The Effect of Nicotine Administration on Physical and Psychological Signs of Withdrawal Syndrome Induced by Single or Frequent Doses of Morphine in Rats

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ABSTRACT

Introduction: Morphine addiction and morphine withdrawal syndrome are the two main problems of today's human society. The present study has investigated the effects of nicotine on the strength of physical and psychological dependency in single and repeated doses morphine administrated rats.

Methods: Male Wistar rats were subjected to morphine consumption with single or frequent dose protocols. In the single dose protocol, rats received only one dose of morphine and 24hrs later they also received one dose of nicotine 30 min prior to injection of naloxone. In the repeated dose protocol, rats received incremental doses of morphine for 7 days and 24hr after the last dose (the 8th day) were given naloxone. However, the nicotine regimen of this group was injected 15 min before the morphine injection, for 4 days, from the 4th to the 7th day. Five minutes after naloxone injection, each rat′s behavior was captured for 30 min, and then physical and psychological signs of withdrawal syndrome were recorded. Data were analyzed by ANOVA followed by Tukey tests and $p<0.05$ was considered as significant difference.

Results: Results showed that the injection of frequent and single doses of morphine lead to morphine dependency. In single dose protocol, nicotine consumption attenuated the signs of withdrawal syndrome, especially weight of excrement and total withdrawal score. In frequent dose protocol, in addition to these effects, nicotine induced weight loss and place aversion.

Discussion: The inhibitory effects of nicotine on signs of withdrawal syndrome may involve a dopaminergic portion of the central nervous system and is mediated by central nicotinic receptors. There is also a cross-dependence between nicotine and morphine.

Key Words:
Morphine,
Nicotine,
Withdrawal Syndrome,
Rat

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1. Introduction

Opioid addiction is one of the main problems of human societies. Opiates are used in medicine as analgesic drugs and abused for their recreational effects. Chronic or even acute exposure to these compounds leads to tolerance and physical dependence which are characteristics of opiate addiction. Following chronic administration of morphine, lack of drug injection leads to withdrawal syndrome, which is characterized by severe pathophysiological and behavioral manifestations (Mohammad Allahtavakoli, 2010). Opioid tolerance is a decreased analgesic effect of opioid and dependence is a behavioral state requiring continued opioids to avoid a series of aversive withdrawal syndromes (Haghparast A, 2008). Morphine withdrawal is typically produced either by the termination of chronic and even acute morphine exposure or by administering or prescribing an opiate antagonist to morphine pretreated rats. In fact, withdrawal signs may be presented by an opioid antagonist only after a few widely extensive administrations of an opioid (Parker LA, 1998). In animals, administration of a single or frequent dose of morphine-like agents followed by an opioid antagonist can result in a number of physiological and behavioral changes, which are known as opiate withdrawal syndrome (Cui, Suemaru, Li, Kohnomi, & Araki, 2009). Furthermore, the ability of such withdrawal serves as an aversive, incentive stimulus (Cui et al., 2009). It has been reported that naloxone can induce withdrawal signs after acutely administrated morphine and produce an aversive, incentive state that becomes associated with place cues in a place conditioning paradigm (Cui R, 2009) .

Relapse and returning of taking drugs is done due to the avoidance of aversive withdrawal signs; enhancing mood and drug withdrawal strengthen learning mechanisms. Finally, it increases the risk of the occurrence of later relapses (Dong Z, 2008). Even thought the exact dependence mechanisms on opioid and the withdrawal syndromes have not yet been identified, it seems that during morphine withdrawal, neurotransmitters, including the dopaminergic system, lose their balance (z. M. Dizgah IM, Sohanaki H. , 2006). When the dopaminergic system is stimulated by morphine, it shows the same reactions such as movement actions, changing body temperature, controlling yawns, erection, and the appearance of withdrawal syndrome (z. M. Dizgah IM, Sohanaki H. , 2006) .

