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Research Article

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The Role of $GABA_B$ Receptor Agonist (Baclofen) on Visceral Pain Induced by 1% Acetic Acid in Rats

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ABSTRACT

This study was conducted to investigate the effect of baclofen in acetic acid induced visceral pain in rats. In this study, adult male Wistar rats with a weight range of 250-200 g purchased from Tehran School of Veterinary Medicine were employed. All experiments were performed in 8 to 15 intervals and each animal was used once. In this study, sterile normal saline solution, a 1% acetic acid solution was used. Standard Writhing Test was used to create and examine visceral pain. For visceral pain by Writhing method, intraperitoneal injection of 1% acetic acid into the animal was employed. After intraperitoneal injection, visceral pain response was studied after in doses of 2.5, 5 and 10 mg per kg of body weight. Each experiment was conducted based on completely randomized design with 6 replications. PROC GLM in SAS software (9.3) was used to compare the mean. In each test, Duncan and Dennett's tests were used to compare means in each test as well as for comparing means in control group. In injection of baclofen in dose of 2.5 mg per kg of body weight, latency time to the first contraction of the abdominal wall and full contraction of the abdominal wall were calculated 989/67 and 1/0691 seconds, respectively and implied that baclofen had no impact on the full contraction of the abdominal, P-value> 0/05 and significantly reduced pain by 1% acetic acid. It can be said that the activation of GABAergic system in visceral pain by injecting saclofen did cause acid pain.

Keywords: *Baclofen, GABAergic system, rats, pain reduction*

Introduction

Pain is one of the most complex and extraordinary senses in humans. It is the most common symptom of diseases and common reason for visiting the doctor. Nociceptive pain includes not only stimulate the nerve fibers and transfer it to the center console of pain, but also can be changed by influencing by the quantity and quality of a wide range of experiences. This shows complex neural mechanisms for intervention and psychological response to pain experience (1, 2). Receptors are defined as free nerve endings that don't adapt unlike other sensory receptors in the body, or their adaptation is incredibly low. This non-adaptation allows the pain receptors to make aware person of damage stimulus that cause pain. The pain receptors are sensitive to chemical, mechanical, and thermal stimuli, and followed by tissue damage and release, chemical mediators such as bradykinin, histamine and prostaglandin are stimulated and send the pain signals by nerves to the central nervous system and eventually will feel pain by stimulating the cerebral cortex (3).

In addition, visceral pain is the complex pain that results from the stimulation of pain receptors in different organs of the body such as the colon, bladder and stomach in a variety of pathophysiological reasons and data is transmitted to

the central nervous system by afferent pathways. According to various studies, neurotransmitters participating in opioid and non-opioid analysis of pain are divided into two categories. The two systems can closely work together to regulate pain mechanisms. Non-opioid systems can be categorized as adrenergic, cholinergic, serotonergic, histaminergic and GABAergic systems (4).

Gamma-Aminobutyric acid (GABA) has been proposed as Paracrine and autocrine factors compounds for regulating the activity of B cells (5, 6). GABA is mainly found in neurons and central nervous system (CNS) which has an inhibitory effect, although in some tissues, their irritation effects have also been reported. The presence of mediator has also been reported in other tissues including pancreas (7). Immunocytochemistry studies have shown that GABA and its sanitizer's enzyme, i.e. decarboxylase glutamate are also present in A and B cells (8). It was found that GABA in CNS has three receptors, which its two receptors are belonged to Ainoreceotors ($GABA_A$) and ($GABA_C$) and meta- receptors ($GABA_B$). The expression of the beta cells has also been demonstrated (9). In relation to the effect of GABA mechanism on B cells, there is no complete agreement. Some studies have reported that GABA acts through GABAB receptor. It has been shown that $GABA_B$ receptor agonist baclofen have analgesic activity in humans and animals (10-12). Baclofen creates analgesia (11). It acts through spinal cord and supraspinal parts in the body (13) and is mainly recognized as antispasmodic agent for clinical use and reduces pain associated with spasticity (14) and also is useful in the treatment of trigeminal nerve (15). The involvement of neurotransmitters in the pharmacological effects of baclofen has been shown to support by the results of biochemical studies that baclofen had a significant impact on the content, release, construction and demolition these factors (13). Therefore, the aim of this study was to investigate the effect of $GABA_B$ receptor agonist (baclofen) on visceral pain induced by acetic acid in rats.

