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ORGINAL PAPER

Neonatal Handling, Sweet Food Ingestion and Ectonucleotidase Activities in Nucleus Accumbens at Different Ages

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Abstract Neonatal handled rats ingest more sweet food than non-handled ones, but it was documented only after puberty. Here, we studied the purinergic system in the nucleus accumbens, a possible target for the alteration in the preference for palatable food. We measured the ATP, ADP and AMP hydrolysis mediated by ectonucleotidases in synaptosomes of the nucleus accumbens in periadolescent and adult rats from different neonatal environments: non-handled and handled (10 min/day, first 10 days of life). Before adolescence, we found a decreased ingestion of sweet food in the neonatally handled group, with no effect on ATP, ADP or AMP hydrolysis. In adults, we found a greater ingestion of sweet food in the neonatally handled group, with no effect on ATPase or ADPase activities, but a decreased AMP hydrolysis. The nucleus accumbens is a site of intensive interaction between the adenosinergic and dopaminergic systems. Therefore, adenosine may modulate accumbens' dopamine neurotransmission differently in neonatally handled rats.

Keywords Neonatal handling · Adenosine · Nucleus accumbens · Dopamine · ATPase–ADPase activities; 5′-nucleotidase activity

Introduction

Mother–infant interactions promote an adequate environment for neurodevelopment [1–2] and are very important for the establishment of a healthy adult life [3]. Precocious interventions in this relationship may lead to persistent alteration of several aspects, including behavioral [4], neurochemical [5] and neuroendocrine responses to stress [6].

Previous studies from our laboratory have shown that neonatal handling, a brief and apparently innocuous separation from the mother in the neonatal period, can lead to increased sweet food consumption in adulthood, without differences in standard lab chow ingestion [7]. Since this alteration occurs only with palatable food, it appears that hedonic mechanisms must be involved. These rats also present a faster and consistent search for sweetened snacks, although they are less prone to place conditioning related to this food (Silveira et al., unpublished results).

Sucrose licking is known to increase accumbens dopamine [8], and a quantitative relationship has been demonstrated between the concentration-dependent rewarding effect of orosensory stimulation by sucrose during eating and the overflow of dopamine in the nucleus accumbens [9]. In addition, repeated access to sucrose increases dopamine turnover in the accumbens [10].

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The co-expression of adenosine A_{2A} and dopamine D2 receptors in the same GABAergic medium spiny neurons is a characteristic feature of the nucleus accumbens [11]. These receptors appear to present synergy for protein kinase A (PKA) signaling in response to ethanol [12], and there have been suggestions that adenosine in the nucleus accumbens plays a significant role in activity reward, reinforcement and drug-seeking behavior [13, 14].

Adenine nucleotides are thought to be an important potential source of extracellular adenosine [15, 16]. These nucleotides are hydrolyzed by an extracellular cascade of enzymes, which includes ecto-ATPase (NTPDase2, CD39L1, EC 3.6.1.3], ATP diphosphohydrolase (NTPDase1, CD39, ecto-apyrase, EC 3.6.1.5) and ecto-5′-nucleotidase (lymphocyte surface protein, CD73, EC 3.1.3.5) [17, 18]. In the central and peripheral nervous systems, ATP is hydrolyzed to adenosine by the conjugated action of NTPDases and 5′-nucleotidase [19, 20]. These ectonucleotidases, acting together, control the availability of ligands (ATP, ADP, AMP and adenosine) for both nucleotide and nucleoside receptors and, consequently, the duration and extent of receptor activation.

Previous findings have suggested that the neonatal handling-induced increase in sweet food consumption may be observed just in adulthood, and not in younger rats. At the neurochemical level, it is important to correlate changes in behavior with neurobiological modifications, such as altered neurotransmission. In this paper, we aimed to verify the sweet food ingestion in neonatally handled rats before and after puberty and to determine ATP, ADP and AMP hydrolysis in synaptosomes from the nucleus accumbens in these two ages.

