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Research Report

Enhancement of lactate metabolism in the basolateral amygdala by physical and psychological stress: Role of benzodiazepine receptors

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Abstract

Lactate is considered to play a significant role in energy metabolism and reflect neural activity in the brain. Using in vivo microdialysis technique, we measured extracellular lactate concentrations in the basolateral amygdaloid nucleus (BLA) of rats under electric footshock or psychological stress. We also attempted to determine whether the stress-induced changes of extracellular lactate concentrations in the BLA are attenuated by diazepam, an agonist at benzodiazepine receptors, and whether FG7142, an inverse agonist at benzodiazepine receptors, have a facilitative effect on energy metabolism in the BLA. Both footshock and psychological stress led to an increase in extracellular lactate concentrations in the BLA. Similar increment of extracellular lactate levels was observed by administration of FG7142. Pretreatment with diazepam attenuated the ability of FG7142, as well as physical or psychological burden, to increase lactate levels in the BLA. These results indicate that a variety of stressors enhances energy metabolism in the BLA, and suggest that some stress-induced changes in energy metabolism are regulated by benzodiazepine receptors.

Theme: Disorders of the nervous system
Topic: Neuropsychiatric disorders

Keywords: Footshock stress; Psychological stress; Lactate; Brain energy metabolism; Basolateral amygdaloid nucleus; Benzodiazepine receptor; Anxiety; Panic disorder

1. Introduction

Glucose has long been considered to be the substrate for neural energy metabolism in the brain. However, in vitro studies using hippocampal brain slices have shown that lactate supports the normal synaptic function in the face of glucose deprivation [12,38]. Moreover, even in the presence of glucose, brain tissues have been demonstrated to use lactate as an energy substrate in vitro [19–21,39]. On the other hand, extracellular lactate in the brain, as monitored with intracerebral microdialysis, has been shown to be of local origin and not influenced by plasma levels [18]. Local increases in extracellular lactate concentrations have been observed after neural stimulation (e.g., electroconvulsive shock, local administration of kainic acid) [16,17]. Local administration of tetrodotoxin (TTX), thought to block the electrical activity of neurons by inhibiting Na^+ channels [27], does not affect the basal levels of extracellular lactate concentrations, while TTX attenuates the electroconvulsive shock [17] or immobilization stress [45] induced increment of extracellular lactate levels. Moreover, inhibition of glycolysis by addition of 2-deoxyglucose to the dialysis perfusate causes an immediate decrease in lactate levels in extracellular fluid [17]. These observations suggest that extracellular lactate levels reflect the neural activity and glucose metabolism in the brain [17]. More recently, it was suggested that lactate is produced by astrocytes and released

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in the extracellular space to form a pool readily available for neurons in case of high energy demands [30].

Various types of stressors (e.g., tail pinch, immobilization) have been shown to increase extracellular lactate concentrations in the medial prefrontal cortex, hippocampus, and the striatum in the rat [5,7,16,37,40]. However, only a few studies have focused on cerebral blood flow or energy metabolism in the amygdala during exposure to stress. Thus, conditioned fear stress has been shown to increase local cerebral blood flow in the amygdala of rats, as measured by quantitative autoradiography with ^{14}C-labeled iodoantipyrine as a ligand [22]. We previously reported that immobilization stress increases extracellular lactate concentrations in the BLA, which is attenuated by stimulation of benzodiazepine receptors [45]. The amygdala has been implicated in the production of behaviors associated with fear and anxiety. Information from all sensory modalities reaches the amygdala via projections from the cortex and a variety of subcortical structures, most notably the thalamus and parabrachial complex, which converge on the basolateral amygdaloid complex, i.e., the lateral and basolateral subdivisions [23]. Sensory and cognitive information is relayed to adjacent amygdala subdivisions and other forebrain areas that ultimately mediate the physical and psychological manifestations of anxiety [4]. Various neurotransmitters are released in larger quantities in the BLA during emotional arousal than control conditions. These include noradrenaline [34,41,47], serotonin [2,14], dopamine [10,46,49], and acetylcholine [25].