It has also been shown that the structure of dopaminergic neurons will change, including increase in the activity of the receptor gene, dopamine release and the formation of its metabolites, during the chronic administration of morphine and the opposite will happen when morphine is not used. Nucleus accumbens (NAC) and locus coeruleus play prominent roles in generation of withdrawal syndrome (z. M. Dizgah IM, Sohanaki H. , 2006). During elevation in withdrawal syndrome, the amount of brain dopamine decreases, while the release of glutamate in locus coeruleus increases. Then, D2 and D1 dopamine receptor agonists in locus coeruleus lead to decrease in the intensity of the withdrawal syndrome. Therefore, NMDA receptor is playing an important role in tolerance and morphine dependency (K. M. Dizgah IM, Zarrindast MR, Sohanaki H. , 2007).

Nicotine, similar to D1 and D2 dopamine receptor agonists, can attenuate the intensity of withdrawal syndrome. Studies have shown that nicotine increases the activity of cholinergic as well as dopaminergic, and increases the release of dopamine from the limbic system and striatal slices (Haghparast A, 2008). Nicotine also increases the release of dopamine from NAC (Nucleus Accumbens). Dopamine encodes information of incentive salience or reward expectation (Mao D, 2010). Nicotine causes the C-fos gene expression in the central amygdaloid nucleus (CeA) to rise and play a role in the activation of the opioid systems (Gerdeman GL, 2003). It leads to the release of different opioid endogen peptides such as inkephalines in the specific brain nuclei and the adrenal chromaphin`s cells. In addition, it also increases the opioids gene expression in different places of the brain (z. M. Dizgah IM, Sohanaki H. , 2006). It has been proved that people who smoke cigarette and the ones that are addicted to opioids have the same unpleasant feelings when they tend to quit smoking (z. M. Dizgah IM, Sohanaki H. , 2006). We can expect that morphine and nicotine can neutralize some of their effects. The cross-tolerance between morphine and nicotine in antinociception influences and physical dependence has been already studied.

Until now, no definitive treatment for morphine addiction has been found. This study assesses the effect of nicotine consumption on different physical and psychological signs of withdrawal syndrome in rats that underwent two methods of single and repeated doses of morphine-dependency.

2. Methods

2.1. Animals and Groups

64 male Wistar rats were used in this study, weighing about 200-270 g. In each cage there were four rats, kept in Rafsanjan Medical University's "Animal's House" under alternating 12hr light/dark cycle, temperature 22±2°C and free access to the standard rodent breeding diet and tap water. They were divided into 8 groups (n=8) including: "control", "morphine-dependent" (morphine group), "morphine- dependent but under treatment with nicotine" (morphine + nicotine group) and finally the group under treatment with nicotine only (nicotine group). They were addicted by single dose or frequent doses of morphine.

In these experiments, we used nicotine hydrogen tartarate, morphine sulfate, and naloxone hydrochloride. All drugs were dissolved in normal saline and were injected intraperitoneally.

2.2. Experiments

2.2.1. The Assessment of the Effects of Nicotine on Single Morphine Dose Addicted Rats

Each rat was put into place-aversion apparatus for 15 min. The animals which were kept more than 250 sec in one room were excluded from the test. The apparatus consisted of two small wooden rooms with 30×35×25 cm in dimension; the rooms were connected through a guillotine-like door. In one of the rooms the floor was carpeted with sandpaper 20 while in the other the floor was wooden (like the surrounding wooden walls) and no sandpaper was used. The walls and floors of the both rooms had dark brown color (Cui et al., 2009). On the second day, in all groups, each rat was injected with 1ml/kg normal saline and after 15 min put into one of the rooms of the place-aversion apparatus for 30 min. On the third day, the morphine and the morphine + nicotine groups were injected with 15mg/kg morphine. The other two groups were also injected with 1ml/kg saline. Then, all the rats were put back into their cages. All groups were injected with 0.5 mg/kg naloxone on the fourth day (24 hr after the injection of morphine or saline); after 5 min each rat was put into a chamber opposite the one used in the second day, which was called the "treatment-paired" chamber, for half an hour. Afterwards, physical signs of withdrawal syndrome including the weight of excrement, weight loss, jumping, rearing, wet dog shake (O. R. Dizgah IM, Sadeghipour-roodsari HR, Karimian SM, Sohanaki H . 2009), and psychological signs of withdrawal syndrome including grooming reactions as: body scratching, front paws licking, penile licking and head washing was filmed. The conditional place aversion was induced by free locating of the rats from all groups into the place-aversion apparatus, 48hr after injection of naloxone, and the time during which they stayed in chambers was recorded (O. R. Dizgah IM, Sadeghipour-roodsari HR, Karimian SM, Sohanaki H . 2009).