Experimental procedure

Subjects

Pregnant Wistar rats bred at our own animal facility were randomly selected. They were housed alone in home cages made of Plexiglas (65 × 25 × 15 cm) with the floor covered with sawdust and were maintained in a controlled environment until offspring: lights on between 07:00 and 19:00 h, temperature of 22 ± 2°C, cage cleaning once a week, food and water provided. All litters were culled within 24 h to eight pups and were maintained intact unless for handling procedures, which were carried out between 10:00 and 15:00 h.

Weaning was on postnatal day 21. Two male pups were used per litter per experiment. Rats were housed four to five per cage. Fifty-two experimental male rats were used in the different experiments, derived from 21 different litters. Rats had free access to food (standard lab rat chow) and water, except during the period when the behavioral tasks were applied. Tasks were performed between 13:00 and 16:00 h.

All animal treatments were approved by the Institutional Ethical Committee (Ethical Committee, UFRGS, #200270) and followed the recommendations of the International Council for Laboratory Animal Science (ICLAS).

Neonatal handling model [7]

Non-handled group—Pups were left undisturbed with the dam until weaning. It was stated on the cage that these animals should not be touched, not even for cage cleaning. Dirty sawdust was carefully removed from one side of the cage, without disturbing the mother and the nest, and replaced by clean sawdust at that side by the principal researcher. Handled—Pups were removed from their home cage and were placed into a clean cage lined with clean paper towel, inside an incubator at 34°C. After 10 min, pups were returned to their dams. This procedure was carried out for the first 10 days of life, after which pups were left undisturbed until the 21st day of life.

Sweet food ingestion

For sweet food ingestion, animals were placed in a lightened rectangular box (40 × 15 × 20 cm) with floor and side walls made of wood and a glass ceiling. Ten Froot loops (Kellogg's®—pellets of wheat and cornstarch and sucrose) were placed in one extremity of the box. Each animal was submitted to four exposures, of 3 min each, on different days, and the total number of ingested pellets across the days was measured. This procedure was performed under food restriction (80% of habitual ingestion of standard lab chow). A protocol was established so that when the animals ate part of the Froot loops (e.g., 1/3 or 1/4), this fraction was considered. This protocol was started when the animals reached 23 days of age or at 60 days of age.

Animal preparation and subcellular fraction

Animals were sacrificed by decapitation and their brains were removed and placed in ice-cold isolation medium (320 mM sucrose, 5 mM HEPES, pH 7.5, and 0.1 mM EDTA) and were cut coronally. Nucleus accumbens of both hemispheres were immediately dissected on ice and gently homogenized 1:10 (w:v) in ice-cold isolation medium with a motor-driven Teflon-glass homogenizer. In adults, accumbens from two animals were pooled. In the case of young animals, we used three animals for each pooled sample. The synaptosomal fraction was isolated as

previously described [21]. Briefly, 0.5 ml of crude mitochondrial fraction was mixed with 4 ml of an 8.5% Percoll solution and layered onto an isosmotic Percoll/sucrose discontinuous gradient (10/16%). The synaptosomes that banded at the 10/16% Percoll interface were collected with wide tip disposable plastic transfer pipettes. Synaptosomal fractions were washed twice at 15,000 × *g* for 20 min with the same ice-cold medium to remove the contaminating Percoll and the synaptosome pellet was resuspended. The material was prepared fresh daily and maintained at 0–4°C throughout preparation.

Enzyme assays

The reaction medium used to assay the ATP and ADP hydrolysis was essentially as described previously [22]. The reaction medium contained 5.0 mM KCl, 1.5 mM $CaCl_2$, 0.1 mM EDTA, 10 mM glucose, 225 mM sucrose and 45 mM Tris–HCl buffer, pH 8.0, in a final volume of 200 µl. The synaptosome preparation (10 µg protein) was added to the reaction mixture and preincubated for 10 min at 37°C. The reaction was initiated by the addition of ATP or ADP to a final concentration of 1 mM and was stopped after 30 min by the addition of 200 µl 10% trichloroacetic acid. The released inorganic phosphate (Pi) was measured as previously described [23].

