opioids include β-endorphin, encephalin and dynorphin (Uyar and Eyigör 2008). In addition to these opioids, there are also opioid containing drugs which are mainly used in analgesia and addiction treatment (Holden et al. 2005). Both endogenous opioids and opioid containing drugs have significant effects on the immune system (Boland and Pockley 2018). Opioid receptors are located on the surface of various immunologic cells. It is proposed that immune response is changed or suppressed as a result of interaction between these receptors and opioids (Boland and Pockley 2018, Khosrow-Khavar et al. 2019).

In this study, efficacy of current drug treatments in opioid addiction, vaccine treatments developed against opioids, efficacy enhancing studies in vaccines and difficulties in vaccine treatments will be discussed.

Efficacy and adverse effects of current drug therapies

Addiction is usually treated with pharmacotherapy combined with psychotherapy (Uğurlu et al. 2012). Although such therapies are partially effective, they may not be satisfactory (Yılmaz et al. 2014). Many stimulants do not target a directly defined chemoreceptor. Stimulant substances act on transmitters in order to increase the amount of dopamine,

norepinephrine and serotonin in the synaptic cleft present in other reward centers and mainly the nucleus accumbens (Hahn et al. 2011). Therefore, it is difficult to achieve successful treatment outcomes with receptor antagonists (Uğurlu et al. 2012, Yılmaz et al. 2014).

Pharmacologic agents approved for opioid use disorders include opioid agonists (e.g., methadone and buprenorphine) and opioid antagonists (e.g., naloxone and naltrexone). Opioid agonists are used for detoxification of heroin and illicit opioid users (Evren et al. 2000). Opioid antagonists are used for reducing craving and prevention of recurrences (Kulaksizoğlu et al. 2019).

Both types of treatment are useful for abstinence (Tellioğlu 2010, Evren 2019). However, they can also have some adverse effects. The most frequently seen adverse effects are headache, constipation, sleeplessness, asthenia, somnolence, nausea, balance problems, sweating and loss of libido. Elevation of liver enzymes is also another problem (Evren 2019). However, methadone and buprenorphine have the potential for abuse and have lethal risks like respiratory depression at excessive doses (Bell et al. 2009). Death from methadone overdose is reported to be more frequent than buprenorphine (Bell et al. 2009). Naltrexone which is an opioid antagonist is a treatment option used in the maintenance treatment following treatment for abstinence (Kulaksizoğlu et al. 2019). Adverse effects like energy loss, sleep problems, increased anxiety, nausea, vomiting, joint/muscle pain, headache and abdominal pain have been reported in one of ten patients (Evren 2019, Uğurlu et al. 2012). One of the most important problems related to naltrexone treatment is increased mortality risk due to drug overdose when patients treated with naltrexone return to using opioid (Darke et al. 2019). Patients increase the dose of opioid in order to surpass the antagonistic effect. And this leads to unwanted intoxications and risk of death. It was proposed in the studies performed in previous years that naltrexone caused impairment of endogenous opioid and hormone balance (Crowley et al. 1985; Kosten et al. 1986). In a prospective study including a small sample group staying sober for approximately one year to four years, patients using naltrexone developed dysphoria at a substantial degree (Crowley et al. 1985).

Considering these disadvantages, immunotherapy for opioid use disorder can be a method for decreasing opioid use in the long term and carries less risk for adverse effects compared with the drugs (Kosten et al. 2002, Maurer et al. 2005, Cornuz et al. 2008). The fundamental purpose in immunotherapy involves recognition of psychoactive substances used as antigens and their capture by antibodies (Wainer et al. 1973, Bonese et al. 1974). Specific antibodies that develop against the substances bind to psychoactive substances and prevent their passage through the blood/brain barrier. Thus the reward effect created in the brain by the substance and possible side effects are prevented (Li et al. 2015). Absence of euphoria effect despite substance use is thought to facilitate addiction treatment to a great extent (Kosten and Owens 2005, Shen and Kosten 2011). The most important advantage of this treatment is absence of adverse effects on the central nervous system usually occurring during pharmacotherapy (Anton and Leff 2006, Li et al. 2011), because psychoactive substance captured by the antibody cannot pass to the brain or passes very little. Data obtained from animal and human studies reveal that vaccines developed against

psychoactive substances present a favorable safety profile (Kosten et al. 2002, Maurer et al. 2005, Cornuz et al. 2008). With these effects, immunotherapy seems to be a very promising therapeutic approach.

