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Journal of Cellular Biochemistry 113:1182–1189 (2012)

Journal of Cellular Biochemistry

Hypothalamic Action of Glutamate Leads to Body Mass Reduction Through a Mechanism Partially Dependent on JAK2

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ABSTRACT

Glutamate acts in the hypothalamus promoting region-, and cell-dependent effects on feeding. Part of these effects are mediated by NMDA receptors, which are up regulated in conditions known to promote increased food intake and thermogenesis, such as exposure to cold and consumption of highly caloric diets. Here, we hypothesized that at least part of the effect of glutamate on hypothalamic control of energy homeostasis would depend on the control of neurotransmitter expression and JAK2 signaling. The expression of NMDA receptors was co-localized to NPY/AgRP, POMC, CRH, and MCH but not to TRH and orexin neurons of the hypothalamus. The acute intracerebroventricular injection of glutamate promoted a dose-dependent increase in JAK2 tyrosine phosphorylation. In obese rats, 5 days intracerebroventricular treatment with glutamate resulted in the reduction of food intake, accompanied by a reduction of spontaneous motility and reduction of body mass, without affecting oxygen consumption. The reduction of food intake and body mass were partially restrained by the inhibition of JAK2. In addition, glutamate produced an increased hypothalamic expression of NPY, POMC, CART, MCH, orexin, CRH, and TRH, and the reduction of AgRP. All these effects on neurotransmitters were hindered by the inhibition of JAK2. Thus, the intracerebroventricular injection of glutamate results in the reduction of body mass through a mechanism, at least in part, dependent on JAK2, and on the broad regulation of neurotransmitter expression. These effects are not impaired by obesity, which suggest that glutamate actions in the hypothalamus may be pharmacologically explored to treat this disease. J. Cell. Biochem. 113: 1182–1189, 2012.

KEY WORDS: LEPTIN; OBESITY; NEUROTRANSMITTER; FEEDING

Glutamate elicits orexigenic and/or anorexigenic responses when injected directly in the hypothalamus. These effects depend on the site of injection and other variables such as time-course and dose [Guard et al., 2009; Stanley et al., 2011]. All three ionotropic glutamate receptor subtypes, NMDA, AMPA, and KA are known to play a role in these responses and defining the mechanisms behind this control may provide valuable information for the development of drugs for the treatment of obesity and related disorders [Doane et al., 2007; Stanley et al., 2011].

Recently we reported that rats submitted to two different pro-thermogenic conditions, that is, cold exposure and feeding on a high-fat diet, would selectively and coincidently modulate only a minority of hypothalamic genes, suggesting that the products of such genes would play important roles in energy homeostasis [De Souza et al., 2008]. One of the genes is NMDA2B, which codes for a subunit of the NMDA receptor. Upon both cold exposure and high-fat feeding the expression of NMDA2B increases by approximately threefold [De Souza et al., 2008].

A number of studies have evaluated the mechanisms by which NMDA plays a role in the control of food intake [Zhang and Fogel, 2002; Guard et al., 2009; Stanley et al., 2011]. At the cellular level, the activation of NMDA leads to increased excitability and neurotransmitter release [Zhang and Fogel, 2002; Guard et al., 2009; Stanley et al., 2011]. Depending on the neuron type responding to glutamate, orexigenic, or anorexigenic neurotransmitter can be released [Zhang and Fogel, 2002; Guard et al., 2009; Stanley et al., 2011]. In neurons of the arcuate nucleus, insulin, and leptin act in concert to provide the most robust anorexigenic signals [Figlewicz and Benoit, 2009]. These signals control both neurotransmitter expression and release, and the activation of JAK2 provides the cross-talk between the signaling systems of these hormones [Villanueva and Myers, 2008]. Here we tested the hypothesis that

Grant sponsor: Fundação de Amparo à Pesquisa do Estado de São Paulo.
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Received 2 November 2011; Accepted 3 November 2011 • DOI 10.1002/jcb.23445 • © 2011 Wiley Periodicals, Inc.
Published online 17 November 2011 in Wiley Online Library (wileyonlinelibrary.com).

hypothalamic glutamate modulates food intake and energy homeostasis by mechanisms dependent on JAK2 activation and neurotransmitter expression. Our results reveal that intracerebroventricular injection of glutamate results in body mass loss through a mechanism at least in part dependent on JAK2 activation.

