

Evidence that the Immune System Participates in the Expression of Opiate Withdrawal Behavior

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Received: April 01, 2020

Accepted: June 05, 2020

Published: June 08, 2020

Citation: Dafny N. 2020. Evidence that the Immune System Participates in the Expression of Opiate Withdrawal Behavior. *J Addict Sci* 6S(1): S12-S16.

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Abstract

The objective of this manuscript is to summarize studies that demonstrate that the immune system participates in the expression of opiate withdrawal. Five groups of animals were used: 1. Chronic morphine control group; 2. The immune system was ablated in morphine-dependent rats; 3. In morphine-dependent animals the immune system was ablated and followed by reconstitution of the immune system from intact normal donor animals; 4. The immune system was ablated prior to chronic morphine exposure; and, 5. The immune system in morphine-naïve animals was ablated followed by immune component reconstitution from donor animals and then exposed to chronic morphine. All of the chronic morphine exposure animals were injected with 1.0 mg/kg naloxone to precipitate the behavioral withdrawal symptoms. In the first group, naloxone precipitated the classical behavioral syndrome; in groups 2 and 4 withdrawal symptoms were significantly attenuated and eliminated in some animals; and, in groups 3 and 5 naloxone injection resulted in severe withdrawal behavior. These experiments demonstrated that the immune system participates in opiate withdrawal expression and suggest the use of immunotherapy to control the opioid epidemic.

Keywords

Morphine, Naloxone, Withdrawal, Immune system, Destruction, Reconstitution

Introduction

Opioids are legally prescribed pain medications used to treat both acute and chronic severe pain. Opioids are a class of drugs that act on the central nervous system to relieve pain and also produce feelings of pleasure. Morphine is a pain medication of the opioid family. The primary source of morphine is from the poppy seed of the opium plant. Morphine dependence is classified as substance use disorder, a complex and often chronic health condition with social and behavioral implications [1]. Morphine's primary therapeutic value is as an analgesic and sedative but it is a highly addictive substance. Charts of the overdose death rate in America since 1980 increases in an exponential curve of 76% per year and reaches 50,000 per year [2]. Allison, Putt, Keother, Humphreys, and Margaret Brandeau from Stanford University estimate that just over half a million Americans will die from opiate overdose from 2016 to 2025 [2]. The opioid epidemic began in the 1990s with over-prescription of opioids as pain relief medications. Opioids quickly became the most prescribed class of medication in the USA exceeding antibiotic and heart medications. About 20 to 30 percent of patients, who are prescribed opioids for chronic pain, misuse it [3].

About 80 percent of heroin users first misuse prescription opioids [4]. In 2014, in the US, about 435,000 people used heroin. In the same year about 4.3 million used narcotics for nonmedical purposes. In 2015, an estimated 20,100 deaths were due to prescription painkillers and 12,940 deaths were due to heroin use and 591,000 people had a substance use disorder [5]. In 2016, more than 20,000 deaths in the US were caused by an overdose of prescription opioids and another 13,000 deaths resulted from heroin overdose [6], while other 2016 reports stated over 64,000 drug overdose deaths. There are more opioid overdose deaths in the US every year than deaths due to car accidents and gun shots [7].

During a 12- month period ending in Nov. 2017, 69,948 lives nationwide were lost due to opioid overdose making it one of the most serious overdose crises the country has ever had to face [2]. More than 210 million opiate prescriptions were filled in 2010 with close to 12 million people admitting to taking these drugs for non-medical reasons. Misuse of prescription opioids affects millions of Americans. As the opioid crisis continues to devastate families in the USA it is essential to investigate new approaches to combat the crisis [8].

Morphine withdrawal occurs when the drug is discontinued or when the opiate antagonist such as naloxone is injected into morphine-dependent subjects. Morphine withdrawal symptoms can last for a long period of time. In humans, morphine withdrawal expresses by typical physiological and behavioral symptoms that include intensive anxiety tremors, body shakes, muscle cramping, joint and deep bone pain, diarrhea, swatting, restlessness and more [9]. In rats, morphine withdrawal is expressed by locomotor hyperactivity, wet-dog shake movements, teeth chattering and more [10-14]. The degree of opiate dependency correlates directly with the intensity of the expression of the severity of opiate withdrawal symptoms [11, 15]. The objective of this manuscript is to present studies that demonstrate that the immune system participates in the expression of morphine withdrawal symptoms, suggesting an out-of-the-box treatment for morphine addicted subjects with immunotherapy.