General characteristics of humoral immune system

The humoral immune system is made of antibodies produced by B cells. The antibodies target antigens outside the cells. After binding to these antigens, antibodies have the function of neutralizing or eliminating them (Abbas et al. 2012, Durmaz 2013). Development and maturation of B cells occur in the bone marrow in approximately 2-3 days, independently from antigens (Delves and Roitt 2000a). Receptors of B cells which have never encountered antigens (mature naive) are IgM and IgD molecules. Antigen specificity of these surface antibodies is extremely high and can recognize 107-1011 types of different antigens (de Souza et al. 2010). This immunity formed by mature naive B cells is the primary immune response. This immune system has a slow response which develops within several weeks. It produces antibodies with low affinity against various antigens (Delves and Roitt 2000b).

Some of mature naive B cells take place in the secondary immune system which is antigen dependent by migrating to peripheral lymphoid tissues. These cells recognize the antigen but cannot produce antibodies. They need to be activated in order to produce antibodies (helper T cell mediated or not) (Mesquita Júnior et al. 2010). B cell antigen receptors can recognize polysaccharides, lipids, glycolipids, nucleic acids and small soluble molecules (Ollila and Vihinen 2005). These products somehow stimulate B cells independently from T cells and lead to the production of antibodies. However, help of CD4+ T cell (Helper T Cell) is needed to recognize antigens containing proteins. While the early phase of T cell mediated humoral immune response occurs at the border of primary follicles and regions rich in T cells, the late phase occurs at the germinal centers of secondary lymphoid follicles (Mesquita Júnior et al. 2010, Durmaz 2013).

Dendritic cells present protein containing antigens to helper T cells (Yılmaz Göler et al. 2015). When these antigen presented T cells and ready B cells find each other, the protein antigen is taken inside the cell through endosomal vesicles. After these protein antigens pass through a series of processes, various interactions occur between helper T cells and B cells (Cambier and Getahun 2010). Following these interactions, activation steps like proliferation of B cells, differentiation, antibody production, change in heavy chain isotype/class and formation of memory cells are stimulated (Ollila and Vihinen 2005). Nevertheless, IL-2, IL-4, IL-5 and IL-6 cytokines released from active helper T cells allow proliferation and differentiaton of B cells. While some proliferated B cells transform into active antibody releasing effector B cells, others transform into memory B cells (Abbas et al. 2012). These processes of transformation and development in the immune system are shown in Figure 1.

The immunotherapy method aimed in substance use disorders is generally similar to the treatments in other infectious diseases (tuberculosis, measles, whooping cough etc.) (Anton and Leff 2006, Li et al. 2011). But there are some small differences. Sizes of the substances used for psychoactive purposes are rather small (Pravetoni and Comer 2019). Therefore,

