ACTA NEUROBIOLOGIAE EXPERIMENTALIS

Research paper Acta Neurobiol Exp 2014, 74: 307–316

Tiapride impairs the aversive effect of electrical stimulation of the parabrachial complex in a conditioned place task

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The parabrachial complex has been related to various rewarding or aversive behavioral processes, including taste aversion learning and conditioned place aversion. This study examined the effect of tiapride, an antagonist of D2/D3 dopaminergic receptors, on place aversion induced by electrical stimulation of the external lateral parabrachial (LPBe) nucleus. Results obtained show that brain-stimulated animals avoid the area of the maze associated with electrical stimulation but show no such behavioral rejection when they receive an injection of 30 mg/kg tiapride. Furthermore, tiapride did not appear to affect the horizontal motor activity (crossing) of the animals. These results are discussed in the context of the different natural and artificial modalities used to induce aversive behavior and their relationship with dopamine systems.

Key words: parabrachial complex, brain electrical stimulation, dopamine tiapride, place aversion learning

INTRODUCTION

The parabrachial complex, a dorsolateral pontine region, has been related to various regulatory and adaptive behavioral processes (Yamamoto et al. 1994a, Poon 2009, Andrade-Franzé et al. 2010). Specifically, this region has been implicated in rewarding (Ferssiwi et al. 1987, Zafra et al. 2002, Simón et al. 2007) and aversive (Bernard et al. 1994, Yamamoto et al. 1994a,b, Nader et al. 1996, Mediavilla et al. 2000) processes. The parabrachial complex is divided into two areas (medial and lateral) separated by the upper cerebellar peduncle (Fulwiler and Saper 1984, Lundry and Norgren 2004).

Various studies have described the involvement of the lateral parabrachial region in taste aversive learning (Yamamoto et al. 1994b, Tokita et al. 2007), and large lesions of the lateral parabrachial area were found to interrupt the acquisition of taste aversions (Agüero et al. 1993a, b, Yamamoto et al. 1994b, Zafra et al. 2005). In particular, a role in taste aversion learning has been demonstrated for the external lateral parabrachial (LPBe) nucleus, one of the brain subnuclei that are activated when animals undergo taste aversion learning tasks (Yamamoto et al. 1994a,b, Sakai and Yamamoto 1997). Moreover, specific lesions of this subnucleus impair concurrent taste aversive learning, an implicit learning modality (Mediavilla et al. 2000, 2005). Furthermore, electrical stimulation of the LPBe nucleus can induce rejection of the stimuli (taste or place) with which it is associated (Simón et al. 2007, 2008). Thus, the LPBe appears to be part of a potential anatomical axis that has been related to taste aversion learning and would include other components, such as the vagus nerve and the nucleus of the solitary tract (Arnedo et al. 1990a,b, 1993, Mediavilla et al. 2000, 2011). It has also been reported that the LPBe nucleus may be part of the spinal-(trigeminal)-pontine-amygdaloid pathway, which is related to the affective and autonomic components of pain (Bernard et al. 1994, Gauriau and Bernard 2001).

In this regard, the dopaminergic system has been found to play an important role in different aversive behaviors and learning (D`Angio et al. 1987, Salamone 1994, Fenu et al. 2001). Dopaminergic levels in different brain regions have been reported to increase during stressful situations, such as tail-pinch (Cenci et al. 1992, DiChiara Loddo and Tanda 1999), immobiliza-

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Received 09 March 2014, accepted 06 July 2014

tion (Imperato et al. 1992, Doherty and Gratton 1997), prolonged handling (Cenci et al. 1992, Fuchs et al. 2005), anxiogenic drug administration (McCullough and Salamone 1992), and electric shock application (Thierry et al. 1976, Deutch and Tam 1985, Wilkinson et al. 1998). Conversely, the administration of dopaminergic inhibitors impaired the acquisition of taste aversions (Lorden et al. 1980, Reilly and Trifunovic 2000, Fenu et al. 2001) and place aversions (DiScala and Sandner 1989) as well as inhibiting active avoidance or escape behaviors (Cooper et al. 1974, Sanger 1987, White et al. 1992, McCullough et al. 1993, Hoebel et al. 2007). In this context, it was recently shown that the tiapride, a D2/D3 dopaminergic antagonist, impairs concurrent but not sequential taste aversion (Mediavilla et al. 2012). This drug has preferentially been used to treat agitation and aggressiveness in the elderly (Scatton et al. 2001) and in patients with late dyskinesia (Soares and McGrath 1999) and to alleviate the abstinence syndrome and craving in patients undergoing alcohol detoxification (Soyka et al. 2002, Bender et al. 2007). From an anatomic point of view, the dopaminergic system appears to include the parabrachial complex and some of its efferent projections, e.g., those projecting to the ventral tegmental area (Ikemoto and Panksepp 1999, Coizet et al. 2010).