MATERIALS AND METHODS

ANTIBODIES, CHEMICALS, AND BUFFERS

The reagents for SDS–polyacrylamide gel electrophoresis and immunoblotting were from Bio-Rad (Richmond, CA). HEPES, phenylmethylsulfonyl fluoride (PMSF), aprotinin, dithiothreitol, Triton X-100, Tween-20, glycerol, and bovine serum albumin (fraction V) were from Sigma (St. Luis, MO). Nitrocellulose membrane (BA85, 0.2 μm) was from Amersham (Aylesbury, UK). Anti-NR2B (sc-1469, goat polyclonal), anti-NPY (sc-28943, rabbit polyclonal); anti-POMC (sc-20148, rabbit polyclonal); anti-AgRP (sc-18634, rabbit polyclonal); anti-JAK2 (sc-278, rabbit polyclonal); anti-pospho [Tyr] JAK2 (sc-16566-R, rabbit polyclonal); anti-Akt (sc-1618, goat polyclonal); anti-phospho [Ser^{473}] Akt (sc-7985-R, rabbit polyclonal); anti-ERK (sc-94, rabbit polyclonal); anti-phospho ERK (sc-7383, mouse monoclonal); anti-MCH (sc-28931, rabbit polyclonal); anti-CRH (sc-5543, rabbit polyclonal); and FITC or rodhamin conjugated goat and rabbit antibodies were from Santa Cruz Biotechnology (Santa Cruz, CA). L-glutamic acid ($C_5H_9NO_4$ P.M: 147.13) was from Synth (Diadema, Brazil) and the JAK2 inhibitor AG490 was from EMD Chemicals (Darmstadt, Germany). ELISA kit to leptin serum analysis was from Millipore (Cat.#: EZRL-83K; Kit lot#: 1907400).

ANIMAL MODEL AND EXPERIMENTAL PROTOCOLS

In all experiments, 8-week-old, male Wistar rats with a body mass of 250–300 g were employed. The animals were maintained on a 12:12 h artificial light–dark cycle and housed in individual cages. After random selection, rats were submitted for 8 weeks to a control or high-fat (HF) diet, as presented in Table I. The investigation followed the University guidelines for the use of animals in experimental studies and conforms to the Guide for the Care and Use of Laboratory Animals, published by the US National Institutes of Health (NIH publication No. 85-23 revised 1996). The animals were stereotaxically instrumented to receive a cannula placed in the lateral ventricle, following the stereotaxic coordinates: anteroposterior, 0.2 mm/lateral, 1.5 mm/depth, 4.0 mm. After 7 days, the correct location of the cannula was tested by injecting 2.0 μl angiotensin II (10^{-6} M) and determining the thirst response. For this, rats were water deprived for 2 h and immediately after icv injection of angiotensin II, a bottle containing 10.0 ml water was made available. Only the rats spontaneously drinking at least 5.0 ml water in 30 min were considered correctly cannulated and used in the experiments. For evaluation of relative expression of mRNA by real-time PCR rats were treated twice a day for 5 days with 2.0 μl of saline, glutamate (30 nM) or glutamate (30 nM) + AG490 (10 nM). For evaluation of signal transduction, rats were treated with a single 2.0 μl dose of saline, or glutamate (1.0, 2.0, 10, or 30 nM) and specimens were collected after 10 min.

TABLE I. Macronutrient Composition of the Diets

	Standard chow		High-fat chow	
	g%	kJ%	g%	kJ%
Protein	20	19	20	14
Carbohydrate	76	72	45	31
Saturated fat	4	35	55	
kJ/g	17.5	24.1		

IMMUNOBLOTTING

For evaluation of protein expression and activation of signal transduction pathways, the hypothalami of anesthetized rats were excised and immediately homogenized in solubilization buffer at 4°C [1% Triton X-100, 100 mM Tris–HCl (pH 7.4), 100 mM sodium pyrophosphate, 100 mM sodium fluoride, 10 mM EDTA, 10 mM sodium orthovanadate, 2.0 mM PMSF, and 0.1 mg aprotinin/ml] with a Polytron PTA 20S generator (model PT 10/35; Brinkmann Instruments, Westbury, NY). Insoluble material was removed by centrifugation for 40 min at 11,000 rpm in a 70 Ti rotor (Beckman) at 4°C. The protein concentration of the supernatants was determined by the Bradford dye method. Aliquots of the resulting supernatants containing 0.2 mg of protein extracts were separated by SDS–PAGE, transferred to nitrocellulose membranes and blotted with antibodies. Specific bands were detected by chemiluminescence and capture was performed with a Syngene GBox (Imgen Technologies, Alexandria, VA).

REAL-TIME PCR

The expressions of hypothalamic neurotransmitter mRNAs were measured in hypothalamus obtained from rats treated icv according to the protocols described above. Intron-skipping primers were obtained from Applied Biosystems (Carlsbad, CA). Glyceraldehyde-3-phosphate dehydrogenase primers were used as a control. Real-time PCR analysis of gene expression was performed with an ABI Prism 7500 sequence detection system (Applied Biosystems). The optimal concentration of cDNA and primers, as well as the maximum efficiency of amplification, were obtained through seven-point, threefold dilution curve analysis for each gene. Each PCR contained 3.0 ng of reverse-transcribed RNA, 200 nM of each specific primer, TaqMan™ (Applied Biosystems), and RNase free water in a final volume of 10 μl. Real-time data were analyzed using the Sequence Detector System 1.7 (Applied Biosystems).

MEASUREMENT OF SERUM BLOOD LEPTIN CONCENTRATION

The leptin content of serum blood was determined with enzyme immunoassay system from Millipore (Cat.#: EZRL-83K; Kit lot#: 1907400) in according to manufacturer's instructions.

