Amyloid-β peptide absence in short term effects on kinase activity of energy metabolism in mice hippocampus and cerebral cortex

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ABSTRACT
Considering that Alzheimer’s disease is a prevalent neurodegenerative disease worldwide, we investigated the activities of three key kinases: creatine kinase, pyruvate kinase and adenylate kinase in the hippocampus and cerebral cortex in Alzheimer’s disease model. Male adult Swiss mice received amyloid-β or saline. One day after, mice were treated with blank nanocapsules (17 ml/kg) or meloxicam-loaded nanocapsules (5 mg/kg) or free meloxicam (5 mg/kg). Treatments were performed on alternating days, until the end of the experimental protocol. In the fourteenth day, kinases activities were performed. Amyloid-β did not change the kinases activity in the hippocampus and cerebral cortex of mice. However, free meloxicam decrease the creatine kinase activity in mitochondrial-rich fraction in the group induced by amyloid-β, but for the cytosolic fraction, it has raised in the activity of pyruvate kinase activity in cerebral cortex. Further, meloxicam-loaded nanocapsules administration reduced adenylate kinase activity in the hippocampus of mice injected by amyloid-β. In conclusion we observed absence in short-term effects in kinases activities of energy metabolism in mice hippocampus and cerebral cortex using amyloid-β peptide model. These findings established the foundation to further study the kinases in phosphoryltransfer network changes observed in the brains of patients post-mortem with Alzheimer’s disease.

Key words: Alzheimer’s disease, nanoparticles, meloxicam, energetic metabolism, phosphoryltransfer network.

INTRODUCTION
Alzheimer’s disease (AD) is the most common form of dementia and cognitive impairment (Cai et al. 2012), (Garcez et al. 2015). AD is characterized by accumulations of amyloid-beta (aβ) peptide known as plaques and neurofibrillary tangles composed of the microtubule protein tau and synaptic and neuronal loss in several areas of the brain (Cai et al. 2012). Moreover, an essential feature of AD is implicated in synaptic dysfunction, dendritic spine loss, excitotoxicity and destabilization of neural networks that are considered major cellular...
mechanisms (Isono et al. 2013). Several researches have shown alterations in brain energy metabolism are associated with neurodegenerative disorders (Beal 1995, 2000), (Bubber et al. 2005), (Zahid et al. 2014). Abnormal hyperphosphorylation of tau have been associated with the activation of several kinases (Park et al. 2012). In fact, aβ-peptide aggregates, it generates reactive oxygen species that can induce membrane lipid peroxidation in neurons (Mattson et al. 2002). This fact causes in impairment function of membrane ion-motive ATPases and glucose transporter proteins, which, in turn, disrupts cellular ion homeostasis and energy metabolism (Mattson et al. 2002).

Previous reports have shown energy metabolism related enzymes were frequently altered in AD (Brooks et al. 2007), (Liang et al. 2008). The thiol-containing enzymes, as kinases, are crucial for brain energy metabolism and function, and their deficiency is associated to neurodegenerative diseases. Creatine kinase (CK), pyruvate kinase (PK), and adenylate kinase (AK), which are thiol-containing enzymes involved in the phosphoryl-transfer network, are critical for energy metabolism in almost all mammalian tissues (De Franceschi et al. 2013). CK is used as an indicator of various physiological abnormalities, such as the determination of brain damage. CK has been shown to have a lower activity in AD (David et al. 1998). Indeed, enzyme oxidation, such CK in cellular metabolism, has been involved in the neurodegeneration mechanism of AD brain (Castegna et al. 2002). Besides, creatine, a product of CK, is considered a neuroprotective agent in animal models of neurodegenerative diseases (Bortoluzzi et al. 2014).

Regarding to PK, this enzyme is crucial enzyme of glucose metabolism, and main pathway that provides energy for brain function (Gemelli et al. 2013). Pyruvate, an endogenous metabolite this pathway, can work as an anti-toxicity agent and it has been shown protective role in central nervous system neurons, protecting them against excitotoxic and metabolic insult (Bortoluzzi et al. 2014).

