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Age-related changes in the antinociception induced by taurine in mice

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Abstract

Taurine is a nonessential amino acid that is of medical interest for the nutrition of infants. Taurine has been found in the central nervous system of rodents and humans, and among its potential therapeutic uses, it is interesting to remark its analgesic actions. It is also well known that concentration levels during the fetal and prenatal periods are higher than in adulthood. The data obtained so far indicate that taurine is involved in the development process of the brain and possibly other organs. The taurine levels in old age are still unknown, but it is presumed that they will be different from those of younger animals. Data about age-related alterations and functional modifications of this and other amino acids are still scarce. The aim of the present work was to study the antinociceptive effect of taurine and its relationship with aging in mice. No differences were found between prepubertal and young adult animals; on the contrary, old animals showed significantly reduced sensitivity to the antinociception induced by taurine; in fact, at the tested doses, taurine did not induce antinociception in this group of mice. The mechanism underlying this effect has not been clarified because there are several mechanisms and neurotransmitter systems involved in the antinociception induced by taurine.

Keywords: Taurine; Nociception; Analgesia; Experimental antinociception; Aging

1. Introduction

Taurine is a nonessential amino acid that can be obtained from the diet or from methionine after the first stages of development. Apart from its widely accepted medical interest for the nutrition of infants, taurine presents a series of actions, which have potential therapeutic repercussions (Barbero et al., 1990; Hernández et al., 1984; Huxtable, 1992; Huxtable and Barbeau, 1976; Kuriyama et al., 1983; Miñano et al., 1985; Serrano et al., 1985; Sturman et al., 1978). Among the various aspects studied, several researchers in experimental tests have demonstrated its analgesic action. It has been found that this amino acid has a dose-dependent antinociceptive action in which opioid, adrenergic, and serotonergic mechanisms are involved (Hornfeldt et al., 1992; Rios et al., 1999; Serrano et al., 1990a,b, 1994, 1996, 1998, 1999; Serrano-Martino et al., 1996, 1997; Silva et al., 1993; Smullin et al., 1990).

Concentrations of this amino acid have been found in the central nervous system (CNS), blood, and other tissues in humans and rodents. Furthermore, it is well known that concentration levels during the fetal and prenatal periods are higher than in adulthood (Sturman, 1988). The data obtained so far indicate that taurine is involved in the development process of the brain and, possibly, other organs. The levels in old age are accepted to be smaller than those in adulthood (Oja et al., 1990; Dawson et al., 1999a,b).

One of the most interesting of the therapeutic-related topics, in today's biomedical research, focuses on studying the physiological aging process and on finding out how age-related changes can affect the pharmacological responses in young and elderly individuals.

The role that taurine, as well as other amino acids, plays in cerebral neurotransmission is well established in many aspects. However, information about age-related alterations is still scarce (Banay-Schwartz et al., 1989). Considering that taurine plays an important role mainly during development, it could be interesting to test if the responsiveness to the pharmacological administration of this amino acid may be modified at each end of the age scale.

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Neurotransmitting mechanisms progressively develop in young animals and, gradually, deteriorate in the aging individuals. These developmental processes may be determined in the existence of a small number of membrane receptors and a limitation in the operational synaptic pathways, which depend on the various neurotransmitters (Lee et al., 2001). How these processes specifically affect nociception in the elderly is still not well known, although there is an increasing interest in this topic (Gagliese and Melzack, 2000; King et al., 2000; Barr, 1998) and their physiological, physiopathological, and therapeutic consequences are important.

Taking all the previous premises into account, the aim of our study was to assess whether there are any age-related changes in the antinociception induced by this amino acid in old, young, and prepubertal rodents.

2. Methods

The animals used for this study, CD-1 male mice, were supplied by Iffa-Credo, (Les Orcins, France) a company of Charles River. The animals were taken to the experimental laboratory at least 1 week before performance. Room temperature was kept at 22 ± 1 °C. A 12-h light–dark cycle was started at 8:00 am, at constant humidity. They were given free access to food and water. The older animals (35–42 g) were more than 9 months, whilst the prepubertal animals (15–17 g), which had not been previously manipulated, were used 30 days after birth (i.e., 1 week after being weaned). The young adults used (25–27 g) were approximately 2 months old (Wolfensohn and Lloyd, 1998).

For this study, the experimental test used was the acetic acid writhing test. Firstly, the effect of the intraperitoneal administration of 10 ml/kg acetic acid (0.6%) was measured by quantifying the number of writhing responses in the three groups of animals over a 10-min period. Responses were measured starting 5 min after the algogen agent was administered.

The animals in the different groups (prepubertal, adult, and aged mice) were redistributed in five groups, one of which was used as the control group. The remaining four were pretreated with 25, 50, 100, and 200 mg/kg taurine, administered by the intraperitoneal route, 15 min before the algogen agent. Control mice were treated with 10 ml/kg saline solution.