OXYGEN CONSUMPTION/CARBON DIOXIDE PRODUCTION AND RESPIRATORY EXCHANGE RATIO DETERMINATION

Oxygen consumption/carbon dioxide production and respiratory exchange ratio (RER) were measured in fed animals through a computer-controlled, open circuit calorimeter system LE405 Gas Analyzer (Panlab—Harvard Apparatus, Holliston, MA). Rats were

singly housed in clear respiratory chambers and room air was passed through chambers at a flow rate of 0.8 L/min. The air flow within each chamber was monitored by a sensor Air Supply and Switching (Panlab–Harvard Apparatus). Gas sensors were calibrated prior to the onset of experiments with primary gas standards containing known concentrations of O_2, CO_2, and N_2 (Air Liquid, Sao Paulo, Brazil). The analyses were performed in triplicate of 6 min for each chamber. Therefore, each rat was evaluated for 18 min. Outdoor air reference values were sampled after every four measurements. Sample air was sequentially passed through O_2 and CO_2 sensors for determination of O_2 and CO_2 content, from which measures of oxygen consumption (VO_2) and carbon dioxide production (VCO_2) were estimated. The VO_2 and VCO_2 were calculated by Metabolism 2.2v software and expressed in $ml\,h^{-1}\,g^{-1}$, based on Withers equation and the RER was calculated using VCO_2/VO_2.

IMMUNOFLUORESCENCE STAINING

For histological evaluation, hypothalamic tissue samples were fixed in 10% formaldehyde and processed routinely for embedding in paraffin block. The samples were submitted to dehydration (alcohol at 70%, 80%, 90%, 95%, and absolute) being diaphanized by immersion in xylol and embedded in paraffin. Hydrated (alcohol at absolute, 95%, 90%, 80%, and 70%) 5.0 μm paraffin sections were processed for immunofluorescence staining. The expressions of NDMA and hypothalamic neurotransmitters were analyzed. The images were obtained using a Confocal Laser Microscopy (LSM510, Zeiss, New York, NY). Analysis and documentation of results were performed using a Leica FW 4500 B microscope.

STATISTICAL ANALYSIS

Mean ± SE values obtained from the experiments were compared utilizing Student's *t*-test for paired samples or by repeat-measure analysis of variance (one-way or two-way analysis of variance) followed by post hoc analysis of significance (Tukey test) when appropriate. A $P < 0.05$ was accepted as statistically significant.

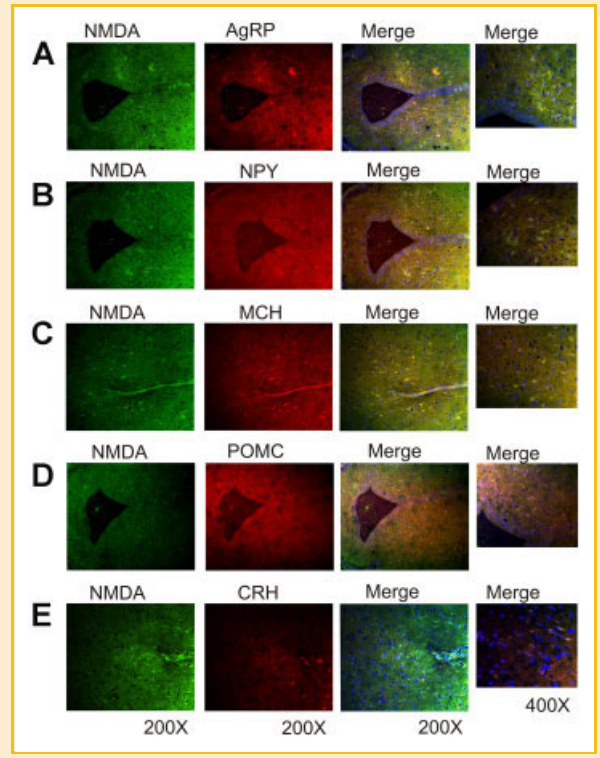

Fig. 1. Cellular distribution of NMDA receptors in the hypothalamus of rats. Five μm sections of hypothalamic specimens obtained from male Wistar rats were stained using an anti-NMDA receptor antibody in parallel with anti-AgRP (A), anti-NPY (B), anti-POMC (C), anti-MCH (D), or anti-CRH (E) primary antibodies. FITC- (for NMDA) and rodhamine- (for the remaining neurotransmitters) conjugated secondary antibodies were used. Nuclear staining was obtained with DAPI. In all assays, sections obtained from the anterior, intermediate, and posterior hypothalamus were evaluated. Panels are representative of three independent assays for each pair of antibodies. [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/jcb]

RESULTS

NMDA IS EXPRESSED IN SEVERAL SUBPOPULATIONS OF NEURONS IN THE HYPOTHALAMUS

Double staining immunofluorescence assays were employed to determine the distribution of NMDA receptors in hypothalamic neurons of rats. In the arcuate nucleus NMDA co-localized with AgRP (Fig. 1A), NPY (Fig. 1B), and POMC (Fig. 1C). In the lateral hypothalamus only MCH neurons expressed NMDA (Fig. 2A), while in the paraventricular hypothalamus only CRH neurons expressed NMDA (Fig. 2B). In orexin and TRH neurons, no expression of NMDA was detected (not shown).