AK catalyzes the nucleotide phosphoryl exchange reaction maintain the consistent concentration and fixed ratio of adenine nucleotides. This is the major regulator of energetic, metabolic monitoring and cellular process in a living cell (Park et al. 2012). However, the role of AK expressed in the brain, especially in neurodegenerative disease, is not understood yet (Park et al. 2012). Moreover, the expression levels of AK markedly elevated in hippocampal neurons of AD patients and Tg2576 and APP-J20 AD mouse model and it has found AK expression increased in the cortical neurons after exposure to aβ (Park et al. 2012).

Several clinical studies indicated nonsteroidal anti-inflammatory drugs (NSAIDs) could reduce the prevalence of AD (Moore and O’Banion 2002), (Galimberti et al. 2003), (Townsend and Pratico 2005). Nevertheless, meloxicam is a NSAID that poorly crossed the blood–brain barrier (BBB), thereby limiting the use of this drug for treatment in neurodegenerative disorders (Carvey et al. 2009). In this way, our previous studies demonstrated meloxicam-loaded nanocapsules (M-NC) prevented AD induced by aβ in mice (Ianiski et al. 2012). Besides, Bernardi et al. (2012), using another type of NSAID, the indomethacin-loaded lipid-core nanocapsules, have shown strong evidence that neuroinflammation triggered negatively modulates in vitro and in vivo caused by aβ culminating in the amelioration of synaptic integrity, cell survival, and cognitive performance. Therefore, nanoparticles represent very promising drug-delivery systems for the prevention and treatment of various diseases (Khayata et al. 2012).

Considering that there are not publications on phosphoryltransfer network in AD model induced by aβ (25-35) in mice and AD is a prevalent neurodegenerative disease worldwide, we sought to investigate the involvement in activities of enzymes CK, AK and PK in the hippocampus and cerebral cortex of AD model by aβ (25-35) in mice, to evaluate in this model the ability to change these
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MATERIALS AND METHODS

CHEMICALS

aβ (fragment 25-35) was dissolved in sterile filtered water and aggregated by incubation at 37 °C for 4 days before use and was purchased from Sigma (St. Louis, MO, USA). aβ (fragment 25-35) is the most toxic (Vitvitsky et al. 2012). All other chemicals and solvents used were of analytical or pharmaceutical grade.

Suspensions of M-NC were prepared by interfacial deposition method of preformed polymer adapted from Fessi et al. (1989), at a concentration of 0.3 mg/ml. Organic phase was composed by meloxicam, poly-e-caprolactone, sorbitan monostearate, caprylic/capric triglyceride and acetone. Organic phase was added under magnetic stirring into an aqueous phase. Suspensions of blank nanocapsules (B-NC) were prepared using the same protocol of suspensions above cited for M-NC, however, without the presence of drug. For free meloxicam (M-F) solution, meloxicam was dissolved in sorbitan monostearate, polysorbate and water.

These nanocapsules were characterized using photon correlation spectroscopy. Samples were diluted in Milli-Q water (1:500) and the analysis was performed at 25 °C, using a Zetasizer® (Nan series, Malvern, UK). For encapsulation efficacy, it was used high performance liquid chromatography, showing around 98 %. Each sample was analyzed in triplicate. All parameters did not demonstrate significant difference. Physical-chemical analyses demonstrated that the particle diameter was 247 ± 9 nm and 212 ± 10 nm for M-NC and B-NC, respectively, and polydispersity index was 0.14 ± 0.02 for M-NC and 0.10 ± 0.01 for B-NC. The zeta-potential was -36.4 ± 4.4 mV for M-NC and -35.0 ± 2.5 mV for B-NC.

ANIMALS

In the present study, we used male Swiss mice (20–25 g) of 5 weeks old that were obtained from a local breeding colony. They were kept on a 12-12 h light/dark cycle in acclimatized room at constant temperature (22 ± 2 °C) and had free access to water and commercial chow (Guabi, RS, Brazil) containing 20.5 % protein (predominantly soybean supplemented with methionine), 54 % carbohydrate, 4.5 %, fiber 4 %, lipid 7 % ash and 10 % moisture. We applied strict ethical criteria in our study to minimize the pain and suffering. The animals were used according to the guidelines of the Committee on Care and Use of Laboratory Animals of the Franciscan University Center of Santa Maria, Brazil, under number 019/2012.

