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Saffron (*Crocus sativus L.*) and morphine dependence: A systematic review article

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Abstract

Morphine dependence is considered as a major health problem in word wide. However, the efforts for overcoming the problem are failed because of the severity of drug dependence nature. In recent years, focus on the herbal drugs for treatment of drug dependence increases. *Crocus sativus Linn* (saffron) plant has potential therapeutic usage such as depression and Alzheimer disease. Some evidences reported that saffron has interaction with opioid system. In this review, the attempts were made to categorizing the accumulating data indicating the possible interaction of some constituents of saffron extracts on morphine-induced psychological or physical dependence. Saffron extract consists of several constituents including safranal; crocin and crocetin which may interact with several physical and psychological signs of the morphine dependence. Administration of saffron extract can reduce the morphine sensitization and morphine tolerance. Also aqueous and ethanolic extracts may have interaction with the opioid system to reduce withdrawal syndrome in morphine dependence

Keywords

Behavioral Sensitization, Tolerance, Opioid System

1. Introduction

Opioid dependence is defined as a chronic disorder that is characterized by physical and psychological signs such as unlimited drug taking and intense craving. Morphine as a major opioid has a wide clinical usage for pain killing. Morphine induces its effects by occupying opioid receptors especially mu subtype within the central nervous system. However, chronic morphine usage can lead dependence which is identifying by serious symptoms when the drug is not available and/or the opioid receptor antagonists were used. Psychological morphine dependence is proposed to be mediated in the mesocorticolimbic dopamine system which initiated in the ventral tegmental area (VTA) in mesencephalon whom axons innervating the nucleus accumbens in the basal forebrain. The physical dependence to morphine is thought to be occurred both in several parts of the central nervous system including the locus ceroleus, pre-aqueductal gray matter, nucleus raphe Magnus, as well as periphery such as the intestine. The cellular and molecular mechanisms occurred during morphine dependence also is well recognized. In this matter, increase in CAMP production by neurons under chronic morphine influence, decrease in Ca^{+2} entry and increase in K^{+} efflux is considered as the major events which are occurred after chronic morphine usage. In the clinical view, however, the safety of morphine usage is limited by the hazardous of morphine dependence which can lead to morphine addiction. Investigations which were focused on reduction of morphine dependence hazard, or overcoming the problem, are in central area of interest for investigators (Koob G. F. 2008; Yamada K. 2008; Hyman S. E. and Malenka R. C. 2006; Moala M. L. and Koob G. F. 2007; Linlin Sun. et al. 2013).

Herbal medicine which focused on the herbal materials for treatment of disease is growing in the recent years because of their relative safety (Sarris et al. 2013). Saffron

(*Crocus sativus*) is among the important herb which is used as medication for several centuries in different parts of the world such as India, China, Spain, Italy, Greece, and in Iran. The stigmas of saffron used as a flavoring spice in the cooking, in different parts of the world. The main active constituents of this plant are crocin, crocetin, safranal, and picrocrocin. Crocin is di-gentiobioside ester of the crocetin (Hosseinzadeh H 2010; Geromichalos et al. 2012; Jaliani H. Z. et al. 2013; Shams et al. 2009; Sadeghnia et al. 2013). The stigma of saffron used also in traditional medicine. For example, Avicenna mentioned that saffron is useful for treatment of some kind of depression (Hosseinzadeh and Nassiri-AslM. 2013). Also, several recently studies showed that some actions of saffron on central nervous system have been attributed to its effects on opioid system. In the modern investigations, saffron extract is used for treatment of Alzheimer disease (Modabbernia and Akhondzadeh S. 2013) and depression (Modabbernia et al. 2012 ; Ettehadi et al. 2013) in human as well as memory improvement in the animal models. The extract also can inhibit morphine-induced memory impairment in the rat (Naghibi et al. 2012).

Recent investigation also revealed that saffron extract can increase dopamine and glutamate concentration in the rat brain as well, which may discuss the possible cellular and molecular mechanism underlying the extract effect on depression and memory improvement (Ettehadi Hosseinali et al. 2013; Linardaki et al. 2013). In this review, we focus on the studies dealing with the interactions of morphine reward and dependent with saffron extract.