GLUTAMATE MODULATES NEUROTRANSMITTER EXPRESSION IN THE HYPOTHALAMUS

Lean and obese rats were icv cannulated and treated for 5 days with glutamate or glutamate plus AG490. In lean rats, the effects of glutamate were discrete, leading to an increased expression of NMDA2B (Fig. 2A), which was accompanied by a reduction of NPY (Fig. 2B), POMC (Fig. 2D), and orexin (Fig. 2F). No changes in the expression of AgRP (Fig. 2C), CART (Fig. 2E), MCH (Fig. 2G), CRH (Fig. 2H), and TRH (Fig. 2I) were induced by glutamate. The simultaneous treatment with AG490 inhibited the effect of glutamate only on the expressions of NPY and POMC. In obese rats, glutamate promoted increases of expression of NMDA2B (Fig. 3A), NPY (Fig. 3B), POMC (Fig. 3D), CART (Fig. 3E), orexin (Fig. 3F), MCH (Fig. 3G), CRH (Fig. 3H), and TRH (Fig. 3I), and reduction of AgRP (Fig. 3C), only. Simultaneous treatment with AG490 was capable of completely inhibiting the effect of glutamate on all of the neurotransmitters.

ICV GLUTAMATE REDUCES BODY MASS THROUGH A MECHANISM DEPENDENT ON THE REDUCTION OF FOOD INTAKE

In lean rats, glutamate produced a significant reduction of food intake (Fig. 4A) which resulted in a reduction of body mass (Fig. 4B). This was not accompanied by changes in oxygen consumption/carbon dioxide production and respiratory quotient (Fig. 4C–E), but was paralleled by a reduction of spontaneous activity (Fig. 4F). The simultaneous treatment with AG490 was not sufficient to revert the

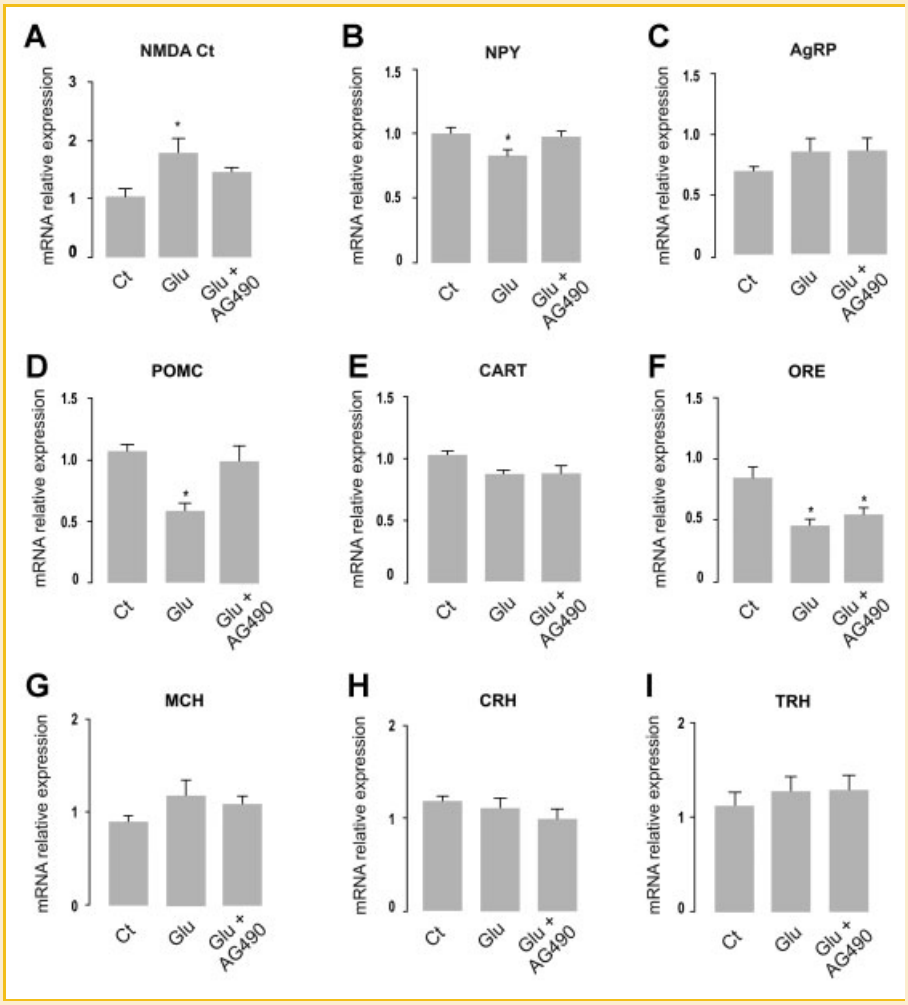

Fig. 2. Effects of glutamate and JAK2 inhibition on NMDA and hypothalamic neurotransmitter expression in lean rats. Icv cannulated lean rats were treated twice a day for 5 days with saline (2.0 μl) (C_t), glutamate (2.0 μl, 30 nM) (Glu), or glutamate + AG490 (2.0 μl, 30 nM, and 10 nM, respectively) (Glu + AG490) and, on the sixth day, hypothalami were obtained for RNA preparation for real-time PCR for NMDA2B (A), NPY (B), AgRP (C), POMC (D), CART (E), orexin (F), MCH (G), CRH (H), and TRH (I). In all experiments, n = 5, *<0.05 versus C_t.