Materials and Methods

In this study, adult male Wistar rats with a weight range of 250-200 g purchased from Tehran School of Veterinary Medicine were used. Mice were kept in groups of six in polyethylene cages, and a room with environmental conditions and standard temperature of 2 ± 23 ° C 12 hours in light and darkness and fed a commercial pellet diet and had free access to food and water. All experiments were performed in the interval of 8 to 15 and each animal was used once. All the principles of laboratory animal care were taken into consideration in terms of standard laboratory temperature and humidity. In this study, sterile normal saline solution, a solution of 1% acetic acid was used: the solution was prepared of pure acetic acid and after dilution. Saclofen purchased from Sigma Company were used. In this study, Writhing Test as one of the standard tests was utilized to create and examine visceral pain. For visceral pain by Writhing method, acetic acid (1ml, 1%) was injected into the intraperitoneal area of the animal. Before the test, to avoid stress as well as habituate the animals to laboratory conditions, animals were kept in a glass container with dimensions 20 × 30 × 40 cm for 30 minutes (which it is called the period of adaptation) so that the animal may be adapted to new conditions. After adaptation period, the animal was slowly brought out of the enclosure glass and after the drug's injection, the peritoneal injection of one ml acetic acid was carried out and immediately the animal was put in the chamber glass. Moreover, latency time (Latency Time) and time to first abdominal cramps and number of contractions for an hour with an interval of five minutes of acetic acid infusion were recorded in special forms. A device called pain mirror was used to check visceral pain. The device has a wooden frame, a glass cube container with 20 × 30 × 40 cm and a mirror the size of 30 × 40 cm with an angle of 45 degrees inside it. While creating and recording of abdominal cramps in the animal, the mirror makes viewing more comfortable. After injection of saclofen for 5 mg per kg of body weight, visceral pain response was studied. Each experiment was conducted based on completely randomized design. PROC GLM in SAS software (9.3) was used to compare the mean. In each test, Duncan and Dennett's tests were used to compare means in each test as well as for comparing means in control group.

Results

In intraperitoneal injection of baclofen in dose of 2.5 mg per kg of body weight, latency time to the first contraction of the abdominal wall and full contraction of the abdominal wall were calculated 989/67 and 1/0691 seconds, respectively and according to the results, baclofen had no impact on the full contraction of the abdominal well, and significantly decreased 1% acetic acid, P-value< 0/05.

Table 1. The main effects of acetic acid

Writhing test (NO)	Latency time (sec)	%	
2/035 [b]	[a]/01478/0	0/5	Acid acetic
12/375 [a]	[b]466/0	1	Acid acetic
9/208 [a]	[b]386/8	2	Acid acetic
1/615	79.812%	SEM	
0.0013%	00010/<	P-value	

Table 2. Effects of different doses of baclofen

Writhing test (NO)	Latency time (sec)	$^{mg}/_{kg}$	
1/0552 [ab]	880/8 [a]	2/5	baclofen
1/2498 [a]	868/5 [a]	5	baclofen
0/9163 [b]	940/7 [a]	10	baclofen
0/085	72/419	SEM	
0/0433	0/0142	P-value	

Discussion and conclusion

Since no many studies have been done on analgesic effect of baclofen in rats, and because GABA has been shown as an inhibitory neurotransmitter in the central nervous system in mammals, showing the relationship between baclofen and GABAergic system in the modulation of visceral pain is important. It seems that each opioid receptor has a separate specific activity. In mice where their opioid receptors were knocked out, μ pain receptors were affected in response to chemical, mechanical and thermal pains in supraspinal part. K receptors in the spinal cord mediate visceral, thermal and chemical pain as well as δ receptors mediate mechanical and inflammation pains (16). Studies in this research revealed the therapeutic ineffectiveness of the $GABA_B$ receptor antagonists especially baclofen (17). Research conducted on mice has shown that baclofen suppressed some substances, such as nicotine and methamphetamine (18-20). Zai and Stein reported that baclofen reduced self-prescription of heroin in rats (21). And two other studies have shown that baclofen decreases symptoms of opioid withdrawal in morphine -dependent animals (11, 22). In this study, it was also found that activation of GABAergic system in visceral pain by injecting baclofen reduced acetic pain and the role of GAB_B was emphasized in the above mentioned phenomenon. On the other hand, activation of GABAergic system in visceral pain by injecting baclofen as $GABA_B$ receptor antagonists reduced pain in mentioned part. In the end, we can conclude that there is an association between visceral pain, opioids and GABAergic systems which has somewhat proven in the present study.

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