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Does Essential Oil from Carum Copticum Extract Have Effects on Mu Opioid Receptors?

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Abstract: In the previous study, the antinociceptive effects of essential oil from Carum Copticum were evaluate by formalin test in mice. The purpose of this study was to evaluate opiates receptors of essential oil from Carum Copticum. In this study formalin test was used as a standard pain inducing test. The analgesic effect of interperitoneal injection of 20 ml kg^{-1} of essential oil (prepared by steam distillation) were compared with naloxone (5 mg kg^{-1} bodyweight., i.p.) as an opioid antagonist. Our findings show that pretreatment with naloxone reverse the analgesic effect observed in the formalin test, which is not significant. (P = 0.497). It seems that mechanisms other than opioid system involved in the analgesic activities because naloxone an opioid antagonist could not reverse the analgesic effect in inflammatory phase of formalin test.

Key words:

INTRODUCTION

The analgesic effects may act by different ways and receptors. The most important of analgesics are nitric oxide, indomethacine, hyoscine and opioids, which some of them act by depressed synaptic transmission.

For thousands of years mu opioid agonists such as morphine have been utilized for their analgesic properties. Today, morphine and related compounds are still used as a first line therapy in the treatment of moderate to severe pain. However, despite the clear benefits of mu agonists in pain management, severe side effects such as dependence and respiratory depression are associated with use of these drugs. To date, there are a few approved mu opioid antagonists for use in the treatment of these adverse effects, such as naloxone and naltrexone. However, many other clinical and therapeutic areas have been linked to mu opioid receptor antagonism [1].

Three classical opioid receptors have been studied extensively [2]. Most of the clinically used opioids are relatively selective for mu receptors, reflecting their similarity to morphine. Morphine and most other clinically used opioid agonists exert their effects through mu opioid receptors which therapeutically use as opioid analgesics [3]. The purpose of this study was to evaluate opioid receptors of essential oil from Carum Copticum. It is a plant in Umbelliferae family grows as herb with feliciaform roots, possesses bactericidal, anticholinergic and antihistaminic activities. In addition, it has also beta-adrenergic stimulatory effects [4]. Carum Copticum extract is used as an analgesic on phasic pain [5]. In a previous study, the anti nociceptive effects of essential oil from Carum Copticum were evaluated by formalin test in mice [6].

MATERIALS AND METHODS

Type of study: This is an experimental method on 15 mice which are chosen randomly. They are kept in the same situation of light, air and nutrition and are separated into 3 groups of control, test and sham.

Preparation of sample: For preparing of essential oil, 40 g powdered Carum Copticum fruits added to 200 ml of distilled water. Then, the essential oils separated by steam water distillation which is a popular method. The sample with concentration of 20 mg kg^{-1} body weight is prepared. Tween 80 is used as a co-surfactant and cosolvant [7, 8] to increase viscosity or absorption. The sample is injected intraperitoneal (20 mg kg^{-1}) and the analgesic effects are measured by formalin test. The mean score results of paw licking behavior were compared with morphine (1 and 2 mg kg^{-1}) and also for assessing the receptors of essential oils, pretreatment of naloxone (5 mg kg^{-1}) an opioid antagonist were examined.

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Formalin test is one of the standard tests for assessment of pain which is used in the animal model. In this method, injection of formalin leads to a biphasic pain response. The first phase is the fast response which is follow by one late response.

Method of data analysis: The data were collected every 5 min during one hour and pain scores were calculated. The data were analyzed by SPSS software using T-test and analysis of variance.

RESULTS

In the previous study we found that the essential oil have an analgesic effect during one hour and it significantly reduced paw licking behavior in compare with control subjects in formalin test ($p = 0.000$). it is not significant as compared with 1 mg kg^{-1} of morphine sulphate and Pretreatment of naloxan (5 mg kg^{-1} BW., i.p.) an opioid antagonist, could not reverse the analgesic effect observed in the formalin test and it is not significant with effect of essential oil ($p = 0.497$) Table 1, 2 and 5.

Table 1: The mean and standard deviation of pain scores during one hour (every 5 minutes) in case essential Oil and control and Naloxan

Naloxan 5 mg kg^{-1}		Essential oil 20 mg kg^{-1}		Control normal saline		G
M	S.D	M	S.D	M	S.D	Time (min)
2.25	0.19	2.31	0.23	2.48	0.46	5
1.1	0.34	0.91	0.46	1.31	0.43	10
0.6	0.68	0.46	0.30	1.17	0.55	15
0.76	0.05	0.12	0.21	0.94	0.83	20
0.55	0.17	0.27	0.20	1.33	0.51	25
0.57	0.07	0.69	0.76	1.53	0.12	30
0.45	0.14	0.84	0.82	1.34	0.55	35
0.45	0.27	0.42	0.38	1.33	0.68	40
0.35	0.18	0.19	0.23	1.43	0.40	45
0.43	0.12	0.40	0.75	1.52	0.36	50
0.40	0.07	0.63	0.81	1.42	0.55	55
0.20	0.22	0.23	0.18	1.54	0.50	60