On the fourth day, the nicotine group and morphine + nicotine group were intraperitoneally injected with 0.1mg/kg of nicotine just half an hour before the injection of naloxone (O. R. Dizgah IM, Sadeghipour-roodsari HR, Karimian SM, Sohanaki H . 2009).

Among the psychological and physical signs of withdrawal syndrome, the following signs were assessed and scored. Afterward, the total withdrawal score was obtained on the basis of Rasmussen's regulated method (Jin C, 2005).

In order to facilitate processing the data, the evaluated factors were divided into the following three groups:

a. The studied factors on the basis of the numbers: 1. jumping, 2. rearing, 3. wet dog shaking, 4. body scratching, 5. front paws licking, 6. penile licking and 7. head washing.

b. The studied factor on the basis of the percentage: percentage of the reduced weight.

c. The studied factor on the basis of the intensity: the weight of excrement, [very intense = 4 (weight excrement = 7g); intense = 4 (weight excrement = 5-6g); medium = 3 (weight excrement = 3-4g); weak = 1 (weight excrement = 1-2g); nothing = 0 (weight excrement = 0)].

The total withdrawal score from the total scores of every factor was calculated in the following way:

a. The score of the studied factors on the basis of the number equals the number of factors divided by the weight of each (table1).

b. The score of the studied factor on the basis of the intensity with the same formula.

c. The score related to weight loss equals in the percentage of the reduced weight (K. M. Dizgah I M, Zarrindast MR, Sohanaki H. , 2007).

2.2.2. The Assessments of the Effect of Nicotine on Frequent Morphine Doses Addicted Rats

On the first and second days, the process for addiction was done similar to single dose protocol. To produce dependency on frequent morphine doses, the morphine group and the morphine + nicotine group were injected increasing daily doses- from 6 mg/kg to 66 mg/kg at 9 A.M from the third to the 9th day; other groups received saline (1 ml/kg) every day at the same hour (O. R. Dizgah IM, Sadeghipour-roodsari HR, Karimian SM, Sohanaki H . 2009). To study the effect of nicotine on the nicotine and the morphine + nicotine groups, from the sixth to the ninth day (for 4 days) 0.1mg/kg of nicotine was injected to the rats, 15 min before morphine injection, (Haghparast A, 2008). To expose the signs of morphine withdrawal, on the tenth day (exactly 24 hours after the last morphine injection), 2 mg/kg of naloxone was injected to all the groups. After 5 min, the evaluated rats were placed in the "treatment-paired" chamber and for half an hour the behaviors of withdrawal syndrome were recorded by a movie camera (O. R. Dizgah IM, Sadeghipour-roodsari HR, Karimian SM, Sohanaki H . 2009). The total withdrawal score was calculated like the single dose method. After 48 hours, each rat was released to more freely place- aversion apparatus and the stay time in the each room was recorded (joshi, 1998).

2.3. Statistics

All results were shown as mean ± SD. Data were analyzed using the one- way analysis of variance (ANOVA) followed by Tukey′s post test for comparing the difference between the two groups. The symptomificance level was set at $p<0.05$.

