

THE EXPLORATION OF PARTICIPATE L.ARGININE – NITRIC OXIDE SYSTEM IN PAIN PERCEPTION OF BOTH GENDER MICE

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ABSTRACT

The L.arginine-Nitric oxide pathway has shown a role in pain felling which is a mediator with modulation effect in dorsal root of ganglionic neurons of spinal cord. The presented study goal was to clarify the influence of sex on the effects of L.arginine mediated nitric oxide on pain arbitration in both sexes of mice. The response time of hot plat test and latency period of tail flick were recorded the pain perception. The results of both groups of control and treated with L.arginine showed decrease of time response of hot plat in male than female and the same result in tail flick latency period of control group. Where as amplify of hot plat response time of male than female in L.NAME (nitric oxide synthase inhibitor) treated group. Morphine treated group were increase in all groups as compared with control. These findings might be attributed to that pain felling is intercede through diverse mediators in different sexes of mice male and female, this may possible involves sex hormone. In addition, from the result of L.NAME on pain sensation, it may be recommended that L.arginine-nitric oxide pathway is extra vital in male in comparison with female in pain sensation.

INTRODUCTION

Pain, Stimuli elicit intense disagreeable sensation through revelation of tissue to hurtful destruction which called noxious, a knowledge that is eventually incorporated in corticolimbic hub of the brain. L.arginine-nitric oxide system has been show to contribute in frequent biological chain and pathophysiological ailment (Thoma, 2005 and Kao and Schroeder 1995). L.arginine is one peptitergic neurotransmitters in and precursor of nitric oxide (NO) is create in different region of central nervous system by constitutive form of neuronal nitric oxide synthase (nNOS) or NOSII, an enzyme is focused in CNS neurons. The NO is formed from metabolic transformation of L.arginine to the citruline; NO elevate c.GMP levels by activation of guanylyle cyclase. Regarding the nerophysiological tasks of NO in the CNS, reports have emphasized on its participation in the pain perception. A role of NO in nociception signaling was originally based on the localization of neuronal NOS in superficial dorsal horn and intermediate cell column (Dun, *et al.*, 1993), which conducted the concept, that NO adjust both sensory transduction and autonomic tone at the spinal cord media. However, there are a number of conflicting reports concerning the functional key of nitric oxide in pain impression. For illustration, some literatures have exhibited that drop of nitric oxide persuaded antinociception (Moore *et al.*, 1993). Lately, in cancer pain improvement; was treated with nitric oxide donor (nitoprusside compounds) (Lauretti, *et al.*, 2002). The fine known that gender involves the vulnerability to variant pains nature, as well as the females have in

judgment with males have superior jeopardy intended for development of these pains. As well, the shielding modulating role of estrogen in various kinds of pain phenomenon has also been recognized (Sandra, *et al.*, 1999). However, consequently far slight attention was known to the influence of sex on processes which is involved in pain sensation. Therefore, the aim of research was awareness to explore achievable interface of sex and the effects of L-arginine-NO system with intuition of nitric oxide synthase inhibitor (L-NAME) mediating in mice sexes.

MATERIALS AND METHODS

Forty mice of 2–3 months of age, weighing 20–30 g were upholder under regular environmental condition; temperature 25–30 °C, 12 hours light and nourished ad libidum. Both sexes of mice were separated into three equal groups randomly. First, second and third groups were given 0.3 ml Morphine 500 mg/kg B.W, L-arginine 200 mg/Kg B.W and L-NAME (N^Gnitro L-arginine methyl ester) 10 mg/Kg B.W respectively which were given Intaperitoneally, whereas the forth group served as a control and was given normal saline. Hot plate response time and tail flick latency period were measured separately in different groups of both sex groups, which were conducted 20 minute after drugs administration.

A tail flick method were illustrate in Ghafourifar *et al.* (1997) was used to investigation the analgesia. The noxious motivation was produced by a beam of concentrated heater applied on the lower third of the tail. The cut off was 5 second and operator was unwire of the definite treatment of animals of each group.

The hot plat response time was checked for certain different treated groups in hot plat apparatus and was heated to 54 °C, the reaction of animals to hot plat display; hind paw lick, flinch and/or slap were recorded (Carter, 1993).

RESULTS

The results of participation of L-Arginine – Nitric Oxide system in gender influences pain perception were display in table (1).

The consequence of hot plate response time in male showed significant ($P<0.05$) lower than female in control group, where as the L-arginine treated group display significant ($P<0.05$) decrease of response time in male as compared with female, both sex of L-arginine treated group were significant ($P<0.05$) lower than certain sex of control group. There were significant ($P<0.05$) increase of time response in male group of L-NAME treatment as compared with female of certain treated group and male control group, but no significant ($P>0.05$) between female L-NAME treated group and control female group. Morphine treated group exhibited significant ($P<0.05$) increase of hot plat response time in both sex as compared with control group while there was not has significant between both sex of morphine treated group.

The tail flack latency period results showed significant decrease of group of male as compared with female group of control. While no significant were found between both sexes in L-arginine and morphine treaded group, where as male L-NAME treated group and both sex of morphine treated group were significant ($P<0.05$) increase as compared to control group of certain sex.