EXPERIMENTAL PROTOCOL

One day before initiating treatments, mice were randomly divided into two groups, where one group received aβ (fragment 25–35) aggregated form (3 nmol/3 µl/ per site, intracerebroventricular (i.c.v.)) (Ianiski et al. 2012). Other group received saline (3 µl/per site i.c.v.). I.c.v. infusion of aβ or vehicle (saline) was administered using a microsyringe with a 28-gauge stainless-steel needle 3.0 mm long (Hamilton) according to previous report (Haley and McCormick 1957). All animals were anesthetized with ketamine/xylazine (80/10 mg/kg, intraperitoneally). Mice exhibited normal behavior within 1 min after injection.

After this, each group was randomly divided into 3 groups of six animals each. One day after infusion aβ or saline, the treatments with B-NC, M-NC or M-F intragastrically (i.g.) via gavage were initiated. The treatments were performed each other day, until the end of the experimental protocol (Ianiski et al. 2012). The volume used for B-NC (17 ml/kg body weight) and equivalent dose of M-NC or M-F (5 mg/kg body weight) was chosen based on a previous study (Ianiski et al. 2012, 2016),
Mice belonging to αβ and Sham groups received the suspension containing B-NC. Animals of M-NC and M-NC induced by αβ groups received the suspension containing M-NC. Animals belonging to M-F and M-F induced by αβ groups were treated with suspension containing M-F. After fourteenth day of αβ (fragment 25–35) injection, mice were euthanized and hippocampus and cortex were removed for determination of CK, AK and PK activities (Figure 1).

**CK activity**

The creatine formed was estimated according to the colorimetric method of Hughes (1962). CK activity was assayed in the reaction mixture contained 65 mM Tris–HCl buffer, pH 7.5, 7 mM phosphocreatine, 9 mM MgSO₄, and 1 μg of protein (cytosolic or mitochondrial-rich fraction), in a final volume of 0.1 ml. After 10 min of pre-incubation at 37 °C, the reaction was started by the addition of 0.3 μmol of adenosine diphosphate (ADP). The reaction was stopped after 10 min by the addition of 1 μmol of p-hydroxymercuribenzoic acid. The color was developed by the addition of 0.1 ml 2 % a-naphthol and 0.1 ml 0.05 % diacetyl, in a final volume of 1 ml and the samples were read after 20 min at 540 nm in a spectrophotometer. Results were expressed as μmol creatine.min⁻¹.mg protein⁻¹.

**AK activity**

AK activity was measured with a coupled enzyme assay with hexokinase (HK) and glucose 6-phosphate dehydrogenase (G6PD), according to Dzeja et al. (1999). The reaction mixture contained 100 mM KCl, 20 mM HEPES, 20 mM glucose, 4 mM MgCl₂, 2 mM nicotinamide adenine dinucleotide phosphate (NADP⁺), 1 mM ethylenediamine tetraacetic acid (EDTA), 4.5 U/ml of HK, 2 U/ml of G6PD, and 1 μg of protein homogenate. The reaction was initiated by the addition of 2 mM ADP and the reduction of NADP⁺ and then was followed at 340 nm for 3 min in a spectrophotometer. The results were expressed in μmol adenosine triphosphate (ATP) formed min⁻¹.mg protein⁻¹.

**PK activity**

PK activity was assayed essentially as described by Leong et al. (1981). The incubation medium consisted of 0.1 M Tris/HCl buffer, pH 7.5, 10 mM MgCl₂, 0.16 mM NADH, 75 mM KCl, 5.0 mM
ADP, 7 U of L-lactate dehydrogenase, 0.1 % (v/v) Triton X-100, and 10 µl of supernatant, in a final volume of 0.5 ml. After 10 min of pre-incubation at 37 °C, the reaction was started by the addition of 1 mM phosphoenol pyruvate that was followed at 340 nm for 30 sec in a spectrophotometer. All assays were performed at 25 °C. Results were expressed as µmol pyruvate.min^{-1}.mg protein^{-1}.