3. Results

3.1. The Effect of Nicotine Consumption on the Signs of Withdrawal Syndrome in Single Dose of Morphine Dependent Rats

Naloxone was injected intraperitoneally to all the four rat groups exactly 24 hours after receiving the single morphine dose. The results of the syndrome's physical and psychological signs are shown in Table 2. Many signs like the weight of excrement and the total withdrawal score in the morphine group, compared to the control group which was symptomificantly increased, revealed the advancement of the dependence caused by the single morphine dose ($p<0.05$). Because of the diversity of the withdrawal signs and the bidirectional effects of different factors, it is hard to assess the effect of nicotine on the intensity of the withdrawal signs. As a consequence, in this research the total withdrawal score was used as an index for determining the intensity of the withdrawal syndrome. The acute morphine consumption decreased the animals' weight about 0.4%, but the mortality rate did not change. One- way analysis of variance and Tukey′s post test revealed that nicotine injection (0.1mg/kg) 30 min before the naloxone injection, decreased the total withdrawal score (Fig1, $p<0.05$). Among the signs of physical and psychological withdrawal syndrome, the weight of excrement showed a more symptomificant difference between the morphine + nicotine group and the morphine group ($p<0.05$, Fig 2). In the single morphine dose- dependent rats, nicotine consumption had no effects on the place aversion induced by naloxone ($p>0.05$).

B. The Effects of Nicotine Consumption on Withdrawal Signs in The Frequent Morphine Dose-Dependent Rats

Table 3 displays the results for physical and psychological withdrawal syndrome signs in all four frequent morphine doses for 7 consecutive days' rat groups. Many signs like the weight of excrement, the withdrawal weight decrease, rearing, wet dog shake, and head washing in the morphine group, revealed a symptomificant difference, when compared to the control group ($p<0.001$), which is also observed in the total withdrawal score. This indicated the advancement of addiction caused by frequent doses of morphine. The chronic consumption of morphine with increasing doses led to the animals' weight loss of around 4.1 percent and to the death incidence of almost 10 percent. Statistical analysis showed that the injection of nicotine (0.1mg/kg) 15 min before receiving morphine on the 4th, 5th, 6th, and 7th days decreased the total withdrawal score (Fig 3, $p<0.001$). The weight of excrement and the with-

Table 1. Weight factor of behaviors related to morphine withdrawal

Behavior Signs	Weight Factor
Jumping	4
Rearing	20
Wet Dog Shake	5
Penile licking	5
Body Scratching	10
Head Washing	10

Table 2. The Effect of nicotine administration on the signs of withdrawal syndrome induced by single dose of morphine in rats

Signs	Groups				p value
	Morphine	Nicotine	Control	Morphine+ Nicotine	
Jumping	0	0	0	0	0
Rearing	16.251±1068	8.28±3.86865	6.25±3.224257	11.875±3.6471	0.37
Wet Dog Shake	1.5±0.75	0.75±0.48871	0	0.75 ± 0.31309	0.39
Front Paws Licking	21.785±1.46918	16± 5.11534	9.75±6.408	14.125±3.93445	0.198
Penile Licking	18.625±1.78223	12.75±3.17214	9.5±5.04149	11.375±4.2229	0.21
Body Scratching	3.375±0.26305	0.5±0.5	1.5±1.5	0.875±0.58056	0.704
Head Washing	10.875±0.84383	2.5±1.04083	5.5±3.57071	5±3.02372	0.16
The Percentage Of Weight Loss	2.976±0.12493	2.1849±1.81627	0.7284±0.08359	0.9839±0.24413	0.271
Weight Excrement	3.625±0.53243	0	0	0.875±0.35.382#	0.000
Total Withdrawal Score	15.0038±0.48988	8.7974±2.19988	5.5909±2.56986*	7.9151±1.65877#	0.002

Symptomificant difference between morphine+ nicotine and morphine groups ($p<0.05$)

* Symptomificant difference between control and morphine groups ($p<0.05$)