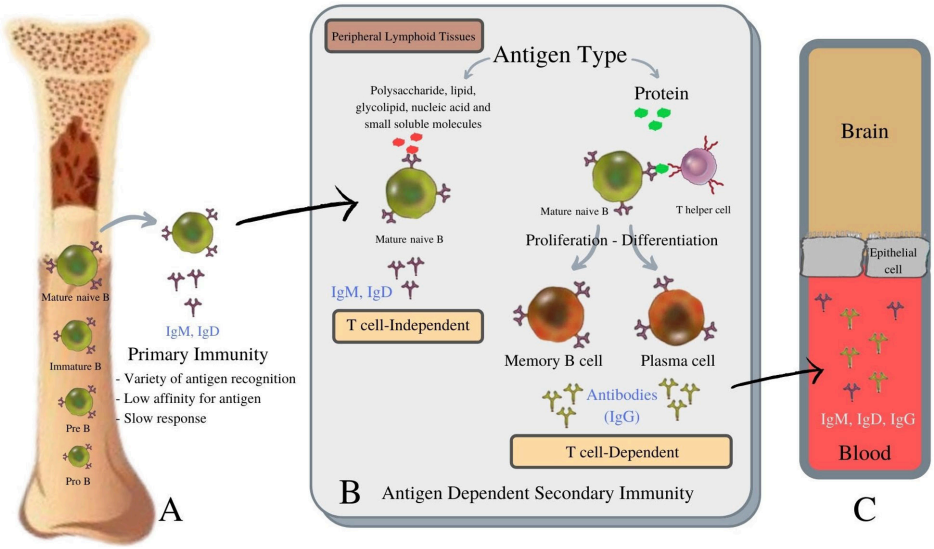

Figure 1. The humoral immune system and antibody development
(A) Development of B lymphocyte in the bone marrow. Mature naive B cell that develops in the bone marrow is involved in primary immune responce. (B) Antigen dependent secondary immune response. B lymphocytes migrating to peripheral lymphoid tissue encounter antigens mediated or not. IgM and IgD occur in non-T cell-mediated exposure, whereas IgG occurs in T-cell-mediated exposure. (C) Blood Brain Barrier. Antibodies (IgM, IgD, IgG) formed as a result of B lymphocytes encountering antigens take place in the circulation.

they can easily pass the blood brain barrier and affect the central nervous system. Their small size makes it difficult for an immune response to be generated against these substances (Pravetoni 2016). In vaccines developed against infectious agents, the parts of these agents that can produce antibodies the most (capsule, toxin etc.) are used (Anton and Leff 2006). These parts can be rapidly recognized by the immune system due to their size. In vaccines developed against psychoactive substances, conjugation with large immunogenic proteins with demonstrated efficiency in other vaccines (tetanus toxin, cholera toxin etc.) is aimed in order to increase the efficacy of vaccines and duration of immunity (Anton and Leff 2006, Li et al. 2011, Pravetoni and Comer 2019). Due to these processes, psychoactive sucbstances cannot pass the blood brain barrier and remain in the circulation for a longer time. And this increases production of antibodies against the substances taken (Kosten et al. 2014). Opioids present in the peripheral circulation are captured by the antiboides produced and are phagocytosed by the phagocytes (monocytes, macrophages). During phagocytosis, a part of opioids combined with hapten and carrying antigenic characteristics is presented to other lymphocytes with the mediation of macrophages. Thus, lymphocytes are activated and antibody production is intensified (Ollila and Vihinen 2005). A simple image of passage of opioids to the brain under conditions with and without vaccine is shown in Figure 1.

Opioids used for psychoactive purposes (heroin, morphine, fentanyl, oxycodone etc.) cannot be sufficient alone for inducing antibody response in the vaccines developed against opioid use disorders and are currently under investigation (Pravetoni and Comer 2019).

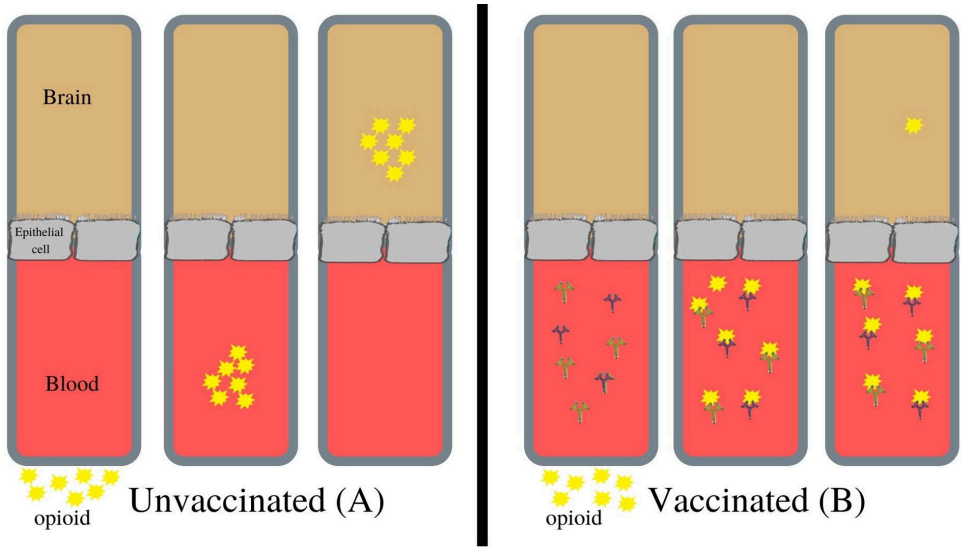

Figure 2. Transition of opioids to the brain in vaccinated and unvaccinated situations
(A) Unvaccinated situation. It easily crosses the Blood-Brain barrier after opioid intake. (B) Vaccinated situation. Antibodies formed after opioid vaccines capture opioids in the circulation. Thus, less opioids enter the brain.