With this background, the objective of this study was to analyze the effect of electrical stimulation of the LPBe nucleus in a place aversion task and to study any impairment produced by the administration of tiapride. For this purpose, we compared the effect of the drug between a group receiving aversive intracerebral stimulation and a control group. We also analyzed similarities and differences between the control group and a sham-operated group. A further objective was to determine any potential motor side effects of this dopaminergic antagonist based on the horizontal (crossing) and vertical (rearing) mobility indexes of animals during tests.

METHODS

Subjects and surgical procedure

Thirty male Wistar rats from the breeding colony at the University of Granada, weighing 280–350 g at surgery, were used in this study. They were randomly distributed into two groups, one implanted with intracranial electrodes in the LPBe nucleus (20 animals) and an intact control group (10 animals). Animals were housed in methacrylate cages, with water and food *ad libitum* (A-04, Panlab Diets S.L., Barcelona, Spain). The laboratory was maintained at 20–24°C with a 12:12 h light/dark cycle. All experimental procedures were conducted during light periods with white noise.

The animals remained under these conditions for an adaptation period of at least 7 days before surgery. All behavioral procedures and surgical techniques complied with the relevant Spanish regulation (Royal Law 23/1988) and European Community Council Directive (86/609/EEC).

Animals were implanted with a stainless steel monopolar electrode (00), with a diameter of 0.30 mm, in the LPBe nucleus of the right hemisphere [Coordinates: AP=−0.16; V=3.0; L=±2.5, according to the atlas by Paxinos and Watson (1998)] using a stereotaxic apparatus (Stoelting Co. Stereotaxic 511.600) under general anesthesia (sodium thiopental, 50 mg/kg, B. Braun Medical S.A. Barcelona, Spain). As prophylactic measures, 0.1 cc penicillin (Penilevel, Level Laboratory, S.A., Barcelona, Spain) was intramuscularly injected and an antiseptic solution was applied around the implant (Betadine. Povidone-Iodine. Asta Médica, Madrid, Spain). There was a post-surgery recovery period of at least 7 days.

Equipment

For the electrical stimulation, a continuous current range of 95–200 μA with rectangular cathodic pulses at 66.6 Hz and 0.1 ms pulse duration was supplied by a CS-20 stimulator (Cibertec, Madrid, Spain) connected to an ISU 165 isolation unit (Cibertec, Madrid, Spain) and HM 404-2 oscilloscope (HAMEG Instrument GMBH, Frankfurt, Germany).

The following three-chamber mazes were used (Carr et al. 1989, Simón et al. 2007):

Model 1: Rectangular maze (70×15×15 cm) oriented East-West, in which the walls of the two lateral compartments were made of black methacrylate, with a round hole in one end-wall and a square hole in the other. The floor was made of brown cork with transverse or longitudinal incisions, respectively. The central area (10×15 cm) had a metal grill floor and the walls were white.

Model 2: Rectangular maze (50×25×30 cm) oriented North-South, in which the walls of the two lateral compartments were painted with black and white 1-cm

wide stripes that were vertical in one compartment and horizontal in the other. In one compartment, the floor was synthetic cork painted with black and white stripes and in the other it was brown cork. The floor of the central area (8×25 cm) was white methacrylate, and the walls were a natural wood color.

