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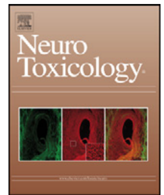

Protective effect of *Nigella sativa* oil against tramadol-induced tolerance and dependence in mice: Role of nitric oxide and oxidative stress

Ahmed O. Abdel-Zaher *, Mahran S. Abdel-Rahman, Fahmy M. ELwasei

Department of Pharmacology, Faculty of Medicine, Assiut University, Assiut, Egypt

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ABSTRACT

Nigella sativa seed extracts and its oil have been exploited for their various health benefits. In this study, the effects of *N. sativa* oil on tramadol-induced tolerance and dependence and possible mechanism(s) of these effects were investigated, for the first time, in mice. Repeated administration of *N. sativa* oil (4 ml/kg, p.o.) along with tramadol (50 mg/kg, s.c.) inhibited the development of tramadol tolerance, as measured by the hot plate test, and dependence as assessed by naloxone (5 mg/kg, i.p.)-precipitated withdrawal manifestations. Concomitantly, nitric oxide overproduction and increase in brain malondialdehyde level induced by repeated administration of tramadol to mice or by administration of naloxone to tramadol-dependent mice were inhibited by co-administration of the oil. Also, the decrease in brain intracellular reduced glutathione level and glutathione peroxidase activity induced by both treatments was inhibited by co-administration of the oil. The increase in brain glutamate level induced by both treatments was not inhibited by concurrent administration of the oil. The inhibitory effect of *N. sativa* oil on tramadol-induced tolerance and dependence was enhanced by concurrent i.p. administration of the NMDA receptor antagonist, dizocilpine (0.25 mg/kg). Also, the inhibitory effect of the oil on naloxone-induced biochemical alterations in tramadol-dependent mice was enhanced by concurrent administration of dizocilpine. Similarly, concurrent i.p. administration of the NO synthase inhibitor, L-N(G)-nitroarginine methyl ester (10 mg/kg) or the antioxidant, N-acetylcysteine (50 mg/kg) enhanced these inhibitory effects of *N. sativa* oil. On the other hand, these effects were antagonized by concurrent i.p. administration of the NO precursor, L-arginine (300 mg/kg). These results provide evidence that *N. sativa* oil appears to have a therapeutic potential in tramadol tolerance and dependence through blockade of NO overproduction and oxidative stress induced by the drug.

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1. Introduction

Tramadol is a centrally acting analgesic with weak μ-opioid receptor agonist affinity (Raffa et al., 1992). It has been postulated that its analgesic activity may be mediated by both opioid and non-opioid (i.e. norepinephrine and serotonin reuptake inhibition) mechanisms (Raffa et al., 1992; Liu et al., 1999; Nossaman et al., 2010).

The analgesic potency of tramadol was found to be equal to codeine and 10 times less than morphine (Marquardt et al., 2005). Some clinical and experimental studies demonstrated that tramadol does not induce tolerance and dependence on repeated administration (Miranda and Pinardi, 1998; Kitahara et al., 2009). On the other hand, many studies have indicated that long-term use of tramadol can precipitate tolerance, physical dependence and withdrawal symptoms (Rafati et al., 2006; Tjaderborn et al., 2009; Lanier et al., 2010).

Augmented glutamate release has been found to play an important role in opioids tolerance, dependence and withdrawal symptoms (Sepulveda et al., 1998; Wen et al., 2004). Activation of the ionotropic N-methyl-D-aspartate (NMDA) subtype of glutamate receptors has also been implicated in the development of morphine analgesic tolerance and dependence (Bajo et al., 2006; Murray et al., 2007). It has been established that many glutamate actions mediated through NMDA receptors result from the subsequent activation of nitric oxide synthase (NO synthase) and the formation of nitric oxide (NO) (Kolesinikov et al., 1993). Moreover, Glutamate was found to induce oxidative stress in neuronal cells (Penugonda et al., 2005).

Nitric oxide was postulated to be involved in the analgesic effect of tramadol (Dal et al., 2006). Furthermore, Yalcin and Aksu (2005) found that the NO precursor, L-arginine reduced while the NO synthase inhibitor, L-N (G)-nitroarginine methyl ester augmented the antinociceptive effect of tramadol, as determined in mice by the hot plate test.

* Corresponding author. Tel.: +20 882411886.
E-mail address: ahmedosmanaz@hotmail.com (A.O. Abdel-Zaher).

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Nigella sativa Linn is an annual herbaceous plant belonging to the Ranunculaceae family growing in countries bordering the Mediterranean Sea, Pakistan, India and Iran. Many medicinal properties have been attributed to the *N. sativa* seed extracts and/or its oil, including antihistaminic, antihypertensive, analgesic, anti-inflammatory, hypoglycemic, antibacterial, antifungal, anti-tumour and protective effects against hepatotoxicity and nephrotoxicity (Ali and Blunden, 2003; Padhye et al., 2008). *N. sativa* seed was found to contain more than 30% fixed oil, and 0.4–0.45% volatile oil. The fixed oil is composed mainly of unsaturated fatty acids. Thymoquinone is the major active component of the volatile oil (Worthen et al., 1998).