Molecules that cannot induce antibody production alone but show this capacity when attached to a protein are called haptens (Hwang et al. 2018). Therefore, opioids can act as haptens in vaccine studies. Different antigens and adjuvants are added to these haptens (to psychoactive substances) to boost immunity. Most commonly used antigens/modulators are keyhole limpet hemocyanin (KLH) and tetanus toxoid (Bremer and Janda 2017). Most commonly used adjuvants are Freund's adjuvant and aluminum compounds (Alving et al. 2014). Adjuvants are substances added for producing more antibodies and longer immunity. Aluminum compounds are the most important adjuvants used in vaccines developed since 1920s until today (Baylor et al. 2002). Therefore, they are among the best known adjuvants. But inability to stimulate cellular immunity, producing granulomas at infection sites, affection of brain and bone tissues by high levels of aluminum and accumulation in the body in renal disorders are major adverse effects of these adjuvants (Exley et al. 2010). These adverse effects can be a few of the important limitations in adjuvant substance use. Bovine serum albumin can also be used to limit the inappropriate chemical reactions in the vaccines developed for opioid addiction (dissociation of vaccine contents, sticking to the vial surface etc.) (Kosten et al. 2013).

Vaccine therapy

Vaccines at the stage of development against opioids have remained behind the vaccines developed against coaine and nicotine regarding efficacy (Zalewska-Kaszubska 2015). One of the most important reasons for this is the fact that heroin is a precursor (Berber et al. 2011). That is, heroin undergoes changes following intake and metabolites are formed. Therefore, it is dfficult to develop a vaccine against heroin which is not stable in the

body. Heroin is hydrolysed by serum and liver esterases into more stable compounds of 6-monoacetylmorphine (6-MAM) and morphine. Later, morphine can transform into morphine-3-glucuronide (M-3-G) and morphine-6 glucuronide (M-6-G) via the enzymes in the liver and kidneys (Inturrisi et al. 1983, Selley et al. 2001).

These enzymatic activities occur rapidly and opioid containing substances can pass into the central nervous system. Therefore, vaccines developed against opioids are more difficult to develop than vaccines against nicotine and cocaine and their efficacy is less (Zalewska-Kaszubska 2015). When nicotine and cocaine are bound by antibodies, the problem is solved to a great extent (Pravetoni and Comer 2019). But the same process is not true for opioids. Even if antibodies are produced against heroin, toxic effects of opioids continue unless antibodies are produced against the metabolites (Kimishima et al. 2017). Therefore, it is important to develop vaccines not only against heroin but also against its metabolites when developing vaccines against opioids. Thus it will be possible to eliminate the effects of both heroin and its metabolites.

Preclinical studies (Animal studies)

It is known since 40 years that vaccines developed against morphine, heroin, codeine and their metabolites stimulate immune response (Berkowitz and Spector 1972, Wainer et al. 1973, Bonese et al. 1974). Studies have focused on morphine. The vaccine produced in 1972 against 3-carboxymethyl morphine was tried on mice by vaccinating once a week for 16 weeks (Berkowitz and Spector 1972). When morphine was given to mice at a dose of 0.5-1 mg/kg, the selective analgesic effect of morphine was noted to decrease in vaccinated mice. That is, pharmacologic effects of morphine were limited. These results have led to the idea that the effects of morphine can be reduced or completely eliminated. One year after these studies Wainer et al. (1973) have found that, in addition to morphine, antibodies obtained against 6-succinylmorphine also affected heroin and 6-MAM which are each a derivative of morphine. Actually this is exactly the desired result, because individuals with substance abuse disorder can use multiple opioid containing substances at the same time. Production of antibodies against many opioid contents by a developed vaccine is one of the major advances in research. Nevertheless, this study has shown that binding properties vary depending on the hapten used. During the same period, Bonese et al. (1974) have shown that following use of vaccines produced against morphine-6-hemisuccinyl in a heroin addict rhesus monkey, the monkey reduced the amount of morphine it used on its own. This reduction in the morphine they administered to themselves is important regarding the behavioral changes induced by antibodies, because one of the most important targets aimed is reduction of use of and desire for substances in individuals with addiction. These progresses in vaccine studies have started to regress with the use of methadone as an effective treatment option (Scher 1972, Goldstein 1972). Vaccine studies became popular again after the limitations and problems in drug therapies were observed, as discussed above.