Benzodiazepines are among the most widely prescribed therapeutic agents in the psychiatric practice and have anxiolytic, anticonvulsant, sedative/hypnotic, and amnestic properties. The amygdala, especially lateral and basolateral nuclei, is responsible for the manifestation of anxiolytic effects of benzodiazepines and expression of anxiety itself [4,23,43]. The pharmacological effects of benzodiazepines are mediated through allosteric modulation of $GABA_A$ receptors. Benzodiazepine-binding site resides on the alpha subunit of these receptors. Recent studies using genetically modified mice found that the alpha1 subunit of $GABA_A$ receptors may mediate the sedative effects [35], while the alpha2 subunit may be responsible for the anxiolytic effects of benzodiazepines [24]. Immunohistochemical localization of alpha1 subunit shows moderate staining in the BLA, while alpha2 subunits are localized heavily in the BLA [8].

In this study, we used a microdialysis technique coupled with an enzymatic/fluorometric detector for the measurement of lactate, according to the method of Korf et al. [15] with minor modifications [45]. We were particularly interested in the effect of electric footshock or psychological stress on extracellular lactate concentrations in the BLA of rats [46]. Especially, we sought to determine whether physical or emotional stress affects energy metabolism in the BLA. To examine the role of benzodiazepine receptors in the lactate metabolism, we also attempted to determine whether the stress-induced changes of extracellular lactate concentrations are attenuated by diazepam, an agonist at these receptors, and whether administration of FG7142 (*N*-methyl-beta-carboline-3-carboxamide), an inverse agonist at these receptors, has a facilitative effect on extracellular lactate release in the BLA.

2. Results

2.1. Basal extracellular lactate concentrations

The basal concentration of lactate in the dialysate was 42.8 ± 1.4 μmol/l (mean ± S.E.M.). No group differences in basal extracellular lactate levels were found ($F(6,35) = 2.05$, NS).

2.2. Effect of FG7142 on extracellular lactate concentrations

FG7142 (10 mg/kg, i.p.) caused a significant increase in lactate levels at 0–60 min after the injection. They reached the maximum level (129.4 ± 3.7% of the basal levels) after 8 min of injection and gradually decreased. In the rats pretreated with diazepam, extracellular lactate concentrations reached the maximum (111.4 ± 2.5% of basal levels) after 4 min of FG7142 injection and immediately returned to the basal levels. Repeated measures ANOVA revealed a significant effect of diazepam treatment ($F(1,30) = 15.07$, $P = 0.003$) and an interaction between Status (saline, diazepam) and time ($F(1,30) = 3.68$, $P < 0.0001$) on the FG7142-induced increase in extracellular lactate concentrations (Fig. 1).

2.3. Effect of stress on lactate levels

Footshock and psychological stress caused a significant increase in lactate levels at 0–60 min and 2–42 min, respectively, after the start of stress exposure. Extracellular lactate concentrations increased to 167.4 ± 4.8% of the mean baseline value at 10 min after the start of footshock stress and

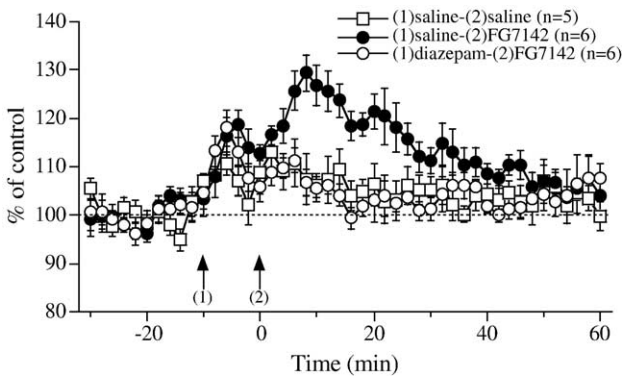

Fig. 1. Time course of the effects of diazepam on the FG7142-induced lactate increment. Diazepam or saline was injected (arrow 1) for 10 min, followed by administration of FG7142 (arrow 2). Saline + saline (open square), saline + FG7142 (closed circle), diazepam + FG7142 (open circle). Arrows indicate the point of drug injection. Data are mean ± SEM.