Table 3. the effect of nicotine administration on the signs of withdrawal syndrome induced by frequent doses of morphine in rats

Signs	Groups				p value
	Morphine	Nicotine	Control	Morphine+ Nicotine	
Jumping	5.2±1.215182	0	0*	19±0.549707#	0.000
Rearing	12.8±1.8660705	18.5±6.360031	9.75±4.571196	7.9±2.277669	0.185
Wet Dog Shake	7.4±1.334999	0.166667±0.166667	0.5±0.288675*	2.4±0.702377#	0.000
Front Paws Licking	10.1±2.496442	13.5±2.741654	19.5±2.598076	6.3±1.789165	0.016
Penile Licking	6.4±4.558752	0.833333±0.307318	1±0.57735	1.4±0.6	0.484
Body Scratching	11.5±3.344149	12.66667±2.551688	17.75±2.625992	6.2±2.327612	0.124
Head Washing	3.9±1.26007	4.1667±1.47007	10±0.912871	2.1±0.72188	0.003
The Percentage Of Weight Loss	4.1677±0432648	0.6965±0.21571	0.7623±0.16421*	2.1787±0.24382#	0.000
Weight Excrement	1.7±0.334996	0	1±0.408248*	3.4±0.426875#	0.000
Total Withdrawal Score	16.3027±1.574	5.58±1.25	8.975±0.3782*	7.8±1.04286#	0.000

Symptomificant difference between morphine+ nicotine and morphine groups ($p<0.001$)

* Symptomificant difference between control and morphine groups ($p<0.001$)

drawal weight loss revealed a more symptomificant difference between the morphine + nicotine group and the morphine group (Fig 4 and 5, $p<0.001$). Fig 6 shows that the naloxone-induced place aversion attenuated by consuming 0.1mg/kg nicotine just 15 min before the injection of morphine ($p<0.001$).

4. Discussion

The results of this investigation showed that the intraperitoneal injection of even a single dose of morphine can cause addiction in rats. Although this has already been reported (Dong Z, 2008), in this report different

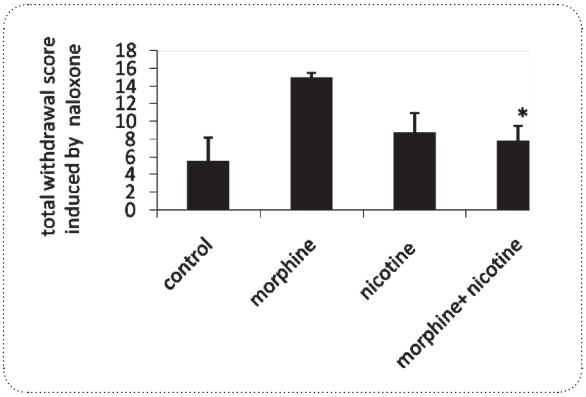

Figure 1. The effect of nicotine on total withdrawal score induced by naloxone in single dose morphine-dependent rats

*: Symptomificant difference with morphine group ($p<0.05$)

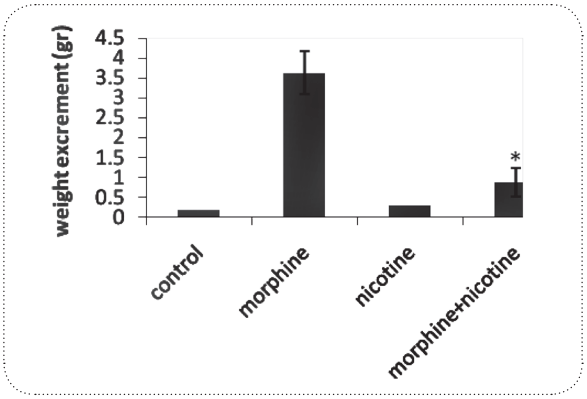

Figure 2. The effect of nicotine on decrease of excrement weight induced by naloxone in single dose morphine-dependent rats