Methods

Five groups of adult male 344 Fischer rats were used for the experiments; N = 8 for each group. Two groups, i.e. N = 16, were used as donors for the immune reconstitution. That is, the immune system components from two donor rats were used to reconstitute one immune ablated animal, i.e., 32 donors rats were used.

Animal preparation

Morphine dependence in the animals was produced by 10.0 mg/kg i.p injections of morphine in the morning and several hours later by subcutaneous implantation of one morphine pellet (75 mg/kg/pellet) under the skin on the backs of the animals [16-18] under light ether anesthesia. After about 72 hours of morphine pellet exposure the residual morphine pellet was removed and naloxone (1.0 mg/kg) was injected to

precipitate the morphine withdrawal behavior. The severity of morphine withdrawal behavioral signs was scored by two independent observers by counting the following behavioral expressions: number of wet dog shakes, teeth chattering, and the number of stool releases respectively. In addition three measures rated the severity of the animals' scream expressions to touch on their backs, exploratory activity, and diarrhea. No effect observed scored 0 and extreme effect rated 5. The score of each animal group was combined and averaged and the standard deviation from the average was calculated. Significant differences were determined for each experimental group in comparison with the control animal group. Neuman-Keuland and Kruskal-Wallis tests were used to determine the level of significant differences between the groups [11, 19].

Immune ablation

Selective ablation of the immune component cells was carried out by whole body irradiation at two different times: 1) 72 hours after morphine pellet implantation; and, 2) prior to morphine exposure in morphine-naïve animals. Rats were irradiated in a model 109 irradiator (T.L. Shepard and Assoc., Glendale California USA), which delivered 518 rad/min of gamma irradiation from a ¹³⁷C source. Animals were exposed in a continuously rotating chamber for 0.92 minutes to deliver a total of 500 rad [11, 19].

Immune reconstitution

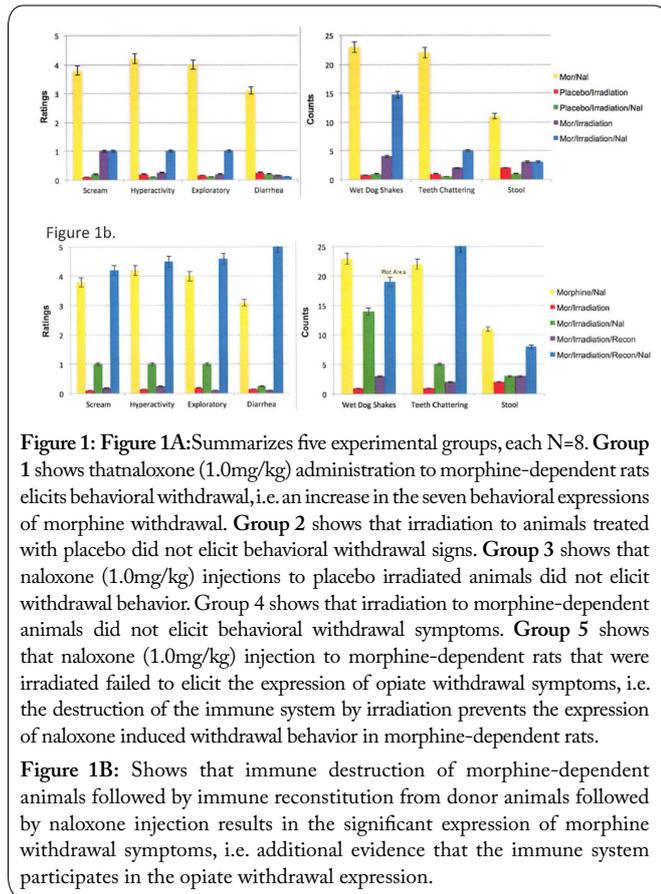
Two donor animals were sacrificed for each irradiated animal. The spleen cells, and axillary, inguinal and popliteal lymph node cells were collected. The lymphoid cells were dispersed and suspended into 50 ml cold Hank's Balance Salt solution (HBBS, GIBCO, +5 ml 7.5% NaHCO₃ and 5 ml 2M HEPES). The cells harvested from these two donors (2-4 X 10⁸ cells) suspended in 1 to 2 ml of medium were transferred intravenously to a single recipient animal [19].

All the experiments described in this manuscript were approved by Animal Welfare Committee and were carried out in accordance with National Institute of Health (NIH) Guide for Care and Use of Laboratory Animals.