The reaction medium used to assay the 5′-nucleotidase activity (AMP hydrolysis) contained 10 mM $MgCl_2$, 0.1 M Tris–HCl, pH 7.0 and 0.15 M sucrose in a final volume of 200 µl [24]. The synaptosome preparation (10–20 µg protein) was preincubated for 10 min at 37°C. The reaction was initiated by the addition of AMP to a final concentration of 1 mM and was stopped after 60 min by the addition of 200 µl 10% trichloroacetic acid; the released Pi was measured as previously described [23]. In all enzyme assays, incubation times and protein concentrations were chosen in order to ensure the linearity of the reactions [22, 24]. Other conditions, such as medium reaction, pH and cation concentrations were used to assure the optimal enzyme activities [22, 24]. Controls with the addition of the enzyme preparation after addition of trichloroacetic acid were used to correct non-enzymatic hydrolysis of the substrates. All samples were run in triplicate. The mean specific activity obtained for control animals in each experimental day was considered 100% for comparisons. Protein was measured by the Coomassie Blue method, using bovine serum albumin as standard [25].

Statistical analysis

Data were expressed as mean ± standard error of the mean, and were analyzed by Student's *t*-test or by Two-way ANOVA [26]. The significance level was accepted as different when the *p* value was equal or less than 0.05. Sample size varies in each experiment and is shown individually in the results section.

Results

Sweet food consumption

When exposed to sweet food between 23 and 26 days of age, neonatally handled rats ate less sweet food than non-handled rats [Student's *t*-test, $t(22) = 2.215$, $p = 0.037$, $n = 9$–15/group]. At adulthood, neonatally handled rats ate more sweet food than the control group [Student's *t*-test, $t(21) = -2.069$, $p = 0.05$, $n = 11$–12/group]. A Two-way ANOVA demonstrated an effect of the age, in which rats eat more as they get older [$F(1, 46) = 40.303$, $p = 0.005$]. There is also interaction between group and time, demonstrating that neonatally handled rats change their pattern of sweet food consumption as the time pass by, while the non-handled group keep the same pattern [$F(1, 46) = 35.970$, $p = 0.007$]. Figure 1 displays these results.

Ectonucleotidases activities

ATPase activity is not different between groups at 21 days of age [Student's *t*-test, $t(8) = 0.727$, $p = 0.488$, $n = 5$/group], nor at 60 days of age [Student's *t*-test, $t(16) = -0.36$, $p = 0.721$, $n = 8$–9/group]. The same lack of effect occurs with ADPase activity at 21 days of age [Student's *t*-test, $t(8) = 1.310$, $p = 0.226$] and 60 days of age [Student's *t*-test, $t(15) = -0.86$, $p = 0.403$]. AMP hydrolysis is

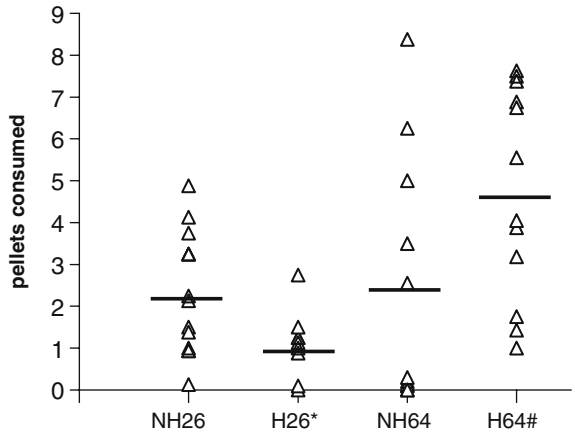

Fig. 1 Sweet food consumption in neonatally handled rats before and after puberty. Data are expressed for each rat for the total number of pellets consumed during the four sessions. The black bar indicates the mean consumption in each group. *Decreased consumption in relation to non-handled rats (Student's *t*-test, $p = 0.037$). # Increased consumption in relation to non-handled rats (Student's *t*-test, $p = 0.05$)

not different between groups at 21 days of age [Student's t-test, $t(8) = 0.184$, $p = 0.859$], but it is decreased by 14.5% in neonatally handled rats at 60 days of age [Student's t-test, $t(15) = 2.11$, $p = 0.05$]. Figure 2 demonstrates these results.