*: Symptomificant difference with morphine group ($p<0.05$)

physical and psychological signs were studied and the total withdrawal score was used as an index for the determination of the intensity of withdrawal syndrome. There was a symptomificant difference between the control group and the single dose of morphine group, especially in the total withdrawal score and weight of excrement. Interestingly, previous studies demonstrated that injecting naloxone to the single morphine dose rats leads to symptomificant increase in C-FOS gene expression only in CeA (Jin C, 2005, Ishida S, 2010). Increased activation of adenylyl cyclase (AC) is also an adaptive response to prolonged MOR (μ opioid`s receptor) activation by all MOR agonists including those that cause rapid MOR desensitization and internalization. Up regulation of AC was also reported in chronically morphine administrated animals (Contet C, 2008).

A study has revealed that in acute morphine-treatment (single dose), mitogene-activating kinases' proteins are phosphorylated through some G-proteins coupled with opioids′ receptors, and are increased in numbers in some brain regions like connective cortices and LC (locus coeruleus); but are decreased in NAC as well as in Amygdale (Bailey CP, 2005).

The present study also showed that naloxone injection to the frequent doses morphine-dependent rats also lead to manifestation of the signs of physical and psychological withdrawal syndrome. But the frequent doses morphine-dependent rats showed more signs compared to the single dose protocol, which indicates symptomificant differences between the control group and morphine group to which we already pointed out in "Finding". Moreover, in frequent doses protocol, the total withdrawal score displayed a more symptomificant difference between the control group and also the morphine group compared to the single dose protocol. This is in parallel with the findings by previous researchers (K. M. Dizgah IM, Zarrindast MR, Sohanaki H. , 2007).

The exact mechanism of opioids dependency and withdrawal syndrome has not been precisely determined yet. Opioids and all addicting drugs like nicotine increase the release of dopamine in NAC (Mao D, 2010).

Opioids increase transmissions of dopaminergic in the mesolimbic pathways by two mechanisms:

a. Opioids inhibit GABA neurons in the VTA causing suppression of the tonic GABAergic inhibition on dopaminergic VTA neurons causing net disinhibition of DA transmission from the VTA to the NAC.

b. Opioids directly modulate neurons in the NAC, causing direct increase in DA firing rates (Ferrea S, 2009). Studies have revealed that exiting the D1 and D2 dopamine receptors in the nucleus of locus coeruleus can have an impact on the intensity of the appearance of withdrawal signs and as a result on their elimination (K. M. Dizgah IM, Zarrindast MR, Sohanaki H , 2007; z. M. Dizgah IM, Sohanaki H. , 2006) .

The results from the present study show that consumption of nicotine before the injection of naloxone or morphine into single dose or frequent dose morphine-dependent rats attenuates different physical and psychological signs of withdrawal syndrome. The observed results for the two protocols are different. In the single

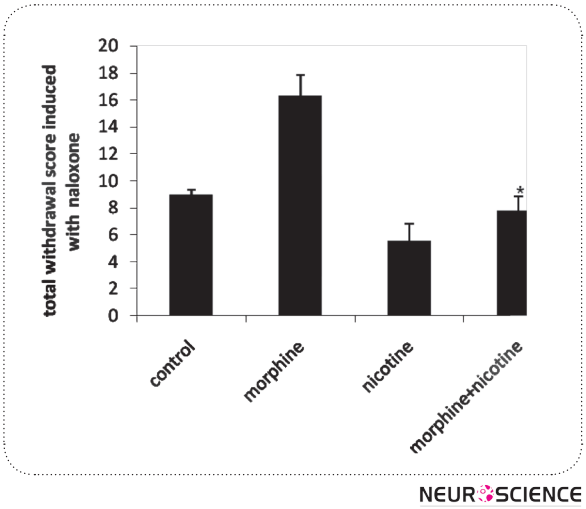

Figure 3. the effect of nicotine on total withdrawal score induced by naloxone in frequent dose morphine-dependent rats