effects of glutamate on food intake (Fig. 4A), body mass (Fig. 4B), and spontaneous activity (Fig. 4F). Similarly, in obese rats, glutamate produced a reduction of food intake (Fig. 5A) and a reduction of body mass (Fig. 5B). As in the lean rats, glutamate produced no changes in oxygen consumption/carbon dioxide production and respiratory quotient (Fig. 5C–E), but led to a significant reduction of spontaneous activity (Fig. 5F). However, in the obese rats, the treatment with AG490 resulted in a reversal of the glutamate-induced reduction of food intake (Fig. 5A).

ICV GLUTAMATE INDUCES THE TYROSINE PHOSPHORYLATION OF JAK2 INDEPENDENTLY OF CHANGES IN BLOOD LEPTIN LEVELS

Because some of the most remarkable effects of glutamate in the hypothalamus were inhibited by AG490, we determined the effect of glutamate on the molecular activation of JAK2, and also AKT and ERK. As depicted in Figure 6A–C, glutamate was capable, on a dose-dependent fashion, to induce the tyrosine phosphorylation of JAK2 (Fig. 6A), but not the serine phosphorylation of AKT (Fig. 6B) nor the tyrosine phosphorylation of ERK (Fig. 6C). These effects were not dependent on the blood levels of leptin, since glutamate induced no changes in the mRNA expression of leptin in the adipose tissue, nor in the blood levels of the hormone (not shown).

DISCUSSION

Glutamate is the most important excitatory neurotransmitter in the mammalian brain [Monaghan et al., 1989]. In the hypothalamus, it acts through three distinct ionotropic receptor subtypes, NMDA, AMPA, and KA, to exert site-specific effects on food intake and energy expenditure [Meister, 2007; Stanley et al., 2011].

In a recent study, we observed that the expression of the NMDA2B subunit of the NMDA receptor is increased in the hypothalamus of rodents exposed to two environmental conditions known to increase food intake and thermogenesis, that is, exposure to cold and high-fat