2. Saffron and Morphine Tolerance

Morphine tolerance is defined as a reduction in pain threshold in the animals after chronic morphine treatment (Chefer 2009; Moala M. L. and Koob G. F. 2007). Morphine tolerance is thought to be a main reason for opioid intake increment, without efficient resolve today. For this reason, investigation on using plant materials in this regard is developed world wide. Saffron extract interaction with morphine tolerance was investigated by using tail flick technique in female NMRI mice and showed that water extract of *Crocus sativus Linn* can ameliorate the expression but not acquisition of tolerance to morphine induced hyperalgesia, which may indicate that the extracts constituent(s) can interact with morphine tolerance (Shams J. et al. 2009).

3. Saffron and Morphine Interaction in Sensitization

Drug addiction is a maladaptive pattern of drug use that identified by compulsion to seek and take the drug, unlimited drug taking and intense craving. The initiation of drug abuse may be affected by genetically background, stress and environmental factors. Long-lasting drugs of abuse lead to behavioral plasticity that increasing the possibility of relapse. Morphine sensitization is a form of long-term plasticity that occur in response to continuous or repeated drug administration, which in rats can last as long as a year after the last administration of the drug (Chefer 2009; Le Merrer L. 2006).

Behavioral sensitization induces a progressive increase in their motor response. It seems that this sensitization may contribute to the development of drug addiction (Linlin Sun. et al. 2013; Robinson TE 2001). Behavioral sensitization is commonly assessed by monitoring motor activity. Repeated exposure to drugs leads to an augmented motor-stimulant response. Also, behavioral sensitization can be accessed by conditioned place preference (CPP) (Ghoshooni et al. 2011; Imenshahidia M. and Zafaria H. 2011). In the CPP paradigm, sensitization is identified by increased time spent in the drug-paired chamber (Maria H. Milekic, Sheena D. Brown, and Claudia Castellini 2006; Mojabi N. et al. 2007; Mojabi N. et al. 2008). The development of behavioral sensitization can be classified to two phases: initiation and expression. Initiation is the immediate neural events that evoke behavioral sensitization, and expression is the long-term consequences of these initial events (Kalivas PW 1991). It seems that initiation step is commonly associated to the ventral tegmental area (VTA), and expression step is associated with the nucleus accumbense (NA) (Li SM and Ren YH 2002).

Saffron extracts interaction with morphine sensitization was investigated by using subcutaneous injection of morphine in N-MARI male mice. Administration of morphine increased the animals' movements but injection the saffron extract 30 min before the effective dose of morphine caused a dose-dependent decrease in locomotion activity (Sahraei H. et al. 2007) . Administration of stigma extracts of flowers can reduce the acquisition of morphine sensitization. So the stigma of saffron flower extracts decreases locomotion activity and the acquisition and expression of behavioral sensitization induced by morphine in male mice (Sahraei H. and Mohammadi M. 2007; Sahraei H. and Shams J. 2006; Shams J. et al. 2009).

Sahraei et al. showed that saffron extract reduced the acquisition of morphine-induced CPP in mice (Sahraei H., Mobasher M., and Sahraei H. 2006). Hosseinzadeh et al. also showed that intraperitoneal administration of aqueous extracts (40 and 80 mg/kg for 4 days) decreased the acquisition of morphine CPP in male NMRI mice. In addition, the aqueous extract (80mg/kg) blocked morphine-induced reinstatement of place preference. Moreover, aqueous extract of saffron by itself produced neither CPP nor CPA (Hosseinzadeh H. 2010; Sahraei H. 2009). So, these results showed that aqueous extract of saffron decreased the acquisition and reinstatement of morphine-induced CPP. VTA GABAergic projections to the NA and mPFC have an important role in behavioral sensitization (Tecuapetla F et al. 2010; Van Bockstaele EJ and Pickel VM 1995). It has been shown that administration of the $GABA_A$ receptor agonist (muscimol) and $GABA_B$ receptor

agonist (baclofen) significantly inhibit the morphine-induced CPP and administration of the $GABA_A$ receptor antagonist (bicuculline) in combination with an ineffective dose of morphine elicits a significant CPP Effect (Rezayof A et al. 2007; Sahraei H et al. 2009). Therefore, GABAergic system may be involved in saffron effect on morphine CPP.