Anton and Leff (2006) have developed a vaccine in the form of morphine-6-hemisuccinate conjugated with tetanus toxin. This vaccine has produced antibodies against morphine and

heroin. This vaccine is very important regarding its hapten structure and providing an efficient immunization against both heroin and morphine. Later, this vaccine could not move on to clinical studies because of its inadequate efficacy (Anton and Leff 2006). Li et al. (2011) have investigated the vaccine containing 6-glutaryl-morphine (6-GM) which weakens the locomotor activity of heroin in rats. Until this study, the substance used as hapten has been morphine-6-succinyl or a similar substance. Li et al. (2011), on the other hand, have used a new hapten (6-glutaryl-morphine). Dopamine levels in nucleus accumbens were found to be significantly low and locomotor activities were less in rats undergoing vaccination compared with those not vaccinated. Elevated antibody levels have reduced heroin craving bahavior. This was shown as an important novelty. One of the important outcomes in this study is increased antibody production specific for morphine and heroin by the vaccine, while no antibodies were produced for other opioid compounds like buprenorphine, methadone, naloxone, naltrexone, nalorphine or codeine. It is very valuable that antibodies are not produced against these drugs, because these results support that vaccine therapies can be used in individuals using any one of these drug threapies for opioid addiction or analgesic purposes. In other words, vaccine therapies and opioid compounds can be used concomitantly in the treatment. These researchers also noted a reduction in heroin craving behavior of mice in the same study. However, this effect markedly decreased 25 days later. Therefore, they conducted a new vaccine study to increase the efficacy of these vaccines, to obtain higher antibody affinity and for better opioid blockage (Li et al. 2015). They used N- (ε-trifluoroacetylproxy) succinimide ester (TFCS) instead of 6-GM in this vaccine. They attached this structure to KLH and created the Morphine-TFCS-KLH vaccine. This vaccine was created after the procedures performed on 6-GM. As in the previous study, the vaccines were administered subcutaneously on days 0, 14, 28 and 42. Similar results regarding dopamine level and absence of production of antibodies against buprenorphine, naloxone and nalorphine were also obtained in this study. With these results, a higher level of antibodies compared with the previous study was obtained and reduction in heroin craving behavior was also observed after the 25th day.

Raleigh et al. (2013) analyzed the distribution of heroin and its metabolites in order to understand how morphine-KLH vaccines altered the behavioral effects of heroin in rats. In this study, 6-MAM was found as the dominant metabolite in the brain a short while after intravenous heroin was administered in rats that were not vaccinated. This metabolite was found to be decreased in the brain in rats vaccinated with morphine-KLH. However, it was reported that there was a decrease in the effects of heroin, methadone and oxycodone, analgesia caused by heroin was decreased and self-administration was decreased. These effects were shown to be related to high antibody levels. Similar to these studies, numerous studies using morphine have been conducted (Kosten et al. 2013, Raleigh et al. 2018). It was found in these studies that basically antibodies were produced, heroin craving behavior was decreased and analgesic effect decreased. But pre-clinical vaccine activities could not provide a complete sufficiency to move on to post clinical studies.