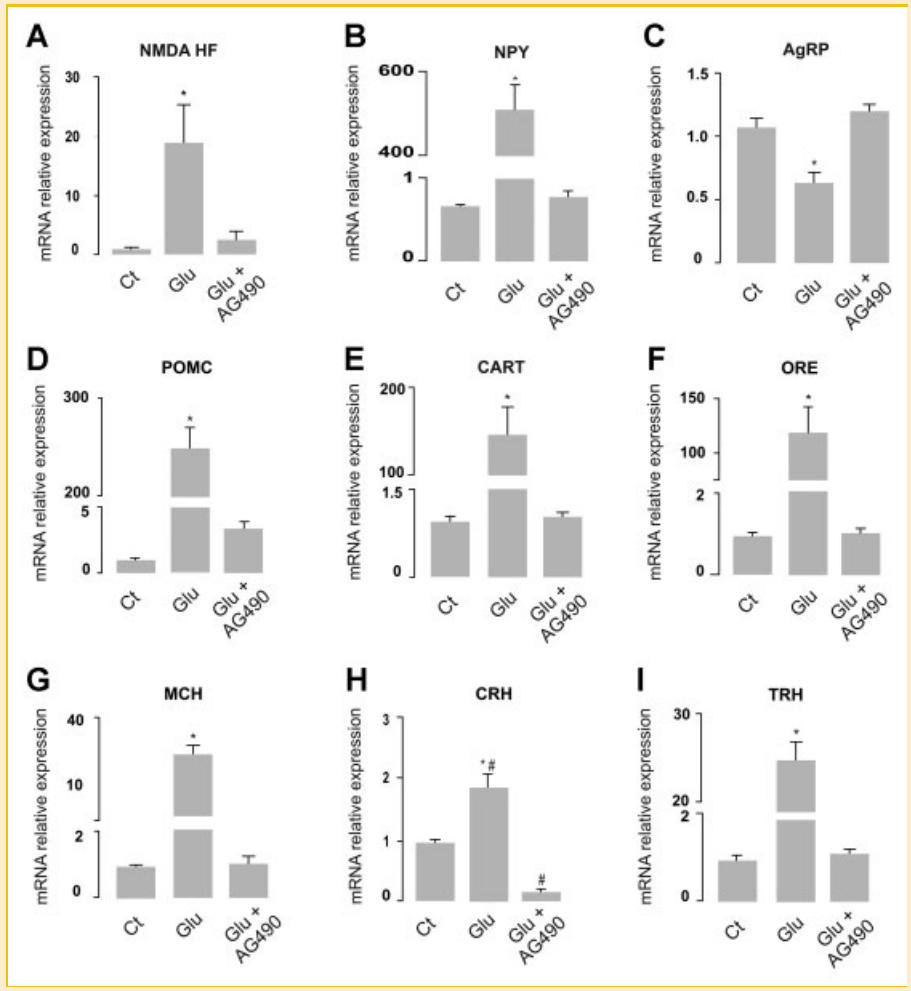

Fig. 3. Effects of glutamate and JAK2 inhibition on NMDA and hypothalamic neurotransmitter expression in obese rats. Icv cannulated obese rats were treated twice a day for 5 days with saline (2.0 μl) (C_t), glutamate (2.0 μl, 30 nM) (Glu), or glutamate + AG490 (2.0 μl, 30 nM, and 10 nM, respectively) (Glu + AG490) and, on the sixth day, hypothalami were obtained for RNA preparation for real-time PCR for NMDA2B (A), NPY (B), AgRP (C), POMC (D), CART (E), orexin (F), MCH (G), CRH (H), and TRH (I). In all experiments, n = 5, *<0.05 versus C_t.

feeding [De Souza et al., 2008]. Under either condition, the control of feeding elicited by hormonal inputs, particularly insulin and leptin, is impaired [Torsoni et al., 2003; De Souza et al., 2008; Velloso and Schwartz, 2011], and defining mechanisms capable of reverting such impairment may provide novel potential targets for the treatment of obesity.

The main intracellular pathway transducing the leptin signal in the hypothalamus depends on the activation of the tyrosine kinase JAK2 [Sahu, 2004]. As a consequence of a cross-talk with the PI3K signaling system, JAK2 modulates not only neurotransmitter expression but also neurotransmitter release, through the regulation of neuronal depolarization [Carvalheira et al., 2001; Bjorbaek and Kahn, 2004]. Therefore, we decided to evaluate if the control of feeding elicited by glutamate would be modulated by JAK2, providing a connection between the rapid effects of glutamate and the more robust effects of leptin.

First, we evaluated the distribution of the NMDA receptor in all hypothalamic nuclei known to play important roles in the control of energy homeostasis in the body. The presence of glutamatergic innervations in NPY and POMC neurons was previously reported [Kiss et al., 2005]. Here we showed that NMDA is expressed in AgRP, NPY, POMC, MCH, and CRH neurons of the arcuate, lateral, and paraventricular nuclei of the hypothalamus. This is in pace with the fact that glutamate exerts distinct actions on feeding depending on the site of injection [Stanley et al., 2011]. It is of particular relevance the series of studies performed by Stanley et al. [2011] exploring the mechanisms by which glutamate increases food intake when acting directly in the lateral hypothalamus.

As our main interest was to investigate an eventual connection between the actions of glutamate and elements belonging to the leptin signaling system, we decided to treat rats with glutamate through a cannula placed in the lateral ventricle. This site is in close anatomical relation with the hypothalamus, and is frequently used in experimentation aimed at studding feeding and thermogenesis. Injection of hormones and drugs through a cannula placed in this site provides a reproducible access to hypothalamic regions involved in the control of these functions [Milanski et al., 2009; Moraes et al., 2009].