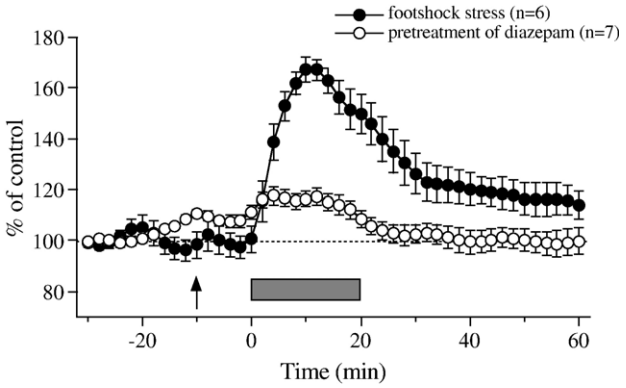

Fig. 2. Time course of the effects of diazepam on the footshock stress-induced lactate increment. Diazepam (open circle) or saline (closed circle) was injected 10 min before footshock stress. For each time point, means are expressed as percent of the respective basal lactate levels (average of ten samples collected before the first administration of drugs). The arrow indicates the point of drug injection. Footshock stress is indicated by the solid bars. Data are mean ± SEM.

then gradually decreased. They did not return to the basal levels for 60 min after the start of footshock stress (Fig. 2). Psychological stress caused an increase in the dialysate lactate levels; they reached 115.0 ± 1.7% of the mean baseline value at 4 min after the start of exposure to psychological stress, and remained so until 20 min (Fig. 3).

2.4. Effect of diazepam on the stress-induced lactate increase

Repeated measures ANOVA demonstrated that pretreatment of rats with diazepam (1.0 mg/kg, i.p.) attenuated the footshock or psychological stress-induced lactate increment ($F(1,30) = 17.07$, $P = 0.002$ and $F(1,30) = 5.97$, $P = 0.035$ respectively). Interactions between Status and time were significant (footshock stress $F(1,30) = 11.67$, $P < 0.001$; psychological stress $F(1,30) = 3.08$, $P < 0.0001$). Lactate levels increased transiently (about 110% at 2–8 min) and immediately returned to the baseline level in the rats pretreated with diazepam (Figs. 2 and 3).

3. Discussion

This study provides the first evidence that physical or psychological stress, as well as administration of FG7142, increases extracellular lactate concentrations in the BLA. Moreover, the ability of these manipulations to elevate lactate concentrations was attenuated by pretreatment with diazepam. The magnitude of footshock stress-induced increase in extracellular lactate concentrations was about threefold of that of lactate elevations induced by psychological stress.

Until recently, glucose has been regarded as the principal metabolic substrate in the mature brain (for example, see [3]). In the conventional view, production of lactate in the brain during increased neural activity is considered to occur when the rate of glycolysis transiently exceeds that oxidative metabolism (e.g., [33]). On the other hand, the astrocyte-neuron lactate shuttle hypothesis has been proposed [30,31,44]. According to this hypothesis, lactate is produced in an activity-dependent and glutamate-mediated manner by astrocytes; lactate produced by astrocytes is released to the extracellular space and taken up by active neurons to fuel neuronal oxidative metabolism [30,32]. Especially, immobilization stress has been reported to activate glycogenolysis and lactate export from glial cells [6]. In the event of acute neuronal activation, the brain tissue has been found to shift immediately to depending on a significant energy supply by lactate [9]. Therefore, extracellular lactate concentrations may vary according to the energy demand of neurons and thus represent some components of the neural activity. On the basis of this, our findings indicate that acute stress, such as footshock or psychological stress, increases neural activity and energy demand of neurons in the BLA.

We previously reported that immobilization stress led to an increase in extracellular lactate levels in the BLA of rats, and that pretreatment with diazepam attenuated the lactate increase, which was blocked by coadministration of flumazenil, an antagonist at benzodiazepine receptors [45]. In the current study, both footshock and psychological stress induced an increase in lactate levels, which was attenuated by pretreatment with diazepam. These observations suggest that extracellular lactate levels in the BLA of rats reflect exposure to physical or emotional burden, part of which is regulated by benzodiazepine receptors. Moreover, administration of FG7142 led to an increase in extracellular lactate levels in the BLA, which was attenuated by pretreatment with diazepam. FG7142 is an anxiogenic inverse agonist at benzodiazepine receptors, and was reported to enhance local cerebral glucose utilization in the limbic structures at doses ranging from 5 to 10 mg/kg [1]. These findings support the speculation that the tonic energy demands of neurons in the BLA was regulated, at least in part, by benzodiazepine receptors.