Behavioral procedure

Phase 1: Place aversion in maze 1 after vehicle administration

The concurrent place conditioning task commenced at 48 h after establishing the individual optimal electrical current. As in previous studies in our laboratory, the appropriate current intensity was individually established for each animal by applying progressive increments of 10 mA and observing in detail the behavior of the animal after each increase, selecting for future experimental phases the intensity level immediately below that at which behavioral signs of nervousness were observed, e.g., unmotivated motor activity or vocalizations. At 30 min before each test, animals received an injection of distilled water as vehicle. After placing each animal in the center of the maze, the voluntary stay of the animal in one of the two compartments was accompanied by the corresponding intracranial electrical stimulation (half of the animals received stimulation in one side of the maze and the rest in the other), and the stay time in each area was recorded. The place in which the animals received stimulation was distributed at random. Each session lasted for 10 min. The neurologically intact animals underwent the same procedure without stimulation.

This process was conducted in two sessions on consecutive days, but results on the second day alone were considered as preference index. In previous studies, three groups of animals could be distinguished according to their responses to this type of stimulation procedure (see Results): "positive" animals, which consistently prefer the area in which they are electrically stimulated; "negative" animals, which consistently avoid this stimulation-associated area; and a third group of "neutral" animals with no consistent place behavior (Simón et al. 2008, 2009). In the present study, the "negative" group comprised all animals that demonstrated an aversion towards the stimulation-associated compartment of the maze, in which they stayed for less than 30% of the time available. Furthermore, the "neutral" group served as a sham-operated group and received no further electrical stimulation.

The following motor activity indexes were also recorded: horizontal activity (counting the number of crossings by the animal from one compartment of the maze to another) and vertical activity (number of rearings).

Phase 2: Place aversion in the model 2 maze after tiapride administration

At 48 h after ending phase 1, we conducted a new place preference conditioning experiment in the model 2 maze (to avoid learning transferences from the previously established learning – carry over), simultaneously recording the same motor activity indexes. The same procedure as in phase 1 was followed except that all animals received an intraperitoneal injection of tiapride (30 mg/kg) at 30 min before being placed in the maze (Tiaprizal, injectable tiapride; Sanofi-Synthelabo S.A., Barcelona, Spain); this is one of the lowest doses utilized in this study modality and avoids undesirable side effects (Cohen et al. 1997). In addition, only the animals from the "negative" group in phase 1 underwent brain electrical stimulation, not the controls.

Histology

After the behavioral tests, the animals were anesthetized and a small electrolytic lesion was made (0.3 mA/5 s), followed by the intracardiac perfusion of isotonic saline and 10% formaldehyde solution. Brains were extracted and kept in 10% paraformaldehyde

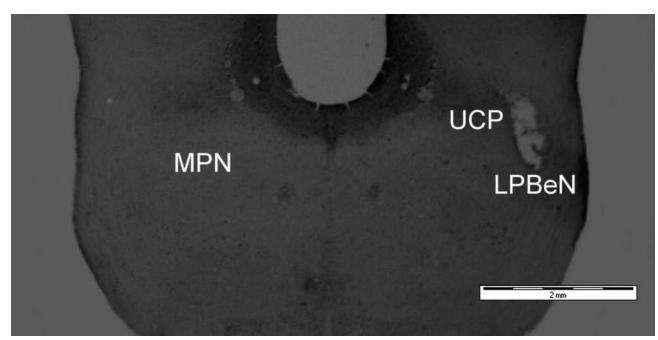

Fig. 1. Localization of the electrode in the external lateral parabrachial nucleus (LPBeN) of an animal from the stimulated group. (MPN) medial parabrachial nucleus; (UCP) upper cerebellar peduncle.

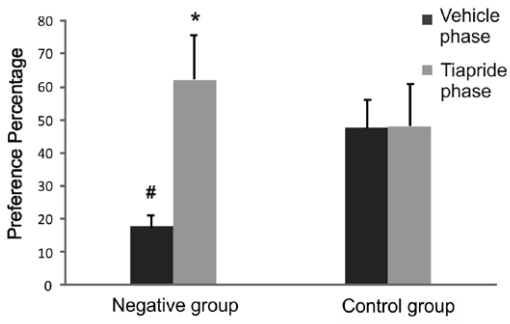

Fig. 2. Graphic representation of the results obtained in the concurrent conditioning place aversion task. The ordinate represents the percentage of preference (in seconds) of the Negative and Intact Control groups during both phases of the experiment (*P<0.05 Negative group, phase 1 *versus* phase 2; #P<0.05 Phase 1, Negative group *versus* Intact Control group).

until sectioned in 60-micron coronal slices. These were stained with Cresyl Violet, examined under a stereoscopic magnifying glass (VMZ-4F, Olympus, Tokyo, Japan), and photographed with a PM-6 camera (Olympus, Tokyo, Japan) (see Fig. 1).