Results

Animal behaviors were observed on day 1 before and after morphine exposure and after irradiation as well as after irradiation and immune reconstitution, and again on day 3. Animals that obtained the morphine pellet exhibited depression, catalepsy, and catatonia that lasted for several hours and at the end of the day their behavior appeared to be the same as before the morphine treatment.

Destruction of their immune system as well as destruction and immune reconstitution followed by morphine administration did not interfere with the morphine effect on the animals' behavior (Figure 1 and 2). Moreover, animals from all groups were observed for an additional three months and no detectable differences were observed between the control group and the irradiated or the irradiated and immune-reconstituted rat groups. Naloxone injection to morphine



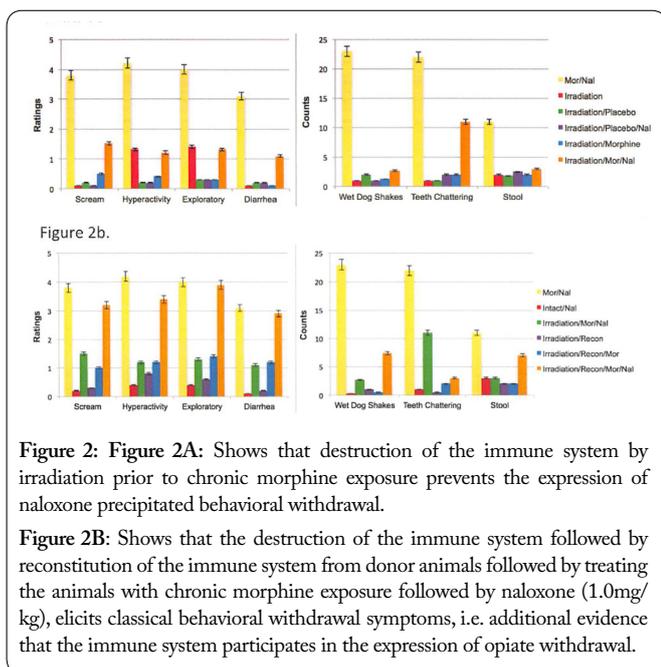
pellet-implanted animals on day 3 elicited the expected withdrawal behavior in group 1 - the morphine control group (Figure 1 Control), irradiation 72 hours after morphine pellet implantation (group 2) on day 3 did not elicit any detectable behavioral signs different from the control group. Naloxone (1.0 mg/kg i.p) injection to the irradiated animal group on day 3 (group 2) exhibited significant ($p < 0.001$) reduction in all seven recorded withdrawal signs (Figure 1). Irradiating

the animals on day 1 prior to chronic morphine exposure (group 3) and challenging the animals with Naloxone (1.0 mg/kg) on day 3 resulted in significant ($p < 0.001$) reduction in the recorded morphine withdrawal sign (Figure 1). Figure 2 summarizes the experimental groups 4 and 5. In group 4 the immune system was ablated in morphine dependent animals (day 3) and after the irradiation, the immune system was reconstituted (each from two donor animals) followed by naloxone (1.0 mg/kg) injection. In group 5 the immune system ablation and the immune system reconstitution were done prior to chronic morphine exposure on day 1. Naloxone (1.0 mg/kg) injection to these two groups of animals (groups 4 and 5) elicited the expected seven behavioral expression signs of opiate withdrawal (Figure 2).

Discussion

Opioids are legitimately used for treating pain and bring about a sense of well-being that can be addictive. Repetitive use of opioid results in the development of tolerance and dependence. Opioid dependence is a long-lasting (chronic) brain disease that can result in major health, social, and economic problems. Opioid addiction is characterized by a powerful, compulsive urge to use opioid drugs again when they are no longer required medically. It is accompanied by well described physical dependency with withdrawal syndromes. Opioid use changes the chemistry of the brain and leads to drug tolerance, which means that over time the opioid dose needs to be increased to achieve the same desired effects [20]. When the drug is withdrawn, it produces severe psychological and behavioral withdrawal symptoms. Addiction, a chronic medical condition, is a relapsing brain disease characterized by an individual pathologically pursuing reward and/or relief by continuing use of opioids or other substances of abuse. Addiction is a chronic medical condition that takes much more than will power to relieve. A new therapeutic approach is needed.