Table 2: The mean and standard deviation of pain score during one hour in essential Oil, control and group which received Naloxan with essential oil

Naloxan X±S.D.	Essential oil X±S.D.	Control X±S.D.
0.67±0.54	0.62±0.58	1.44±0.36

Table 3: Comparison of mean and standard deviation of pain score during one hour in essential oil and control groups

Control M±SD	Essential oil M±SD	P-Value
1.44±0.36	0.62±0.58	0.000

Table 4: Comparison of mean and standard deviation of pain score during one hour in control and naloxan groups

Control M±SD	Naloxan M±SD	P-Value
1.44±0.36	0.67±0.54	0.000

Table 5: Comparison of mean and standard deviation of pain score during one hour in essential oil and naloxan groups

Essential oil M±SD	Naloxan M±SD	P-Value
0.62±0.58	0.67±0.54	0.497

In Table 3 and 4 essential oil and naloxon has compared with control that show the pain score during one hour significantly reduced ($p = 0.000$) but Comparison of mean and standard deviation of pain score in essential oil and naloxan is not significant ($p = 0.497$).

DISCUSSION

On the basis of the present results, naloxon could not reverse the analgesic effect in inflammatory phase of formalin test. It seems that mechanisms other than opioid system involved in the analgesic activities. For thousands of years mu opioid agonists such as morphine have been utilized for their analgesic properties. Today, morphine and related compounds are still used as the first line therapy in the treatment of moderate to severe pain. However, despite the clear benefits of mu agonists in pain management, severe side effects such as dependence and respiratory depression are associated with use of these drugs. To date, there are only two approved mu opioid antagonists for use in the treatment of these adverse effects, that is, naloxone and naltrexone. However, many other clinical and therapeutic areas have been linked to mu opioid receptor antagonism [1]. Enkephalins also produce analgesia by activating both mu-opioid and delta-opioid receptors. Analgesia can also be produced exclusively by mu-opioid receptor at higher agonist doses. Since peptidases prevent the activation of spinal opioid receptors by enkephalins, the coincident release of opioids and endogenous peptidase inhibitors may be required for analgesia [9]. The stimulation of opioid receptors leads to antinociception by mechanisms that include activation of brain H2-receptors [10].

One study on opioid receptor indicate peripheral inflammation enhances the antinociceptive effects of opioid receptor agonists through the activation of peripheral opioid receptors whose expression also increases during inflammatory pain [11]. The involvement of the L-arginine-nitric oxide-cGMP pathway in the opioid mechanisms of action and a better understanding of the pathways that regulate the expression of opioid receptors

during peripheral inflammation are essential to developing improved analgesic/antiinflammatory therapies [11]. Also morphine related antinociceptive effect elicited from the cuneiformis CnF is mediated, in part, by NMDA receptor at the level of the nucleus raphe magnus NRM whereas kainite/AMPA receptor has a net inhibitory influence at the same pathway [12]. One study conducted by Yamamoto *et al.* [13] showed an oral analgesic activity of cyproheptadine, an histamine H1-blocker, in rat formalin-induced pain model.Histamine in the precquductal gray matter may function as a mediator of stress-induced potentiation of opiate antinociception [14]. Histamine with H1 receptors may be involved for its antinociceptive effect on afferent peripheral inputs to the thalamus [15]. Dopamine neurotransmission within nociceptive pathways should provide a broader spectrum of antinociception than dual mechanism of action reuptake inhibitors in animal models of injury-induced [16]. Previous studies has report the modulation of K(+) channels play key roles in the induction of peripheral antinociception induced by many types of drugs. These results suggest that 4-aminopyridine-sensitive K(+) channels may play an important role in the thermal peripheral antinociception produced by lidocaine, but not tramadol [17]. It is proposed that histamine activates the H1 receptor to induce the release of 5-HT which depolarizes the nociceptor by activating 5-HT(3) receptor [18]. The findings that local sympathomimetic amines contribute to the inflammatory temporomandibular joint hyperalgesia by activating beta(2)-adrenoceptors may be relevant to clinical inflammatory pain states less sensitive to nonsteroidal anti-inflammatory drugs [19]. In this study the inhibitory effect of Carum copticum on histamine H1 receptors was examined and the anti-histaminic effects of extracts were tested. The results indicated a competitive antagonism effect of C. copticum on histamine H1 receptors [20]. Therefore because of that mechanisms other than opioid system involved in the analgesic activities and nociceptive action of histamine and with regard to the anti-histaminic effects of C. copticum can be said it may effect by histamine H1 receptors.

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