**Protein**

Protein content of each tissue fraction of hippocampus and cerebral cortex was determined by the method of Lowry et al. (1951), using serum bovine albumin as the standard.

**Statistical Analysis**

Data are expressed as mean ± standard deviation (S.D.). Statistical analysis was performed using a one-way ANOVA followed by the Tukey’s test.

Values of p < 0.05 were considered statistically significant.

**RESULTS**

**CK Activity**

CK activities in mitochondrial-rich and cytosolic fraction did not show a significant differ between the groups (p > 0.05) in mice hippocampus (Figures 2a and 3a).

CK activity in mitochondrial-rich fraction in cerebral cortex of mice demonstrated a significant decrease in M-F induced by aβ group, when compared to the Sham group (p < 0.05) (Figure 2b). However, aβ, M-NC or M-F alone did not change CK activity in mitochondrial-rich fraction in the cerebral cortex of mice (Figure 2b). Furthermore, CK activity in cytosolic fraction in cerebral cortex of mice, did not show a significant differ between the groups (p > 0.05) (Figure 3b).

![Figure 2 - aβ, meloxicam-loaded nanocapsules (M-NC) and free meloxicam (M-F) on mitochondrial-rich fraction creatine kinase activity. Suspension containing blank nanocapsules (Sham). (a) µmol creatine.min^{-1}.mg protein^{-1} in hippocampus mice. (b) µmol creatine.min^{-1}.mg protein^{-1} in cerebral cortex mice. Data represent mean ± standard deviation, n =6/group. (*) p < 0.05 as compared to the sham group.](image-url)
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AK ACTIVITY

AK activity in the hippocampus demonstrated a significant decrease in M-NC induced by aβ group, when compared to the Sham group (p < 0.01) (Figure 4a). However, aβ, M-NC or M-F alone did not change the AK activity in mice hippocampus.

Besides AK activity in cortex of mice, did not show significant difference between the groups (p > 0.05) (Figure 4b).

PK ACTIVITY

PK activity in cytosolic fraction did not show significant difference between the groups (p > 0.05) in the hippocampus of mice (Figure 5a).

PK activity in cytosolic fraction of cerebral cortex in mice demonstrated that M-F significantly increased in PK activity, when compared to the Sham group (p < 0.001) (Figure 5b). Nonetheless, aβ and M-NC alone did not change the PK activity in cytosolic fraction in the cerebral cortex of mice (Figure 5b).

DISCUSSION

In the present study, we have assessed, for the first time, the effects of three kinase activities CK, AK and PK of energy metabolism and treatments with B-NC, M-F and M-NC, in hippocampus and cerebral cortex of AD model induced by aβ (25-35) in mice. Evidence suggests a critical role in changes in brain energy metabolism in the pathogenesis of cognitive disorders (Kapogiannis and Mattson 2011). However, studies about the involvement of these enzymes in the AD diseases are limited.

Surprisingly, we observed absence in short-term effects in kinases activities of energy metabolism in mice hippocampus and cerebral cortex using aβ peptide (25-35) model. Importantly, cerebral
cortex and hippocampus were chosen based on previous studies that demonstrated alterations on these structures in patients with AD (David et al. 1998), (Aksenov et al. 2000), (Clark et al. 2000), (Balderas et al. 2008). Moreover, hippocampus is a cerebral structure essential for memory processing (Clark et al. 2000), (Balderas et al. 2008), (Bernardi et al. 2012). Some studies suggest that altered energy metabolism plays roles in the pathogenesis of AD (Behl 1999), seeing that CK is involved in high-energy production, thus affecting ATP synthesis. On the other hand, in this study, there was no difference of cytosolic and mitochondrial CK activity in the two brain structures. Researches have reported reduction on the CK activity in the cerebral cortex of humans (age between 70 to 85 years old) with AD in post-morten assays (Aksenov et al. 2000). Limitations must be taken into account when interpreting the results of this study. First, this AD model induced by aβ (25-35) is not a clinical representation of most human brain injuries. Thereby, it is known that animal models do not totally reproduce human diseases in their complexity. Furthermore, the substances known to accumulate in human disease may be studied individually or associated against adequate controls (Bortoluzzi et al. 2014).