4. Interaction of Saffron and other Aspect of Opioid System

There are some reports about the interaction of saffron and the opioid system. Naghibi et al. showed that the intra-peritoneal injection of aqueous extracts of saffron (150 and 450 mg/kg) before the training trial in passive avoidance test, increased the time latency in morphine treated mice. Administration of both 150 and 450 mg/kg doses of the extract before retention trials also increased the time latency. So, the saffron extract attenuated morphine-induced memory impairment (Naghibi et al. 2012). The aqueous (80, 160, 320 mg/kg) and ethanolic (400 and 800 mg/Kg) extracts of saffron significantly reduced naloxone-precipitated jumping in morphine-dependent mice (Ghoshooni et al. 2011; Ghoshooni H. et al. 2011; Shams J. et al. 2009). Application of crocin (200 and 600 mg/Kg) also significantly reduced this withdrawal sign (Amin and Hosseinzadeh 2012). Also, the aqueous and ethanolic extract significantly decreased the locomotors activity in open field test. But, crocin showed minor inhibitory effect on locomotors activity. So crocin decreased withdrawal syndrome without reducing locomotors activity (Hosseinzadeh H. 2010). Thus, the interaction of this constituent with the opioid system should be more specific. Administration of safranal potentiated some signs of withdrawal syndrome. Then, it seems that the aqueous and ethanolic extracts and crocin may have interaction with the opioid system to reduce withdrawal syndrome (Hosseinzadeh H. 2010). Alcohol extract of *Crocus sativus* stigma (5 and 10 μg/rat) into the nucleus accumbens shell part of rats, 5 min before morphine (10 mg/kg) administration, caused a decrease in the time spent in drug-paired side. In addition, injection of extract in the animals that received morphine (10 mg/kg) decreased the expression of morphine CPP (Ghoshooni H. et al. 2011). Imenshahidi et al. showed that intraperitoneal administration of crocin (400 and 600 mg/kg) for four days and 30 min before the morphine administration decreased the acquisition and reinstatement of morphine-induced CPP in mice (Imenshahidi M, Zafari H, and Hosseinzadeh H. 2011; Imenshahidia M. and Zafaria H. 2011). Intraperitoneal administration of the ethanolic extract of saffron (10, 50 and 100 mg/Kg) and its constituent, safranal (1, 5 and 10 mg/Kg), reduced the acquisition and expression of morphine CPP (Ghoshooni et al. 2011). Ettehadi et al. showed that the intra-peritoneal injection of aqueous extract of saffron stigma (50, 100, 150 and 250 mg/Kg) significantly increased the release of dopamine in rat brains. Also, the extract significantly increased the release of glutamate only in dose 250 mg/Kg. They also reported that the extract has no effect on serotonin and norepinephrine concentration in the rat brain (Ettehadi Hosseinali et al. 2013). It is now clear that the dopamine and glutamate concentration in the reward regions affected by drug abuse. These neurotransmitters have pivotal contribution in hyperactivity and behavioral sensitization in addicted animals. It is likely that saffron extract modulate morphine-induced behavioral sensitization by alteration of dopamine and glutamate release in the rewarding areas (Ettehadi et al. 2013). Likewise, it was showed that application of NMDA receptor antagonist can prevent morphine induced CPP (Do Ribeiro Couto B et al. 2005). Saffron extract has interaction with NMDA receptors that may have role in the effects of saffron on CPP (Lechtenberg M et al. 2008). Saffron extract and crocin have showed antidepressant activity (Georgiadou, Tarantilis, and Pitsikas 2012; Hosseinzadeh H et al. 2013; Modabbernia et al. 2012 ; Mohamadpour et al. 2013; Ettehadi Hosseinali et al. 2013). It is possible that crocin also act via a similar mechanism to prevent morphine-induced CPP.

These studies demonstrated that saffron extract and its constituent, crocin, have interactions with morphine dependence properties. However, the central mechanisms of saffron on morphine-induced behavioral sensitization are unknown and needs more study.

5. Conclusion

Saffron extract consists of several constituents including safranal; crocin and crocetin which may interact with several physical and psychological signs of morphine dependence. It is note that all of the observed effects of saffron obtained when the extract applied acutely. There is little study about chronic effects of saffron. In addition, the extract has showed a euphoric effect which may be due to its ability for increase of dopamine and glutamate release. However, the central mechanisms of saffron on morphine-induced behavioral sensitization are far from clear and needed several investigations.

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