Together with heroin use worldwide, a considerably high level of opioid prescriptions has been shown (oxycodone, hyrocodone, fentanyl etc.) (Berterame et al. 2016, Neuman et al. 2019). Excessive use of opioids as painkillers is named "opioid epidemic". This increase in opioid prescriptions was also reflected in vaccine studies. Vaccines developed against these opioid containing drugs aim to eliminate both active substances and their metabolites (Pravetoni et al. 2012a, Pravetoni et al. 2012b), because people with opioid addiciton frequently shift among numerous different opioids (Pravetoni and Comer 2019). Also, it is stated that illicit use of prescribed opioids (oxycodone and hydrocodone) in the last 10 years has surpassed heroin use (CBHSQ 2015). This shows the increasing danger of opioid containing drugs. Vaccines developed against oxycodone and hydroxycodone have shown that these substances decrease brain/serum ratios (Pravetoni et al. 2012a, Pravetoni et al. 2012b), drug induced analgesia (Cornuz et al. 2008, Pravetoni et al. 2012c) and self administration (Pravetoni et al. 2014).

Fentanyl is a potent opioid analgesic used for analgesia. On the other hand, its addiction potential was found to be 80 times more potent than morphine (Mounteney et al. 2015). Fentanyl use is gradually increasing and mortality rates related to overdose are also increasing (Morgan 2017). Therefore, Bremer et al. (2016) have performed a study for developing fentanyl vaccine. Researchers have conjugated fentanyl to tetanus toxoid proteins and have undertaken a series of conjugation procedures. Endogenous Ig G antibodies have developed with the Fentanyl-TT (Fentanyl-Tetanus Toxoid) conjugate vaccine admnistered to mice. The analgesic effect of fentanyl disappeared after vaccination and this continued for one month. One of the important results was observing a mortality rate of 55% in the control group when lethal doses of fentanyl analogues were given to mice, while mortality rate was 18% in the vaccinated group. These results show that the vaccine made for fentanyl is rather effective in reducing mortality at high doses.

There is some concern about the vaccines developed against opioids. The first is decrease in drug efficacy as a result of cross reaction of the antibodies with the drugs currently used in threapy (methadone, buprenorphine, naloxone etc.) (Sulima et al. 2018). Therefore, researchers have drawn attention especially to this subject in their studies and have handled in detail the outcomes of cross reactions (Matyas et al. 2014, Sulima et al. 2018). Absence of development of cross reactions means that opioid antagonists or agonists can be used concomitantly with vaccine therapies. The efficacy of these combination therapies is expected to be higher. Naloxone, a major opioid antagonist, is used for emergency therapy of opioid overdose (Giglio et al. 2015). Therefore, it is very important that opioid vaccines do not reduce the effect of naloxone. In the study of Raleigh et al. (2017), both the degree and reversibility rate of respiratory depression treated by naloxone were fully preserved in rats immunized with oxycodone-dimeric KLH vaccine. In this regard, the vaccinated and control groups were comparable (Raleigh et al. 2017). Another concern about opioid vaccines is decrease in vaccine efficacy as a result of suppression of the immune system by opioids. Studies have shown that many opioids and mainly morphine decrease production of antibodies against infectious agents (HIV, HBV, HCV, influenza etc.) or immunogens

(Borg et al. 1999, Quaglio et al. 2002). When this effect of opioid use is considered, decrease in immunity with opioid use in the vaccines developed is a serious problem. Higher doses of vaccines may be needed with the decrease in immunity or a dose of vaccine may be needed. The finding in a study that the immunity produced by a developed opioid vaccine is suppressed with continuous morphine infusion is rather valuable (Raleigh et al. 2017). These results show that vaccines to be developed can be effective despite the suppressive effect of opioids.

Basically, opioid vaccines have been developed with the aim of decreasing the rewarding and euphoria creating effect of opioids. Nevertheless, decreasing the toxic effects caused by opioids such as respiratory depression, bradycardia and coma is another aim. Studies show that the vaccines significantly decrease other lethal signs and mainly respiratory depression. (Raleigh et al. 2017, Raleigh et al. 2018). Considering that 76% of substance abuse related deaths worldwide is high dose opioid use, deaths can be reduced considerably when the vaccines developed are introduced into clinical practice (WHO 2018). The findings obtained from vaccine studies developed against opioids are promising. But, opioid vaccines are not at the phase of clinical research yet. Therefore, studies investigating the efficacy of vaccines are ongoing.