The deposition of aβ in mice could be used as an animal model for the study of AD because it is a well-characterized model (Choi et al. 2014), (Pedrós et al. 2014). In fact, several studies have shown that AD is induced by injections of aβ (25-35) into the brains of mice and it causes various biological effects (Tsunekawa et al. 2008), (Ianiski et al. 2012),

Figure 4 - αβ, meloxicam-loaded nanocapsules (M-NC) and free meloxicam (M-F) on cytosolic fraction adenylate kinase activity. Suspension containing blank nanocapsules (Sham). (a) μmol ATP formed min⁻¹.mg protein⁻¹ in hippocampus mice. (b) μmol ATP formed min⁻¹.mg protein⁻¹ in cerebral cortex mice. Data represent mean ± standard deviation, n =5/group. (**) p < 0.01 as compared to the sham group.

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Therefore, αβ (25-35) injected animals are useful models for understanding various problems of AD, such as the pathogenesis and progression of changes, and for evaluating new therapeutic agents for AD (Tsunekawa et al. 2008), (Choi et al. 2014). We believe that the time interval of αβ injection in our research was not enough to cause changes, and consequently it was not possible to see the change in CK, AK and PK activities. Despite the peptide αβ be considered a toxic substance (Tsunekawa et al. 2008), (Ianiski et al. 2012), (Choi et al. 2014), (Detrait et al. 2014), and, for this model is already reported that the administration of the same cause learning and memory deficits, neuronal loss, intense cellular accumulation and chromatolysis and oxidative stress was increased in mice (Ianiski et al. 2012), definitely this experimental design did not affect these three important kinases of brain energy metabolism.

For mice cerebral cortex, we observed a significant decrease in CK activity on the M-F induced by αβ group in mitochondrial-rich fraction. A study has shown that various compounds may affect mitochondrial bioenergetics (Moreland 1994). In fact, it is known that compounds as meloxicam are uncoupled (Mahmud et al. 1996), promote the increase in permeability of the inner mitochondrial membrane to protons. Thus, there is electrons transfer and, consequently, does not occur synthesis of ATP (Tzagoloff 1982), (Moreland 1994). Moreover, a decrease in CK activity is one of the biochemical markers of the central nervous system cell damage in age-related neurodegenerative diseases, including AD (Hensley et al. 1995), (Aksenova et al.
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The decrease on the CK activity and content in brain of AD correlates well with the hallmarks of neurodegeneration in severely affected regions (Hensley et al. 1995).

Furthermore, in cytosolic fraction of mouse cerebral cortex, it was observed that M-F significantly increased the PK activity. An in vitro study demonstrated that αβ reduced the PK activity in erythrocytes of old rats, but not in erythrocytes of young rats, demonstrating that the age interferes in the effects of glycolytic and antioxidant enzymes in AD (Tikhonova et al. 2014). Nevertheless, we noted a significant decrease in M-NC induced by αβ group on the AK activity in mice hippocampus.

The coupling of spatially separated intracellular ATP-producing and ATP-consuming processes is fundamental to the bioenergetics of living organisms and important to maintain a broad range of cellular activities (Dzeja and Terzic 2003). However, spatially arranged intracellular enzymatic networks are necessitated, because it seems to be insufficient to fulfill all cellular energetic needs (Dzeja et al. 2000). Thereby to support high-energy phosphoryltransfer and signal communication between ATP-generating and ATP-consuming/ATP-sensing processes, these networks need to be catalyzed by CK, AK and enzymes of the glycolysis pathway, in especial PK (Dzeja et al. 1998), (Dzeja and Terzic 2003), (Wallimann et al. 1992). For maintaining the cellular energy homeostasis is indispensable the network between the enzymatic capacities, isoform distribution and the dynamics of phosphoryl flux through the integrated phosphoryltransfer systems tightly correlate with cellular functions, thus indicating a critical role of such networks in efficient energy transfer and distribution (Dzeja and Terzic 2003).