The number of stretches recorded in the control group of aged animals was smaller than the number obtained from adult and young control groups. In order to standardize control groups responses, the effect of smaller concentrations of the algogen agent was tested. The intraperitoneal injection of 0.5% acetic acid in young and adult animals induced a number of stretches similar to those recorded in old mice, then the effect of the same doses of taurine (25, 50, 100, and 200 mg/kg) was again tested.

Each group included approximately 10 animals; those animals showing behavioral alterations were previously discarded. Each animal was used only once. An observer who was unaware of the different treatments carried out the collection of data.

Throughout the experimental procedures, the international ethic standards for pain-inducing experiments in laboratory animals (Zimmermann, 1983) and the European Communities Council Directive of November 24, 1986 (86/609 EEC, November 24, 1986) were complied with.

2.1. Statistical analysis

The results are expressed in mean ± standard error of the mean (S.E.M.) and in inhibitory effect percentages. The subsequent statistical analyses were performed by an analysis of variance (ANOVA) (one- or two-way) and by a Kruskal–Wallis test. These were followed by the Newman–Keuls multiple comparison tests using an SPSS Statistics Packet for Windows, 10.0. The values considered as significant were $P < .05$.

2.2. Drugs

The drugs used and their suppliers were as follows: taurine (Sigma, Madrid, Spain) and acetic acid (Merck, Munchen, Germany).

3. Results

3.1. Modification in the nociception in control animals

No significant differences in the number of writhing responses were found between the prepubertal and adult groups (25.7 ± 0.3, $n = 10$, vs. 30.5 ± 1.7, $n = 11$) after administration of 0.6% acetic acid. However, in the group including the oldest animals, it was found that the number of writhing responses was lower (15.6 ± 1.9, $n = 10$). Differences between mature and prepubertal controls vs. aged animals controls were statistically significant ($F = 62.36$; prepubertal vs. adult, n.s.; prepubertal vs. aged, $P < .001$; adult vs. aged, $P < .001$). When the concentration of acetic acid was reduced to 0.5%, the number of stretches recorded in young (13.8 ± 1.3, $n = 10$) and adult (16.4 ± 1.5, $n = 9$) animals was not significantly different from that previously obtained in old animals.

3.2. Effect of the taurine in the different groups

When different concentrations of acetic acid (0.6% or 0.5%) were injected to adult or prepubertal groups, a dose-dependent reduction of nociception was found after the administration of taurine (Fig. 1). The comparison with their respective control groups was statistically significant for the prepubertal and adult mice. Taurine did not induce statistically significant effects in the group of aged animals in comparison with its control group (Fig. 1).

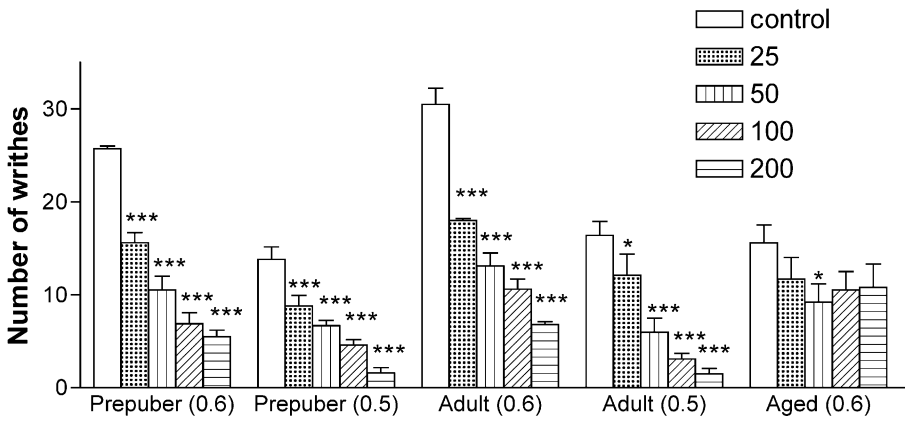

Fig. 1. Effect of taurine (mg/kg ip) in prepubertal, adult, and aged mice. Bars indicate mean number of writhes ±S.E.M. of two different concentrations of acetic acid solution (0.5% and 0.6%) ($n=10$). * Statistically significant difference vs. respective control groups; * $P<.05$, *** $P<.001$.

In order to evaluate differences among the different groups, the percentage of inhibition [% inhibition=(number of control writhing responses − number of posttreatment writhing responses/number of control writhing responses) × 100] of the nociceptive response to taurine is shown (Fig. 2). The antinociceptive effect of taurine was not statistically different in the prepubertal and adults groups of animals that were pretreated with 0.5% or 0.6% acetic acid ($F=0.47$, $P=.709$). Statistically significant differences were found among these groups and the group of aged animals: the two-way ANOVA (age, dose of taurine) of those groups revealed a significant effect of aging ($F=6.08$, $P=0.006$).

Summarizing, the comparison among the different groups showed the following:

1. no statistically significant differences between prepubertal and adult animals in the antinociceptive effect of taurine, this effect being independent of the intensity of the nociceptive stimulation;
2. statistically significant differences between prepubertal and adult animal groups in comparison with that of the oldest animals;
3. the antinociceptive effect induced by taurine on prepubertal and adult animals was dose-dependent, whereas no significant differences were found among the different doses administered to the oldest groups of animals.