RESULTS

Following the behavioral criteria established in previous studies (Simón et al. 2007, 2008, 2009), animals remaining for >50% of the total time (10 min) in the area in which they were stimulated (n=6) were classified as positive and therefore excluded from the study, those remaining <30% of the time in the stimulated compartment (n=6) were classified as negative. In addition to the intact control animals (n=10), those remaining for 30–50% of total time or showing alternating behavior between sessions were classified as neutral and subsequently served as sham-operated group (n=8). During the second learning session in model 1 maze, mean stay times in the stimulated area were: $X_{Negative}$ = 102.7 s.; $X_{Sham\text{-}operated}$ = 226.8 s.; $X_{Intact\ Control}$ = 245.0 s.

A two-way ANOVA was used to analyze the preference percentages of the experimental and intact control groups during phases 1 and 2 followed by planned comparisons, using the Statistica 6.0 program (Statsoft Inc.; Tulsa, OK). Significance was established at P<0.05.

Results obtained showed statistical significance for the group-phase interaction ($F_{1,14}$=4.76; P<0.05) and for the main effect of phase ($F_{1,14}$=5.02; P<0.05), i.e., the effect of the drug. Examination of the effect of the interaction using planned comparisons revealed statistically significant differences between the experimental and control group data in phase 1 ($F_{1,14}$=6.12; P<0.027). Significant differences were also found between phases 1 and 2 in the case of the experimental group alone ($F_{1,14}$=7.82; P<0.014).

In order to test whether the passage of the electrode might have influenced the results, a second two-way ANOVA was performed with the preference percentages of the control and sham groups in phases 1 and 2. According to the results obtained, there was no main effect of group variable ($F_{1,16}$=0.16; P<0.69), phase variable ($F_{1,16}$=0.01; P<0.98), or their interaction ($F_{1,16}$=0.01; P<0.94).

As depicted in Figure 3, the number of crossings by the animals in each group was not changed by the administration of tiapride (*versus* vehicle): negative group:

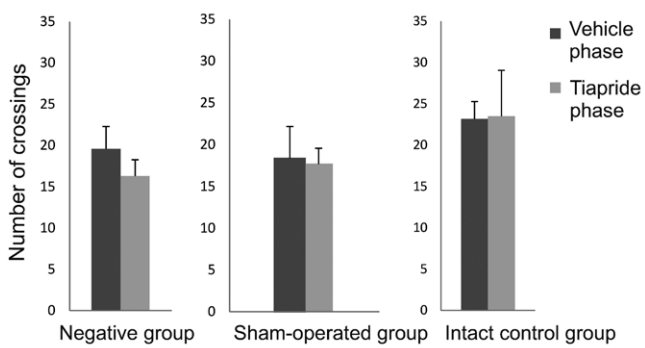

Fig. 3. Results of horizontal motor activity. The ordinate represents the number of crossings during the different study phases by animals in the stimulated, sham-operated, and intact control groups.

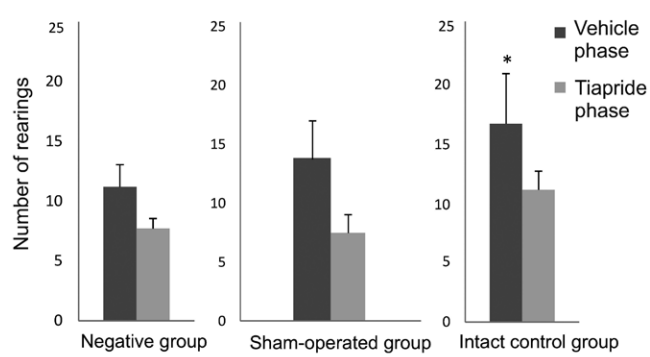

Fig. 4. Results of vertical motor activity. The ordinate represents the number of rearings during the different study phases by animals in the stimulated, sham-operated, and intact control groups (*P<0.05).