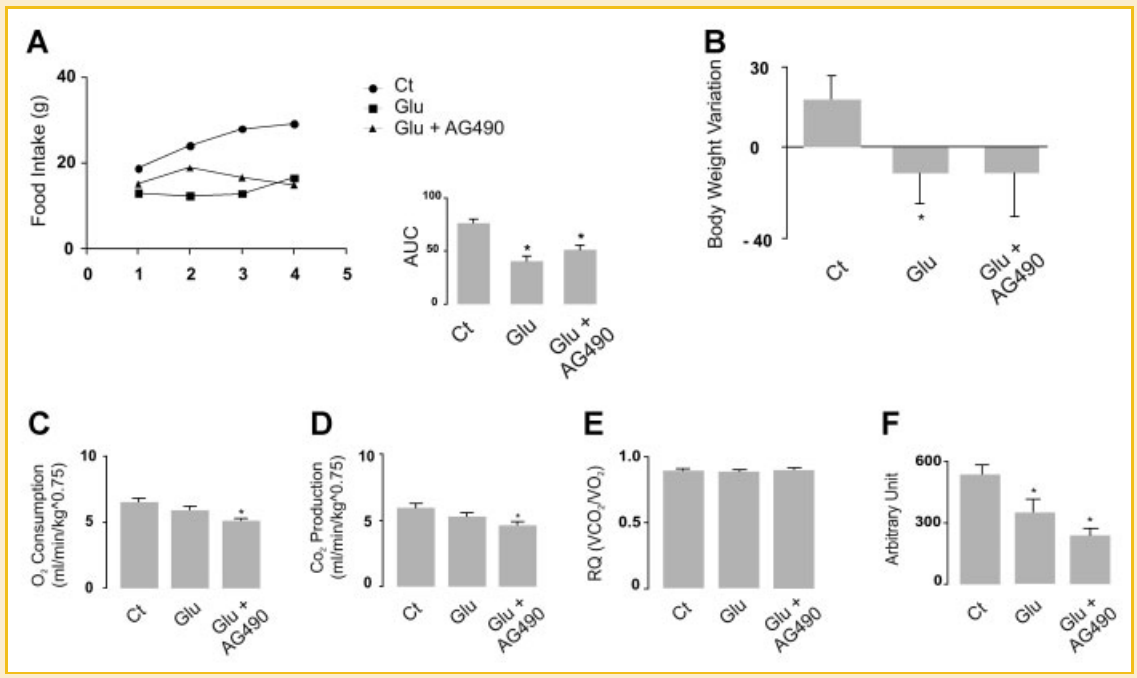

Fig. 4. Effects of glutamate and JAK2 inhibition on metabolic parameters of lean rats. Icv cannulated lean rats were treated twice a day for 5 days with saline (2.0 μl) (C_t), glutamate (2.0 μl, 30 nM) (Glu), or glutamate + AG490 (2.0 μl, 30 nM, and 10 nM, respectively) (Glu + AG490). During the 4 initial days food intake was measured (A) and cumulative intake is presented in the inset (A). Body mass variation during the experimental period was calculated (B). On the fifth day indirect calorimetry was performed to obtain oxygen consumption (C), carbon dioxide production (D), and respiratory quotient (RQ) (E). Also, on the fifth day, spontaneous activity was measured (F). In all experiments n = 5, *<0.05 versus C_t.

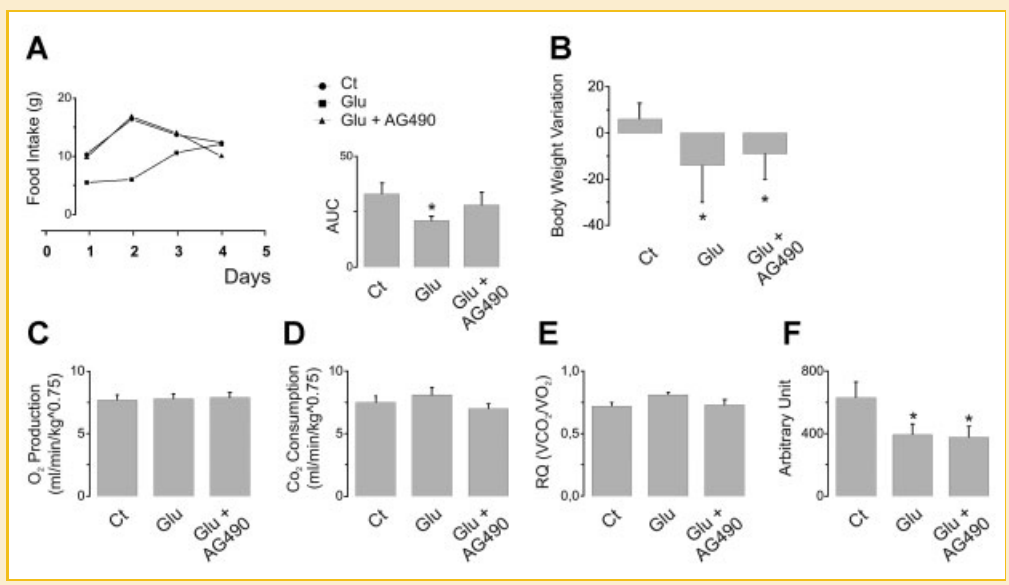

Fig. 5. Effects of glutamate and JAK2 inhibition on metabolic parameters of obese rats. Icv cannulated obese rats were treated twice a day for 5 days with saline (2.0 μl) (C_t), glutamate (2.0 μl, 30 nM) (Glu), or glutamate + AG490 (2.0 μl, 30 nM, and 10 nM, respectively) (Glu + AG490). During the 4 initial days food intake was measured (A) and cumulative intake is presented in the inset (A). Body mass variation during the experimental period was calculated (B). On the fifth day indirect calorimetry was performed to obtain oxygen consumption (C), carbon dioxide production (D), and respiratory quotient (RQ) (E). Also, on the fifth day, spontaneous activity was measured (F). In all experiments n = 5, *<0.05 versus C_t.