The ATP formation rate calculated from the cerebral metabolic rates of oxidized glucose and oxygen is reduced in the brains greater than 50 % of advanced AD patients (Hoyer 1992). A diminished activity of a single enzyme of the phosphoryltransfer network is rather well tolerated. However, a decrease in the activity of two or more enzymes of this network may compromise the brain development (Pietz et al. 2003), (Rojas et al. 2012). In addition, results of observational studies and trials might differ because different NSAIDs have different effects on AD (Gasparini et al. 2004).

Previously, it was reported that nanocapsules showed effective delivery of drugs to the brain and to inflamed tissues (Frozza et al. 2010), (Bernardi et al. 2012), (Ianiski et al. 2012, 2016), (Villalba et al. 2014). In this way, some characteristics of nanoparticulated systems, such as the carrier size, the polymer type, as well as their surface features, might induce steric stabilization of nanoparticles, inhibiting protein binding and increasing the blood circulation time (Brioschi et al. 2007), (Bernardi et al. 2009), (Kreuter 2014), (Voigt et al. 2014). Moreover, nanocapsules can accumulate in inflamed tissues due to the greater microvascular permeability in those sites (Bernardi et al. 2009).

The purpose of this study was to investigate the role of the enzymes CK, AK and PK in hippocampus and cerebral cortex of AD model induced by αβ (25-35) in mice and to determine whether the broad range of impairments that are observed in brain of AD could be, at least in part, reproduced and used in this animal model. As in previous studies, we used similar or slightly different mouse models of AD induced by αβ where there were alterations in behaviors and biochemical analysis (Ianiski et al. 2012), (Detrait et al. 2014). Surprisingly, we observed absence in short term effects in kinase activity of energy metabolism in mice hippocampus and cerebral cortex using αβ peptide (25-35) model. This demonstrates that AD model induced by αβ (25-35) in the short term in mice is not a determining factor to reproduce the enzymatic changes of CK, AK and PK observed in the brains of patient’s post-mortem with AD. In summary, these findings established the foundation to further study the kinases in phosphoryltransfer
network changes observed in the brains of patients post-mortem with AD.

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RESUMO

Considerando que a doença de Alzheimer é uma doença neurodegenerativa prevalente em todo o mundo, buscou-se investigar o envolvimento da atividade de três quinases: creatinaquinase, piruvatoquinase e adenilatoquinase no hipocampo e no córtex cerebral em um modelo da doença de Alzheimer. Os camundongos Swiss, machos, adultos, receberam β-amiloide ou solução salina. Um dia depois, os camundongos foram tratados com nanocápsulas vazias (17 ml/kg) ou nanocápsulas contendo meloxicam (5 mg/kg) ou meloxicam livre (5 mg/kg). Os tratamentos foram realizados em dias alternados, até o final do protocolo experimental. No décimo quarto dia, as atividades das quinases foram avaliadas. A β-amiloide não alterou a atividade das quinases no hipocampo e no córtex cerebral dos camundongos. No entanto, o meloxicam livre diminuiu a atividade da creatinaquinase na fração mitocondrial no grupo induzido pela β-amiloide, mas na fração citósólica observou-se um aumento na atividade da piruvatoquinase no córtex cerebral. Além disso, o tratamento com as nanocápsulas contendo meloxicam diminuiu a atividade da adenilatoquinase no hipocampo dos camundongos induzidos pela β-amiloide. Em conclusão, observamos ausência de efeitos de curto prazo nas atividades das quinases do metabolismo energético no hipocampo e no córtex cerebral dos camundongos, no modelo induzido com o peptídeo amiloide-β. Esses resultados estabeleceram uma base para um estudo mais aprofundado das quinases em alterações na rede de fosforiltransferência observadas nos cérebros de pacientes pós-morte com a doença de Alzheimer.

Palavras-chave: doença de Alzheimer, nanopartículas, meloxicam, metabolismo energético, rede de fosforiltransferência.

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