$F_{1,5}$=0.0028, P=0.9599; sham-operated group: $F_{1,7}$=0.0460, P=0.8364; and intact control group: $F_{1,9}$=3.0428, P=0.1151. Figure 4 also shows that tiapride administration significantly reduced the number of rearings in the intact control group ($F_{1,9}$=5.2878, P=0.0470), but not in the sham-operated group ($F_{1,7}$=2.9823, P=0.1278) or in the negative group ($F_{1,5}$=2.0279, P=0.2137).

DISCUSSION

In this study, electrical stimulation of the LPBe nucleus induced place aversion in a rectangular maze with three compartments. This result is in agreement with previous evidence from our laboratory that the acquisition of taste aversions in concurrent tasks requires the integrity of an anatomical system that includes structures such as the vagus nerve, nucleus of the solitary tract, and the LPBe nucleus itself (Arnedo et al. 1990a,b, Agüero et al. 1993a,b, Mediavilla et al. 2000, 2011).

The fact that electrical stimulation of the LPBe from the same stereotaxic coordinates generates either preferences or aversions suggests that the systems processing rewarding and aversive motivational information may be anatomically very close together (Hoebel 1976, Salamone 1994, O'Doherty et al. 2001). Dissociation among different functional systems that are close to the electrode tip (Yeomans 1990) depends on the specific placement of the electrode within the subnucleus and may also be achieved by modification of the current parameters to activate some or other systems (e.g. stimulus-bound eating and self-stimulation) (Hawkins et al. 1983). Specifically, electrical stimulation of the LPBe nucleus seems to be involved in opposite behavioral processes (Mediavilla et al. 2000, Zafra et al. 2002), as observed with stimulation of other brain areas, such as the lateral hypothalamus, e.g., eating, drinking, self-stimulation, or aversion (Gratton and Wise 1983, Hawkins et al. 1983), or the periaqueductal gray matter (pain or analgesia) (Mayer et al. 1971, Prado and Roberts 1985). Presumably, therefore, electrical stimulation in the "neutral" animals may have simultaneously activated cells that process appetitive and aversive information from neighboring neuronal populations, as observed in other brain regions (Yamamoto et al. 1989, Moufid-Bellancourt et al. 1996, O´Doherty et al. 2001).

The present results also demonstrate that tiapride can block the aversive effect induced by concurrent electrical stimulation of the LPBe nucleus, but it does not impair the horizontal motor activity of the animals. In a recent parallel study, tiapride administration was found to interrupt concurrent but not sequential aversive taste learning in neurologically intact animals (Mediavilla et al. 2012). This aversive effect appears to be specific to the electrical stimulation of this region, given that the neurologically intact animal group showed no consistent preference behaviors for any area in the mazes.

It is possible that electrical stimulation of the LPBe nucleus may have evoked specific behavioral effects that are generated by aversive visceral information under natural conditions (Sakai and Yamamoto 1997, 1998). In turn, the association of this stimulation with environmental cues may induce rejection of a specific localization within the space occupied by the animal. This effect would be similar to that observed after the application of nociceptive agents (Bernard et al. 1994, Gauriau and Bernard 2001, Jasmin et al. 2003) or after the induction of visceral malaise by noxious agents (Mediavilla et al. 2000).

However, anomalous activation of specific taste cells by the electrical stimulation of the LPBe nucleus cannot be ruled out (Yamamoto et al. 1994a), and the motivational consequences of this activation may be associated with environmental cues. Likewise, electrical stimulation of the LPBe nucleus may activate the same aversive neural substrates on which some drugs of abuse act (Bechara et al. 1993, Mansour et al. 1995, Nader et al. 1996). In fact, previous studies implicated the lateral parabrachial area in the processing of the aversive properties of morphine (Bechara et al. 1993, Nader et al. 1996) in interaction with the dopaminergic system (Zito et al. 1988).

Hence, the relationship between the parabrachial complex and aversive processes appears to be well-established (Bernard et al. 1994, Nader et al. 1996, Sakai and Yamamoto 1997, 1998, Mediavilla et al. 2000). The present study suggests that the LPBe nucleus may be important for processing the affective and emotional components of some learning modalities. Previous studies implicated the LPBe nucleus in panic disorders and in the beneficial effects of electrical stimulation of the vagus nerve on mood disorders (Schachter and Saper 1998, Balaban and Thayer 2001, Schachter 2004).