Preclinical studies conducted for ıncreasing vaccine efficacy

despite promising animal studies, vaccines developed against opioids have not met the expectations yet. The basic reason for this is insufficiency of levels of serum antibodies obtained (Kosten et al. 2002, Martell et al. 2009, Hatsukami et al. 2011). These difficulties are also seen in nicotine and cocaine vaccines which are a step ahead of opioid vaccines (Zalewska-Kaszubska 2015). For instance, studies have found IgG levels of 40μg/ml, the threshold accepted for abstinence from smoking and cocaine, in 30%-38% of vaccinated individuals (Martell et al. 2009, Hatsukami et al. 2011). These rates show that nicotine or cocaine vaccines are useful in three of ten individuals vaccinated. Although these rates are partially sufficient, the expected efficacy is higher.

Clinically effective antibody levels have been reached in a very small part of people with the available vaccines. At this stage, the reason of this problem has not been understood yet. Absence of markers that show the efficacy of the vaccines developed or in whom they could be effective is an important problem preventing maturation of vaccine studies. Researchers who have dealt with this deficiency have analysed B cell profiles before vaccination (Taylor et al. 2014). They have reported that naive B cells show higher affinity for the most effective hapten and immunogens and B cells specific for activated hapten are the early proof of vaccine success. Upon these results, researchers have used a paired antigen based enrichment strategy with flow cytometry analysis in their study carried out to increase the number of hapten specific B cells (Laudenbach et al. 2015). As a result of these enrichment studies, they found a higher number of naive and early activated hapten specific B cells in spleen biopsies and blood. This elevated number was similarly found to be associated with high vaccine efficacy. Also in this study, CD4+ T cell dependent B cell activation, number of pre-

vaccination carrier-specific CD4+ T cells and germinal center activation were found to be associated with the efficiency of vaccine.

In another study of Laudenbach et al. (2018), the authors investigated the relationship between major immunomodulators participating in B and T cell lymphocyte activation and activity of vaccines developed against oxycodone. Inhibition of IL-4 transmission has increased vaccine efficacy and decreased distribution of oxycodone in the brain. However, opioid related toxicity occurring in mice has decreased. As part of the study, when IL-4 level was decreased, tetanus-diphtheria-pertussis vaccine was concomitantly administered and the efficacy of these vaccines were also shown to increase. Data of this study show IL-4 as a pharmacologic target for increasing the efficacy of new generation vaccines (Laudenbach et al. 2018).

Clinical studies (Human studies)

Almost all of opioid vaccines have been administered to mice, rats and non-human primates. On the other hand, only two studies were carried out on human volunteers (Akbarzadeh et al. 2007, Akbarzadeh et al. 2009). The first research was a randomized double blind study on 102 individuals aiming to investigate the safety and immunization of morphine vaccine in humans (Akbarzadeh et al 2007). Bovine serum albumin was conjugated to morphine-6-succinyl as carrier protein and aluminum hydroxide as adjuvant. Patients with morphine addiction were followed for 1 year. Patients were vaccinated on days 0, 30 and 60. Samples were divided into 4 groups as the placebo group and groups undergoing administration of morphine vaccines at three different doses (12.5 ug mL, 100 ug mL and 600 ug mL). The most frequently reported adverse effects were local pain and tenderness. These adverse effects were independent of the dose and were found to be similar to placebo. The most frequently seen treatment related systemic adverse events (for all doses) were tachycardia, high fever, hypertension, headache, pharyngitis, twitches and nausea, whereas in the placebo group high fever, hypertension and headache were noted. The first clearly detectable IgG anti-morphine antibody was observed at doses of 100 and 600 ug mL after the first injection and at 12.5 ug mL dose after the second injection. Antibodies reached a peak in three months and did not regress to the baseline level for one year. It was reported at the end of the study that 95% of the patients did not carry DSM III-R morphine addiction criteria and were healed.

A second study was conducted by the same study team on 347 volunteers with morphine addiciton (Akbarzadeh et al. 2009). Morphine-6-succinate, aluminum hydroxide and bovine serum albumin were present in the vaccine. The vaccines were administered on days 0, 30 and 60. The vaccine was systemically well tolerated. On the other hand, local adverse effects were reported to be less compared with other vaccines (BCG, MMR etc.). A detectable increase was noted in the levels of anti-morphine antibodies, total protein and gamaglobulin following the first vaccination. Following the second and third vaccinations, the increase in the amount and concentration of anti-morphine antibody was detected more potently. While antibody amounts reached a peak level in the third month (one month after the last