Table 1: The response time of hot plat test and tail flick latency period test of male and female groups treated with saline(control), Larginine, L.NAME and morphine

Pain test Groups	hot plat response time test (second)		Tail flack latency period test (second)	
	Male	Female	Male	Female
Control	6.91 ± 0.44 ^{Aa}	10.34 ± 0.38 ^{Ba}	2.40 ± 0.21 ^{Aa}	3.73 ± 0.19 ^{Ba}
L.arginine	1.73 ± 0.12 ^{Ab}	2.90 ± 0.24 ^{Bb}	2.00 ± 0.17 ^{Aa}	2.81 ± 0.16 ^{Aa}
L.NAME	22.7 ± 1.09 ^{Ac}	11.0 ± 0.87 ^{Ba}	4.05 ± 0.39 ^{Ab}	3.96 ± 0.27 ^{Aa}
Morphine	30.9 ± 1.43 ^{Ad}	31.2 ± 1.92 ^{Ac}	12.6 ± 1.14 ^{Ac}	12.9 ± 1.00 ^{Ab}

Values are presented as mean ± SE (n=5 mice)

Capital letter P < 0.05 significantly different between male and female.

Small letter P < 0.05 significantly different between treatment group and control of certain sex.

DISCUSSION

In attendance experiment exploration established the pain sensation in the male and female mice, morphine treatment displayed significant in time responses and latency period of both measured tail flick and hot plat tests. Female mice could significantly tolerate pain for a longer time than male. The participation of L.arginine – Nitric oxide system in pain perception was showed administration of L.arginine significant decrease in male than female response time of hot plate test and both was lower than of certain group's control male and female, But significantly lower ($P > 0.05$) than morphine treatment. Whereas, L.NAME treated group complain significant diminishing perception of pain as reflected by an increase in response time of the hot plat in male but not in female mice and no significant ($P < 0.05$) between female treated with L.NAME and control group. Moore *et al.*, 1993 reported the pain feeling producing by L.NAME can reverse by L.arginine administration. Hot plat test is an indicator of supraspinal analgesia while tail flick test is considered to be a measure of spinally mediated antinociception (Ramabadran and Bansinath). It has been speculated that the consequence of nitric oxide for reserve of antinociception is not opioid dependent because nalaxone (morphine antagonist) failed to overturn the antinociceptive outcome of diminishing nitric oxide synthase (Kawabata *et al.*, 1993 and Meller and Gebhart, 1993).

The result of this experiment point to the participation of L.arginine-nitric oxide pathway in mediation of acute pain in female mice is not significant as in male mice. It has been revealed that the inflammatory pain induced by epinephrine treatment in the rat in dependent on sex hormones and NOS inhibitors can provoke the pain only in the male but not in female rats (Dina and Aley 2001). This finding is harmony with our conclusion. On the other hand, at the present, it is obvious the effects of gender are more significant on the hot plate than tail flick. This might be attributed to nociceptors quantities that are triggered by different stimuli. Becker *et al.*, (1984) and Dluzen and Ramires, (1997) accounted that sex differences in numerous neurotransmitter system like vital dopamenergic neurotransmitter as a part

of pain arch. So, as sex is a vital process that influences a multiplicity of neurotransmitter system with model (Angelos, 2003). Taskiran *et al.* (1997) has been reported that the concentration of steady state metabolites of nitrite and nitrate, in the cerebral cortex and hippocampus of rat brain show sex differences, female rat in comparison with male rats have lesser levels in the male.

The conclusion, the present data show that in male mice inhibition of NOS at the level of the brain but not at the spinal result in supraspinal analgesia. The experimental results different modulators which are important in the response to the pain initiation for instance hot plat and tail flick tests mice might propose that sex steroid hormones like estrogen interact with L-arginine - nitric oxide system and had involved a mechanism of pain feeling.

استقصاء مساهمة نظام الال ارجنين – اوكسيد النتريك بادراك الالم في كلا جنسي الفئران

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الخلاصة

يلعب مسلك الال ارجنين- اوكسيد النتريك دورا في الشعور بالالم حيث اظهر تأثيرا وسيطا ومولفا في الجذر الظهري لأعصاب الحبل الشوكي العقيديه. هدفت الدراسة إلى توضيح تأثير الارجنين وسيط اوكسيد النتريك في توليف الالم في كلا جنسي الذكور وإناث للفئران. سجل كل من وقت الاستجابة لاختبار ألصفيحه الحارة و تأخر وقت اختبار انطواء الذيل لأدراك الالم. كانت نتائج مجموعتي الارجنين والسيطرة نقصان لوقت الاستجابة في ألصفيحه الحارة للذكور مقارنة بمجموعة الإناث لنفس المعاملة. ونفس النتيجة أظهرتها مجموعة السيطرة باختبار فترة التأخير لانتشاء الذيل. بينما كان تفخيم لوقت الاستجابة للصفحة الحارة للذكور مقارنة بالإناث في المجموعه المعاملة بالانيم (مثبط خميرة مصنعة اوكسيد النتريك). كانت مجموعة المعاملة بالمورفين قد عانت من زيادة في جميع المجاميع مقارنة بمجموعة السيطرة. هذه النتائج عزيت إلى اختلاف وسائط الشعور بالالم بين ذكور وإناث الفئران ومن المحتمل شمول الهورمونات الجنسية في هذا التأثير. إضافة الى ذلك، من نتائج الانيم في الشعور بالالم من الممكن أن يكون مسلك الارجنين- اوكسيد النتريك ذو فرط حيوية بإحساس الالم في الذكور أكثر منه في الإناث.

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