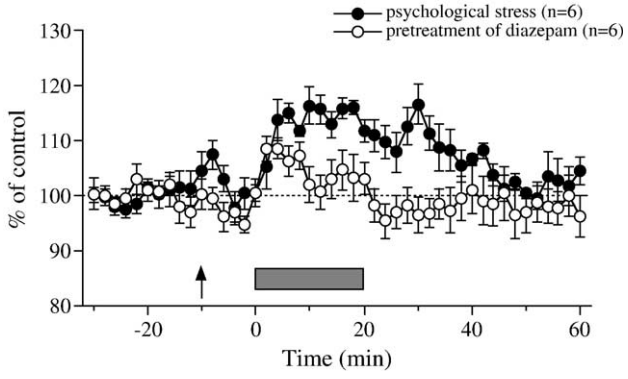

Fig. 3. Time course of the effects of diazepam on psychological stress-induced lactate increment. Diazepam (open circle) or saline (closed circle) was injected 10 min before exposure to psychological stress. For each time point, means are expressed as percent of the respective basal lactate levels (average of ten samples collected before the first administration of drugs). The arrow indicates the point of drug injection. Psychological stress is indicated by the solid bars. Data are mean ± SEM.

According to the astrocyte-neuron lactate shuttle hypothesis, glycogen in astrocytes is specifically mobilized through neurotransmitter-mediated actions (especially noradrenaline) by axons as a consequence of action potential propagation and serve to produce lactate for use by neighboring neurons [30]. Physical (immobilization stress) or emotional (psychological stress) burden has been reported to enhance noradrenaline release in the amygdala [42]. Therefore, glycogen breakdown in astrocytes could occur after exposure to stress, followed by an increase in lactate release in the extracellular space by astrocytes. This speculation is supported by the facts that local perfusion of TTX into the BLA does not affect the basal levels of the extracellular lactate concentration and attenuates the immobilization stress-induced increment of lactate [45]. Diazepam has been shown to attenuate the stress-induced increase in noradrenaline release in the amygdala [42]. Therefore, it is possible that lactate release in the extracellular space was attenuated through receptor-mediated actions of noradrenaline. Second, acute application of diazepam enhances $GABA_A$ receptor-mediated inhibitory postsynaptic currents (Kang-Park et al., 2004) and attenuates the demand for lactate on neighboring astrocytes as an energy substrate. It is speculated that signaling through benzodiazepines receptors may regulate extracellular lactate concentrations in the BLA.

Stress- or FG7142-indeced lactate increments in the BLA were attenuated by pretreatment with systemic administration of diazepam. It is not conclusive whether these effects of benzodiazepines are entirely attributable to local actions in the amygdala. However, as the BLA has a high concentration of benzodiazepine receptors [26], and is one of the important sites of action of anxiolytic drugs [28], the stress- or FG7142-induced increase in extracellular lactate concentrations may be regulated, at least in part, by the actions of diazepam on benzodiazepine receptors in the BLA. It would be worthwhile to further study whether the present data are specific for the BLA, and whether a similar response occurs in the other brain regions, e.g., different amygdala nuclei, prefrontal cortex, and hippocampus.

In conclusion, we have found that pharmacological stressors, as well as physical or emotional burden, enhanced lactate metabolism in the BLA of rats, which was reversed by stimulation of benzodiazepine receptors. These results provide an insight into the mechanisms underlying stress-related energy metabolism in the BLA. In addition, monitoring with intracerebral microdialysis may provide a valid method to assess brain energy metabolism in vivo.

4. Experimental procedure

4.1. Animals

Adult male Wistar rats (Japan SLC, Inc. Japan) weighing 280–300 g were housed 4–5 in a standard cage at 24 ± 2 °C under a 12-h light (7:00–19:00 h)–12-h dark cycle. All experiments were reviewed and approved by the Committee of Animal Research, Toyama Medical and Pharmaceutical University.

4.2. Surgery

The rats were anesthetized with pentobarbital sodium (Nembutal, Abbott Laboratories, USA) (40 mg/kg, i.p.) and were mounted on a stereotaxic apparatus. A dialysis probe (molecular weight cutoff 10,000; 200 μm in outer diameter) was implanted into the left BLA according to the atlas of Paxinos and Watson [29] and was secured with skull screws and dental acrylate. The exposed tip length of the probe was 1.5 mm. Coordinates were A −2.8 mm, L 5.2 mm, V 9.6 mm from the bregma. Following the surgery, the rats were housed in individual cages with free access to food and water.