dose), it was noted to decrease following the fourth month. But this was reported to be an expected situation. One year later, levels of anti-morphine antibodies, total protein and gamaglobulin were found to be above baseline levels. Reseraches have suggested that even though antibody levels are seen to be above baseline levels, a repeat vaccination in the first year would be appropriate. It was reported that during the one-year period of the study, the patients tolerated the vaccine well and did not have serious problems related to psychoactive substances. While antibody responses of the patients induced by the vaccines and adverse effects were evaluated in detail in this study, variables like frequency of substance abuse, the status of meeting addiction criteria after the study, state of euphoria following substance abuse and recurrence rates were not reported. And this has left the question of what the effects of the vaccines are on treatment and recurrence unanswered.

Challenges in vaccine studies

Studies on opioid vaccines have been continuing for a long time (Berkowitz and Spector 1972, Wainer et al. 1973, Bonese et al. 1974). However, due to the difficulties in developing vaccines against opioids and the presence of partially effective pharmacotherapies for opioid addiciton, vaccine studies follow a rather slow course.

One of the basic difficulties in the development of vaccines is the fact that heroin is a precursor substance (Berber et al. 2011). Heroin rapidly separates into its metabolites in the brain and peripheral circulation (Inturrisi et al. 1983, Selley et al. 2001). Developed vaccines should target all these molecules in order to be effective. Although there are partial progresses on this subject, it is still one of the most important problems (Wainer et al. 1973, Kimishima et al. 2017). On the other hand, people with addiciton do not use a single opioid and shift between substances (Pravetoni and Comer 2019). And this is among the reasons that can decrease efficacy of the vaccine.

It is reported in the European Drug Addiction Report (2019) that purity of the opioid is decreased in time and is altered between 9% and 51%. Change in purity means that unknown substances are mixed into the psychoactive substances produced. Mixing opioids with other substances or synthetic products will also reduce vaccine efficacy.

Although available drug therapies do not yield a definite solution, they help the patients overcome their abstinence period with more comfort and provide support in maintenance therapy (Kulaksizoğlu et al. 2019). Costs of these therapies are much lower than vaccine therapies (Brashier et al. 2016). Developing a new vaccine and supporting this vaccine with both preclinical and postclinical studies are both time consuming and costly. The heavy financial burden in developing a vaccine is another cause that hampers immunotherapy methods.

Preclinical studies have produced adequate levels of antibodies following vaccination (Anton and Leff 2006, Li et al. 2015). But these antibodies cannot remain in the blood for a long time (Bremer et al. 2016). Therefore, studies are needed for increasing the efficacy of vaccines and repeated injcections for providing high antibody titers (Akbarzadeh et al. 2009). And this inceases the already heavy financial burden. On the other hand, suppression

of immunity by opioids is a known fact. And this can decrease vaccine efficacy and additional vaccinations may be needed.

Opioid vaccines aim to decrease the euphoria and analgesia induced by the opioids (Kosten and Owens 2005, Shen and Kosten 2011). Reduction of euphoria and analgesia can cause some substance users to use higher doses of opioids in order to achieve euphoria and analgesia. Although it has been shown in preclinical research that vaccinations reduce opioid use related toxicity, opioid overdose is a lethal condition (Raleigh et al. 2017, Raleigh et al. 2018). It seems that developed vaccines need both preclinical and clinical studies carried out on this aspect.

Conclusion

Opioid use disorders are lethal problems worldwide. Although available pharmacologic therapies are effective for abstinence, they are insufficient in the treatment of addicition. Immunotherapy is a promising treatment method for opioid use disorders. Although effective results have been obtained in preclinical studies, prolonged antibody levels in the blood could not be attained. Studies that have reached clinical research stage are very few in number. This shows that we need to wait a little more for clinical research related to vaccine studies. Studies that can increase efficacy of vaccines are ongoing. Although favorable results have been obtained in these studies, there are some difficulties facing vaccine studies. Financial burden of vaccine development, need for repeated vaccination to achieve the necessary antibody levels, suppression of immunity by opioids and changes in purity degrees of opioids are some of these. Despite all these difficulties, immunotherapy for substance addicitions is a treatment method followed by the patients and researches with hope.

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