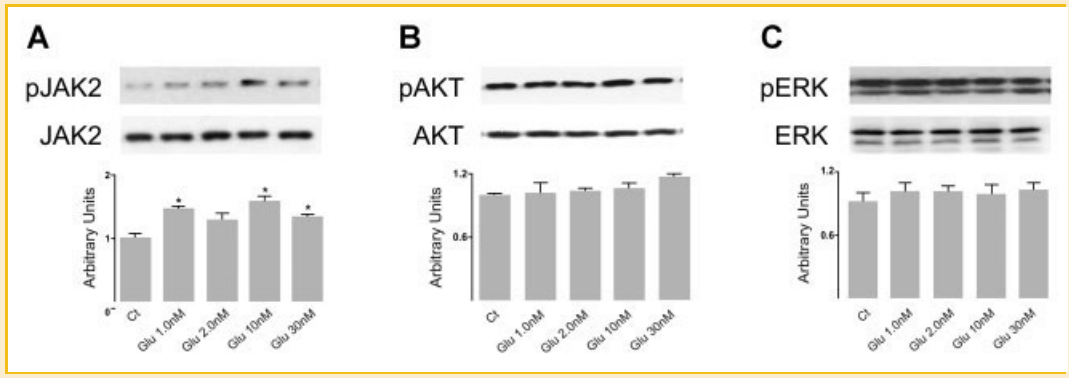

Fig. 6. Effects of glutamate on signal transduction. Icv cannulated lean rats were treated with a single dose of 2.0 μl saline (C_t) or 2.0 μl glutamate on the concentrations as depicted in the figure. After 10 min, hypothalami were obtained and total protein extracts were separated by SDS–PAGE, transferred to nitrocellulose membranes and blotted with anti-phospho JAK2 (A), phospho AKT (B), or phospho ERK (C) antibodies. Membranes were stripped and reblotted with respective non-phospho-specific antibodies. In all experiments $n = 5$, $^{*}<0.05$ versus C_t.

Icv glutamate treatment for 5 days led to an increase in the hypothalamic expression of the NMDA2B receptor subunit either in lean or obese rats. These effects were abolished by the inhibition of JAK2. Interestingly, in lean rats, the treatment with glutamate promoted a reduction in the expression of NPY, POMC, and orexin, while in obese rats, glutamate led to an increased expression of NPY, POMC, CART, orexin, MCH, TRH, and CRH and a reduction of AgRP, only. All the effects of glutamate, either in lean or obese rats, were reverted by the inhibition of JAK2, except for orexin in the lean group.

The effect of glutamate modulating the expression of a number of hypothalamic neurotransmitters provides further support for its broad role in the control of energy homeostasis [Stanley et al., 2011]. However it is interesting that, depending on the energy status of the animal, its effects on neurotransmitter expression can be completely shifted. Recent studies have revealed that in obese rodents and humans, the hypothalamus becomes dysfunctional due to the installation of an inflammatory process [Milanski et al., 2009; van de Sande-Lee et al., 2011; Velloso and Schwartz, 2011]. The expression/activation of inflammatory proteins in the hypothalamus targets leptin and insulin action which results in the loss of the coordinated control of neurotransmitter expression/release, thus, impacting on the neural control of feeding and thermogenesis. We suspect that the shift on the effect of glutamate on neurotransmitter expression when lean and obese rodents are compared is yet another consequence of the diet-induced hypothalamic inflammation/dysfunction. Interestingly, the inhibition of JAK2 was capable of completely reversing the effects of glutamate on almost all neurotransmitters evaluated, and this was independent of the diet type employed. It seems that, although hormone action though JAK2 is impaired in obesity, this kinase is still active when responding to glutamate.

In order to investigate the functional outcomes of glutamate action in hypothalamus, we evaluated food intake, body mass variation, indirect calorimetry, and spontaneous motility. Both in lean and obese rats, glutamate produced a reduction of food intake and body mass without affecting oxygen consumption/carbon dioxide production. In addition, glutamate icv was also capable of reducing spontaneous activity. Upon JAK2 inhibition, only the reduction of food intake in obese rats was reversed.

As a whole, this data suggest that the pleotropic effects of glutamate in the hypothalamus results from its isolated actions in distinct neuronal subpopulations. When all glutamate-responsive neurons of the hypothalamus are activated, the result is a reduction of food intake accompanied by reduction of spontaneous activity. In lean rats, this is associated with the regulation of fewer neurotransmitters and is not modulated by the inhibition of JAK2, while in obese rats, all the major neurotransmitters involved in the control of energy homeostasis are modulated and in all cases, the inhibition of JAK2 results in reversal of the phenomenon.

We suspect that, in lean rats, as the hormonal pathways controlling food intake and energy expenditure are intact, the effect of glutamate on JAK2 is restricted and the capacity of this amino acid to modulate neurotransmitter expression is restricted to a few neuronal subpopulations. Conversely, in obesity, as the hormonal pathways controlling energy homeostasis are impaired, the effect of glutamate on JAK2 and on neurotransmitter expression is enhanced.

In summary, this work shows that glutamate controls neurotransmitter expression in the hypothalamus and part of this effect depends on JAK2. In addition our results suggest that in obesity, glutamate can bypass the impaired signal transduction of leptin through JAK2, to promote a reduction of food intake.

ACKNOWLEDGMENTS

This work was supported by grants from Fundação de Amparo à Pesquisa do Estado de São Paulo. Mr. G. Ferraz and Mr. M. Souza provided valuable technical assistance. We thank Dr. N. Conran for editing the English grammar.

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