*: Symptomificant difference with morphine group (p<0.001)

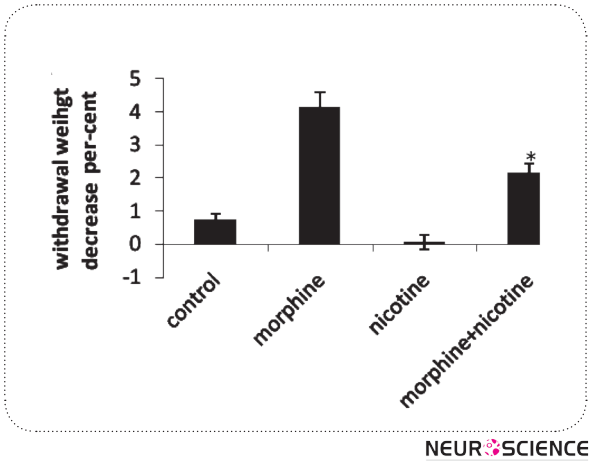

Figure 4. the effect of nicotine on the percentage of weight loss induced by naloxone in frequent dose morphine-dependent rats

*: Symptomificant difference with morphine group (p<0.001)

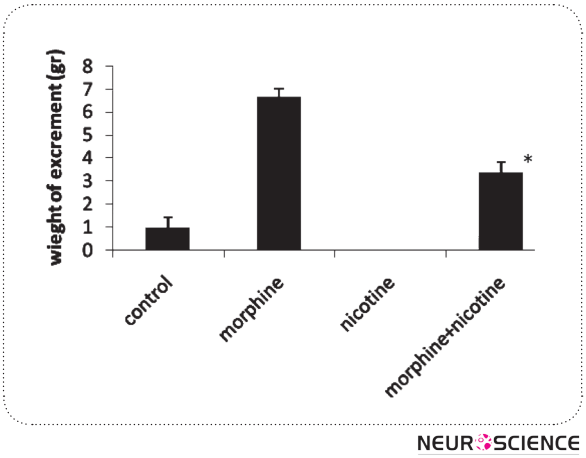

Figure 5. The effect of nicotine on excrement weight loss induced by naloxone in frequent dose morphine-dependent rats

*:Symptomificant difference with morphine group (p<0.001)

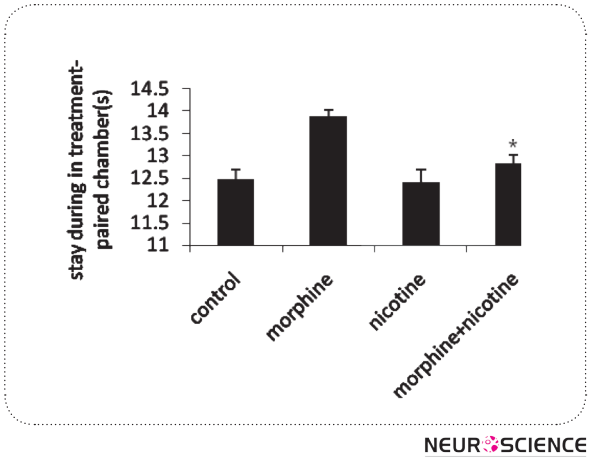

Figure 6. The effect of nicotine on place aversion induced by naloxone in frequent dose morphine-dependent rats