Our findings demonstrate that the administration of tiapride, a dopaminergic antagonist of D2 and D3 receptors, impairs the aversive effect induced by electrical stimulation of the LPBe nucleus. Previous studies demonstrated that the administration of dopaminergic antagonists impairs the place aversion induced by aversive substances such as morphine, naloxone, or anxiogenic drugs (Zito et al. 1988, DiScala and Sandner 1989, Santi and Parker 2001). Conversely, there have been numerous reports of increased dopamine levels in various brain regions in response to aversive stimuli, including the ventral tegmental area, accumbens nucleus, and medial prefrontal cortex (Cenci et al. 1992, Salamone 1994, Doherty and Gratton 1997, Wilkinson et al. 1998, Young et al. 2005).

Experimental evidence on the relationship between dopamine and aversive processing (Salamone 1994) has led authors to propose the involvement of dopamine in processes associated with goal-directed behaviors, such as the attribution of incentive salience or behavioral reactivity (Salamone, 1988, 1992, 1994, Peciña Berridge and Parker 1997, Garris et al. 1999, Cannon and Palmiter 2003, Phillips et al. 2003, Cannon and Bseikri 2004, Roitman et al. 2004, Robinson et al. 2005, Flagel et al. 2011). It has generally been observed that deficits induced by interferences in the dopaminergic system impair the performance of implicit goal-directed behaviors (Mediavilla et al. 2012) and learned instrumental behaviors but have a lesser impact on the affective evaluation of stimuli (Smith et al. 2002, Robinson et al. 2005).

Finally, with regard to the potential motor side-effects of tiapride, its administration in the present study had no significant effect on the horizontal activity of the animals, and this is a key factor in place preference/aversion conditioning tasks that require them to move around different compartments of the maze. However, the vertical activity of all experimental animals was reduced after tiapride administration. Rearing has been considered a sign of the behavioral sensitization produced by drugs of abuse, including morphine, amphetamines, cocaine, and nicotine (Joyce and Iversen 1979, Bechara and Van der Kooy 1992, Brown and Fibiger 1992, Deminière et al. 1992, Balcells-Olivero and Vezina 1997, Schildein et al. 1998). It has also been demonstrated that the administration of opiate antagonists can block the increase in rearing induced by substances of abuse (Dettmar et al. 1978, Balcells-Olivero and Vezina 1997). Hence, this motor activity appears to be at least partly dependent on opiate mechanisms, and its reduction may be related to brain reward systems rather than to motor disability (Balcells-Oliveros and Vezina 1997). Rearing has also been considered an exploratory behavior related to the habituation of animals to novel situations and has even been proposed as an anxiety index (Emmanouil and Quock 1990, Milman et al. 2006). Administration of D3 dopaminergic antagonists can also block the rearing induced by drugs of abuse (Chiang et al. 2003), and doses of 30–60 mg/kg tiapride were able to block alcohol-induced behavioral sensitization (Cohen et al. 1997). In fact, tiapride has become routinely used in clinical alcoholic detoxification programs to treat the withdrawal syndrome and craving (Soyka et al. 2002, Bender et al. 2007).

CONCLUSIONS

In summary, the results of this experiment suggest that electrical stimulation of the LPBe nucleus induces aversive behaviors that may depend on the activation of brain dopamine systems related in some way to motivational and emotional components of behavior. Specifically, aversive anatomical systems that include the LPBe nucleus may be activated naturally *via* taste (Yamamoto et al. 1994a), visceral aversive (Mediavilla et al. 2000, 2005), or nociceptive (Bernard et al. 1994) stimuli, and could be blocked by tiapride, a D2/D3 antagonist. Furthermore, it is possible that aversive brain systems that include the LPBe nucleus and dopamine neurotransmission can also be activated by artificial agents, such as drugs of abuse (Bechara et al. 1993, Nader et al. 1996) or by the intracranial electrical stimulation applied in the present study.

ACKNOWLEDGEMENTS

The authors are grateful to Richard Davies for assistance with the English version of this paper. This research was supported in part by the University of Granada and Spanish Ministry of Education and Culture (National R + D Plan PB98-1284; SEJ2007-61839/PSIC & PSI2010-17400). This study was submitted by the first author in partial fulfillment of the requirements for her PhD degree in Psychology (Psychobiology) at the University of Granada, Granada (Spain).

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