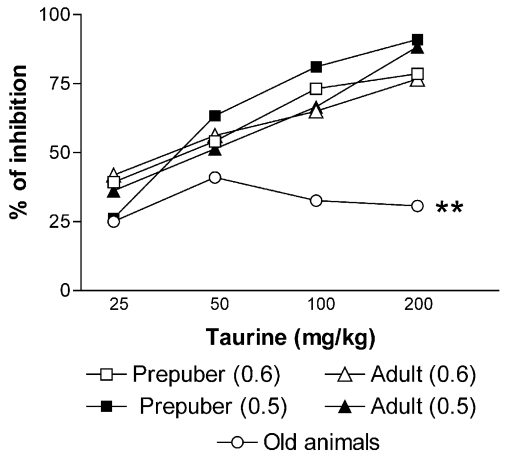

Fig. 2. Percent inhibition of writhes induced by increasing doses of taurine. Data are expressed as means of 10 experiments per dose ±S.E.M. * Statistically significant difference; ** $P<.01$ vs. adult and prepubertal groups.

4. Discussion

As studies about the biological processes that mediate and modulate the perception of pain in the infant and older animals are scarce, nociception during development and aging is still poorly understood. The perception of pain at different ages has been previously studied and seems to vary in different animal species and with the type of test used (Gagliese and Melzack, 2000). In general, no changes have been described on reflexive responses in older rats when the tail shock test was used (Goicoechea et al., 1997) or when the withdrawal reflex was induced by a paw pressure test (Jourdan et al., 2000). Furthermore, as far as pain is concerned, studies have found that young animals showed a higher sensitivity to morphine than adults (D'Amato et al., 1999) and aged animals showed reduced sensitivity to morphine (Jourdan et al., 2000).

Previous studies demonstrated that taurine has an antinociceptive effect in mice that could be evaluated using the acetic acid test or the formalin test, among others. When the formalin test was used, taurine was useful only in the early phase but not in the late phase (Silva et al., 1993). Thus, the information that could be obtained from both tests is quite similar, and for this preliminary study, the acetic acid test was selected.

Our data show that when the acetic acid was administered by the intraperitoneal route, in order to perform a test that induces a tissue injury, the nociceptive response was lower in

old animals. These results are in agreement with those in previous studies in which age differences in pain behaviours were described by means of models inducing tissue injury and inflammation (Gagliese and Melzack, 2000).

As for the antinociceptive effect of taurine, it is widely accepted that this inhibitory amino acid is able to reduce nociceptive behaviors in different experimental models such as the tail flick test in rats (Rios et al., 1999; Serrano et al., 1994, 1996, 1999; Serrano–Martino et al., 1996, 1997), formalin test (Silva et al., 1993), and autonomy after neurectomy in rats (Belfer et al., 1998). According to previous data, the present results show that taurine is able to induce a dose-dependent antinociception in prepubertal and young adult mice.

The nociceptive behavior of older mice was not significantly modified by treatment with taurine; this reduction in the effectiveness of taurine may not be attributed to a modification in the pain sensitivity of aged mice: when the concentration of acetic acid was reduced, in order to avoid differences in control responses, the antinociceptive effect of taurine was not modified in prepubertal and adult groups.

Some data support that taurine levels decrease during the aging process (Dawson et al., 1999a,b). In fact, taurine administration seems to be useful as an antioxidant amino acid in ischemic processes in older animals (Ooboshi et al., 2000), in age-related progressive renal sclerosis (Cruz et al., 2000), and in memory improvement (Rivas-Arancibia et al., 2000). The data suggest that taurine may also act as a neuroprotector amino acid (Saransari and Oja, 1997).

However, age-related taurine modification levels are still unclear. Some authors maintain that taurine concentrations decline with age in a series of tissues such as the CNS structures (Dawson et al., 1999a,b; Pierno et al., 1998). Others found that taurine levels are unmodified by age (Corsi et al., 1997; Saransari and Oja, 1997). Nevertheless, as far as we know, there is no available information about taurine antinociception in old animals. From our data, it is not possible to elucidate the underlying mechanism involved in this age difference, especially because taurine is considered as a modulator of central pain mechanisms and its antinociceptive activity probably involves GABAergic (Serrano et al., 1994), opioidergic (Serrano-Martino et al., 1996, 1997), noradrenergic (Serrano et al., 1999), and serotonergic (Rios et al., 1999; Serrano et al., 1999) systems.

From the present study, it can be concluded that there is an age-related modification of the taurine effect. However, given the complexity of the multiple interrelations, it is difficult to determine whether the lack of effectiveness of taurine in aged animals could be caused by a deficit in taurine functions (Dawson et al., 1999a,b) or by the influence of other factors that mediate the antinociception induced by this amino acid. This latter hypothesis is supported by the generalized reduction of the neurotransmitters involved in the antinociception induced by taurine (Lee et al., 2001; Míguez et al., 1999). It is possible that a combination of mechanisms could be responsible for the absence of taurine effect, and more work is required to analyze all these complex relationships.

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