It has been reported that the aqueous extract of *N. sativa* seeds inhibits NO production (Mahmood et al., 2003) and thymoquinone suppresses NO production and inducible NO synthase expression (El-Mahmoudy et al., 2002) in lipopolysaccharide-stimulated rat peritoneal macrophages. Also, *N. sativa* oil was found to downregulate CCl_4-induced inducible NO synthase mRNA and NO production in rat liver (Ibrahim et al., 2008). Similarly, it has been reported that thymoquinone improves plasma and liver antioxidant capacity and enhances the expression of liver antioxidant genes of hyper cholesterolemic rats (Ismail et al., 2010). Moreover, *N. sativa* oil and thymoquinone were found to inhibit gentamicin (Yaman and Balikci, 2010) and cyclosporine (Uz et al., 2008)-induced oxidative stress and NO overproduction in rat kidney. In addition, *N. sativa* oil and thymoquinone have been demonstrated to prevent oxidative injury during cerebral ischemia-reperfusion injury in rat (Hosseinzadeha et al., 2007) and in a rat model of subarachnoid hemorrhage (Ersahin et al., 2011).

In light of these considerations, the aim of this work was to evaluate the potential role of *N. sativa* oil in attenuation of tramadol tolerance and dependence. In addition, an attempt was undertaken to clarify the possible role of glutamate, NO and oxidative stress in these effects.

2. Materials and methods

2.1. Chemicals

Tramadol hydrochloride was obtained from Misr Co. Pharma (Egypt), dizocilpine hydrogen maleate was purchased from ICN Biomedicals Inc. (USA) and aminoguanidine, L-N (G)-nitroarginine methyl ester, L-arginine, N-acetylcysteine and naloxone hydrochloride dehydrates were obtained from Sigma Chemical Co. (USA). All other chemicals were of analytical grade.

2.2. N. sativa oil

N. sativa seeds, obtained from the local market in Egypt, were authenticated by Pharmacognosy Department, Faculty of Pharmacy, Assiut University. The total crude oil was extracted by cold pressing (hydraulic press) of the dry mature *N. sativa* seeds. The yield was analyzed to comply with the known standard specifications of its fixed and volatile oils. Reversed-phase thin layer chromatography (TLC) was carried out following the method outlined in the British Pharmacopoeia for identification of the fixed oil. 4 μl of a 0.5% (w/v) solution of the oil in chloroform was applied to the TLC plate. The oil was found to contain myristic, palmitic and stearic as main saturated fatty acids as well as oleic, linoleic and linolenic as main unsaturated fatty acids. Thymoquinone, the major active component of the volatile oil, was identified and quantified by HPLC on a reversed-phase Reprosil Gold 120 C18 analytical column (250 mm $\times$ 4.6 mm, 5 μm particle size) using an isocratic mobile phase of water: methanol: 2-propanol (50:45:5%v/v) at a flow rate of 1 ml/min. Ultraviolet monitoring was carried out at 254 nm. The concentration of thymoquinone in the total crude oil was about 0.103% (w/v).

2.3. Animals

Male adult Swiss–Webster mice weighing 20–30 g from the animal house of Assiut University were used in all experiments. The animals were housed in a stainless steel cages under a 12 h light/dark cycle at 25 °C and allowed water and food (laboratory chow) ad libitum. They were divided into groups, 8 animals each. The research was conducted in accordance with the internationally accepted principles for Guide for the Care and Use of Laboratory Animals. The experiments reported here were approved by our institutional ethics committee.

2.4. Treatment of animals

In the first set of experiments, animals of Group-I and II were treated subcutaneously (s.c.) with 50 mg/kg tramadol (1% solution in saline) twice daily at 12 h intervals for 7 and 15 days, respectively. Group-III, IV and V mice received, 30 min before each tramadol injection for 15 days, 2, 4, and 8 ml/kg *N. sativa* oil, respectively. The oil was administered to mice orally (p.o.) by means of a stomach tube.

In the second set of experiments, four groups of mice were used. Animals of these groups were pretreated 30 min before each tramadol injection for 15 days, with 4 ml/kg *N. sativa* oil in combination with dizocilpine (MK-801), L-N(G)-nitroarginine methyl ester (L-NAME), L-arginine (L-ARG) and N-acetylcysteine (NAC), respectively. One group of animals was used for each treatment. MK-801 (0.005% solution in saline), L-NAME (0.25% solution in saline), L-ARG (1% solution in saline) and NAC (1% solution in saline) were injected intraperitoneally (i.p.) at dose levels of 0.25, 10, 300 and 50 mg/kg, respectively.

Control groups of animals were treated likewise with the pure vehicle.

2.5. Hot plate test

In this method, the time taken by the mouse to lick its hind paws or to jump with all four feet within a Plexiglas cylinder placed on a hot plate surface (55 °C) was determined. This reaction time was taken as the end point and the increase in hot plate latency was taken as a measure of the analgesic activity. Prior to administration of drugs, mice were tested on the hot plate for 4 days in order to obtain a stable control response level. The animals were removed from the hot plate if they did not respond within 30 s in order to avoid tissue damage. Any animal that failed to respond within 30 s was excluded immediately and retested again after 30 min. The antinociceptive effect of tramadol was determined 60 min after the first injection on the first, third, fifth, and seventh day. Additionally, the antinociceptive effect was estimated on the eleventh and fifteenth day for animals treated for 15 days with tramadol.

2.6. Induction of withdrawal syndrome

Two hours after the first injection, on the sixteenth day of tramadol treatment, each mice was treated with 5 mg/kg naloxone (0.1% solution in saline) i.p. Immediately after naloxone injection each animal was placed in a transparent acryl cylinder (20 cm in diameter, 35 cm in height) to observe withdrawal manifestations (jumping, rearing, teeth chattering and paw tremor) for 30 min. The withdrawal manifestations were manually evaluated by co-workers blind to the treatment protocol.

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