*: Symptomificant difference with morphine group (p<0.001)

dose morphine protocol, the use of nicotine had a more symptomificant effect on attenuating excrement weight than on other physical and psychological withdrawal syndromes and it reduced the total withdrawal scores. However, in the frequent doses of morphine protocol, where nicotine was used four days before the injection of morphine, there were more signs of withdrawal syndrome, especially place aversion, withdrawal weight loss, and excrement weight which were attenuated; and the total withdrawal score was reduced more. In most cases, the results of the present study are in parallel with previous studies. Some of the results were different, for example, lack of a symptomificant difference between the nicotine group and the control group. According to a study, repeated prescription of nicotine for three consecutive days brought about jumping, as a result of withdrawal induced with naloxone, with the highest numbers of jumping at a dose of 0.1mg/kg.This means that nicotine itself is capable of generating dependence and opioids receptor antagonist (naloxone) can inhibit its rewarding effects and induce the jumping (Haghparast A, 2008) . However, in the present study, the nicotine groups did not show any elevation in the signs of withdrawal syndrome. This difference probably

arises from the animal's different species. Nicotine is a lypofilic substance, so it can enter the neurons without interaction with nAchR (the nicotinic acetylcholine receptor) (Ferrea S, 2009) .

Nicotine stimulates the release of dopamine in the prefrontal cortex, basal ganglia and the mesolimbic pathways; and the activity of the central α4β2 and not environmental receptors, especially in the VTA region, causes the release of dopamine toward NAC (Haghparast A, 2008; Ross S, 2009). Because nicotine receptors are placed in both dopaminergic and glutaminergic neurons, nicotine can stimulate the release of dopamine either directly or through the activation of glutaminergic neurons (Defranza J.R, 2007) . (Araki H, 2004; Cui R, 2009). The highest effect of nicotine in reducing the signs of withdrawal syndromes is achieved at the dose of 0.1mg/kg, which is equivalent to one cigarette smoked by humans (Haghparast A, 2008). Notable in this study is the 0.1, 0.2 and 0.3mg/kg nicotine doses which were tested and the doses of 0.2 and 0.3 mg/kg which caused tension in the rats. The appropriate dose of 0.1 mg/kg was also chosen for the main rat groups.

Another study has shown that the level of C-FOS protein or its mRNA in CeA increases remarkably after the acute nicotine injection into the rats, which have already received single dose of morphine. The same study indicates that the administration of the α7nAchR central receptor antagonists before the administration of nicotine, symptomificantly decreases the number of positive C-FOS cells in the CeA. Therefore, α7nAchR in CeA plays an important role in weakening the withdrawal syndrome. Basically, the α7nAchR receptors in CeA are known as treatment purposes for opioid withdrawal syndrome (Ishida S, 2010) .

The present study arise evidences on the similarities in morphine and nicotine functions. Nicotine may stimulate the releasing and biosynthesis of endogen opioids by super activation of opioid receptors. Naloxone as an antagonist of opioid receptor can inhibit the antinociceptive effects of nicotine and this is an indicator of the disruption between the two systems of opioid and nicotine. It shows that both nicotine acetylcholine receptor and the μ opioid receptor are involved in the antinociception induced by nicotine (Haghparast A, 2008). Both nicotine and morphine can increase the releasing of serotonin and induce parts of their rewarding effects by stimulating nitric oxide synthase enzyme. Cigarette smokers and opioid -addicted people have the same problems when they are quitting. Perhaps, the reason that opioid addicted people smoke lots of cigarettes when they are quitting can be found in the disruptions or similarities in the functions of these two drugs (Sahraei, Faraji, Rostami, Zarrindast, Jalili , 2003). Sahraei et al. reported that nicotine and morphine have cross-sensitivity on each other. This high cross-sensitivity increases the risk related to taking several drugs simultaneously. Perhaps, this is the reason that those people who consume morphine or alcohol tend to smoke cigarettes a lot (F. N. Sahraei H, Ghoshoni H, Rostami P, Zarrindast MR, Zardooze H. , 2005).

The results of this study indicated that the consumption of frequent doses and even single dose of morphine can cause addiction in rats and increase the total withdrawal score. Nicotine consumption before naloxone injection in single dose-dependent rats decreased the weight of excrement and total withdrawal score. Also, in frequent dose-dependent rats, nicotine consumption before morphine decreased the total withdrawal score, the percentage of the weight loss, and excrement weight. Moreover, it attenuated the place aversion induced by naloxone.

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