The role of the immune system in the expression of morphine dependence in rats was demonstrated using four different experimental groups as follows: 1. Destruction of the immune system by selective irradiation in morphine dependent animals significantly attenuates the expression of the naloxone-precipitated behavioral withdrawal; 2. Destruction of the immune system prior to chronic morphine exposure also attenuated the naloxone-precipitated withdrawal in morphine dependent animals; 3. In the morphine dependent animal group the immune system was ablated, and each animal in this group was immune-reconstituted from two intact normal donor animals followed by naloxone administration resulting in these animals exhibiting opiate withdrawal signs; and, 4. Immune destruction followed by immune reconstitution and then exposing the animals to chronic morphine, and 72 hours later treating with naloxone, these animals expressed all of the seven behavioral withdrawal symptoms. The role and contribution of brain structures or organ systems to a particular behavioral or physiological phenomenon are often studied in animal models where the organ or a specific structure was ablated [11, 19, 21-24]. In these studies, the animals were



exposed to 500 Rad for less than 1 minute that resulted in selective ablation of the immune system [19, 25-27]. The use of 137/Cs source delivered about 518 Rad/min enabled rapid exposure with minimal stress to the animals.

Moreover, by using reconstituting the immune system to ablated immune system animals from intact normal animal donors by adaptive transfer of the immune components to the irradiated rodents after or before exposure to chronic morphine [19], it was demonstrated that this restored the severity of opiate withdrawal precipitated by naloxone in these ablated immune system rodents. We assume that irradiation using this dose in morphine-dependent animals modulates the expression of the behavioral withdrawal expression by affecting the glia system. Withdrawal behavior expressions are the result of changes in the CNS synaptic plasticity. Synaptic plasticity consists of changes in synaptic strength that is believed to be the basis of learning and memory. For a very long period of time synaptic plasticity has been a hallmark of neurons. Recent advances in the physiology of glial cells indicate that they possess all the features to participate and modulate the various forms of synaptic plasticity. Indeed, beside their respective supportive and immunologic functions, an increasing number of studies demonstrate that glial cells express receptors for most neurotransmitters and release neuroactive substances that have been shown to modulate neuronal activity and synaptic plasticity. Because glial cells are all around these neurons and release a wide variety of neuroactive molecules during physiological and pathological conditions, glial cells have been shown to modulate synaptic plasticity in many different ways from changes in synaptic coverage to release of chemokines and cytokines up to dedicated "glia" transmitter release. Glial cells were reported to affect synaptic scaling, homeostatic plasticity, metaplasticity, long-term potentiation, and long-term depression [28].

The first step to verifying that morphine may affect the immune system was to establish that the opiate receptors are also expressed in the cells of the immune system, and indeed opiate receptors were localized on the immune system compounds [29] as well as on dendrites that are considered to be part of the immune system [30, 31]. Moreover, it was demonstrated that dendrites produce cytokines, which are suggested to be bio messengers between the immune system and the brain [32-34]. Further studies demonstrate that morphine influences the production of neutrophils and other cytokines. Since cytokines are produced as part of the immediate immunological response (inflammation) it has been suggested that they may also influence pain. In this way, cytokines may be the logical target for analgesic development [31]. Cells of the immune system, like macrophages and T, B, and NK cells were identified in the CNS [35-38] and they presumably were affected by the irradiation with microglia to exert effects on opioid function. The immune system, similar to the nervous and endocrine systems, plays an important role in biological adaptation, contribution to maintenance of homeostasis, and establishes the integrity of the body [11].

In the past two decades, a few studies examined the non-neuronal brain immune consequences of the drugs of abuse. Opiate abuse can provoke other health conditions by

breaking down the body's immune system [39]. The first step to verifying that morphine may affect the immune system was to establish that the opiate receptors are also expressed in the cells of the immune system, and indeed opiate receptors were localized on the immune system compounds [29] and dendritic cells that are considered to be part of the immune system display opiate receptors [31, 40]. It was demonstrated that the morphine-induced activation of the central immune signaling system that contributes to the pharmacodynamics action of the drugs of abuse by enhancing the engagement of the mesolimbic DA neural circuit as well as the withdrawal centers [41]. Hutchinson and Watkins [42], suggested that immune pharmacology products are crucial for the future of addiction therapy based on the fact that immune signaling within the CNS contributes significantly to mesolimbic DA reward signaling induced by drugs of abuse and hence are involved in the expression of reward behaviors. Moreover, the observation reported in this manuscript support [43] observation that there is a direct connection between drug of abuse suppressing the immune system and infection disease that are common in drug abuse patients, i.e., drug abusers are at risk of developing infection disease [43].

Acknowledgments

Supported in part by Grant NIH DA RO1 00803. The author wishes to thank Drs. Jacqueline Sack and Sidish S. Venkataraman for their help in preparing this manuscript.

Conflict of Interest

The authors declare no competing interests, financial or otherwise.

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