4.3. Experimental conditions

Forty-two to forty-eight hours after surgery, the dialysis experiment was carried out on the freely moving rats. Artificial CSF (consisting of 147 mmol/l NaCl, 3 mmol/l KCl, 1.2 mmol/l $CaCl_2$, 1.2 mmol/l $MgSO_4$, 0.4 mmol/l NaH_2PO_2, pH 7.40) was perfused at a rate of 5.0 μl/min into the dialysis probe. The dialysates were mixed on-line with an enzyme solution containing L-lactate dehydrogenase and NAD^+ in a T-tube. The enzyme solution consisted of 5.0 μg/ml LDH (L-Malate: NAD oxidoreductase, E.C.1.1.1.27; isolated from pig heart, specific activity ca.300 U/mg; Roche Diagnostics GmbH, Mannheim, Germany) and 0.5 mmol/l NAD^+ (Roche Diagnostics GmbH, Mannheim, Germany) in a carbonate buffer (62.5 mmol/l, adjusted to pH 9.4 with NaOH). The enzyme solution was pumped using a Model EP-50 microinfusion pump (Eicom, Kyoto, Japan) at the flow rate of 20 μl/min. The mixture from the T-tube was passed for 20-min reaction before reaching a fluorometer equipped with a 12 μl flow-cell (SHIMAZU RF-530, Kyoto, Japan). During transport to the fluorometer, lactate was enzymatically oxidized and the fluorescence of the nicotinamide adenosine dinucleotide diphosphate formed (NADH) was continuously measured with excitation at 340 nm and emission at 450 nm. A standard solution of 100 μmol/l lactate was used for calibration.

4.4. In vivo experimental procedure

FG7142 was obtained from Sigma-Aldrich Co. (St. Louis, USA). Diazepam (1.0 mg/kg i.p., in diazepam solution, 5 mg/ ml, Takeda Chemical Industries, Ltd., Osaka, Japan), or saline as a vehicle, was administered at 10 min before the injection of FG7142 (10.0 mg/kg i.p., Sigma-Aldrich Co.) or the start of the stress. Following intravenous injection of FG7142 (5 or 10 mg/kg), rats appeared very agitated and attempted to escape from

experimental materials (restraint cylinders) and also commenced to gnaw. Moreover, intravenous injection of FG7142 (10 mg/kg) increased local cerebral glucose utilization (LCGU) [1]. In control experiments, the same volume of vehicle (saline) was given. At the end of the experimental sessions, all rats were deeply anesthetized with pentobarbital sodium and sacrificed by decapitation. The position of dialysis probes was verified macroscopically for all rats.

4.5. Administration of stress

Footshock or psychological stress was administered using a plastic communication box according to the method in our previous study [46]. In the footshock experiment, each footshock session consisted of a scramble shock of 0.5 mA for 5 s administered every 30 s for 20 min. In the psychological stress experiment, a scramble footshock was delivered through the floor grid at an intensity of 2.0 mA for a duration of 10 s with 30-s intervals for 20 min. The intensity of a scramble footshock was necessary to show struggling, vocalization, defecating, urinating, and jumping of rats, according to previous studies[11,13,36,46,48]. A plastic plate was placed on the grid floor of the psychological stress compartment to prevent the rat from receiving an electric shock. The rat in the psychological stress compartment was never shocked but was exposed to such stressful environment as observing struggling, vocalization, defecating, urinating, and jumping of the other electrically shocked rats in the surrounding chambers.

4.6. Presentation of the results and statistics

The average of the extracellular lactate concentrations during the period preceding psychological stress, administration of diazepam, or saline (ten measurements performed every 2 min) was used as a control value (100%). Basal concentrations of the lactate in the dialysate were compared by one-factor analysis of variance (ANOVA). The effect of FG7142 administration or stress on extracellular lactate concentrations at each time point was analyzed using paired t test. Between-group comparisons were performed by two-way repeated measures ANOVA. Pretreatment status (Status = saline or diazepam) was treated as between-group variable, and time was treated as repeated measures variable. A probability (P) of less than 0.05 was considered to be significant.

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