Body weight

Mean body weight at 21 days was 45.09 + 11.90 g for non-handled rats and 41.08 + 2.40 g for handled rats. In adulthood, the mean body weight was 319.93 + 21.94 g for non-handled rats and 297.92 + 74.87 g for the handled group. There was no statistical difference between the groups concerning body weight in the different ages (Student's t-test, $p > 0.05$).

Discussion

In this paper, we verified that the alteration in sweet food consumption in adulthood of neonatally handled rats is accompanied by a decrease in 5′-nucleotidase activity in the nucleus accumbens. The reaction catalyzed by 5′-nucleotidase is the rate-limiting step in the extracellular pathway from ATP to adenosine (for a review, see [27]). Since AMP hydrolysis is the major source of extracelullar adenosine [15, 16], we suggest that animals that suffered neonatal handling present a decrease in extracellular adenosine levels in this structure when adults.

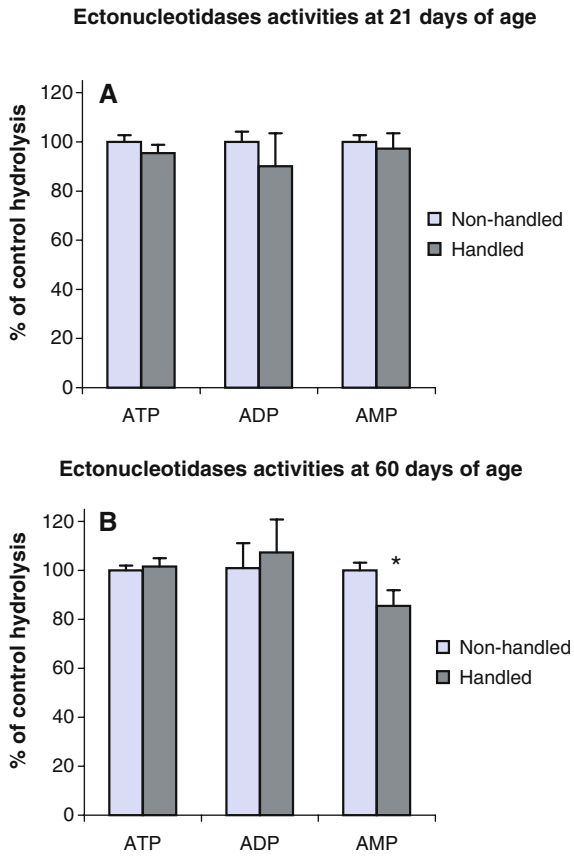

Fig. 2 ATPase, ADPase and 5′-nucleotidase activities in the nucleus accumbens of young (A) and adult (B) neonatally handled rats. Data are expressed as mean ± SEM for % of activity in control animals. *There is a decrease in 5′-nucleotidase activity in adulthood in neonatally handled rats (Student's t-test, $p = 0.015$)

On the other hand, there is a decrease in sweet food consumption in the neonatally handled rats before adolescence. This effect could possibly be related to an increased serotonin content found in several structures (hypothalamus, hippocampus and striatum) in neonatally handled animals at this age, but not in adulthood [28], since serotonin is a known neurotransmitter linked to decreased appetite [29]. Another possible explanation would be a higher dopamine metabolism rate in the hypothalamus, which was found in neonatally handled rats during puberty [28]. This finding was associated with decreased sweetened solution ingestion in other studies [30, 31]. At the same time, neonatally handled rats are not different from controls regarding ATP, ADP and AMP hydrolysis.

Adenosine modulates dopamine and other neurotransmitters, such as glutamate [32, 33], in the nucleus accumbens. This modulation could be involved in the present behavioral findings [34]. Some studies demonstrate that a functional dopamine/adenosine interaction in the nucleus accumbens is necessary to induce the reinforcing effects of rewards [35], and that adenosine is involved in the sweet taste perception [36, 37]. Therefore, since neonatally handled rats show a decreased adenosine function at this site in adulthood, this could mean that these animals present a lower perception of the rewarding effects of sweet food, due to a blunted dopaminergic tonus in the accumbens, in such a way that they may increase consumption of palatable food trying to reach a higher activation of this circuit.

If this is so, the question arises as to why these animals switch from a state of decreased ingestion in puberty to an increased consumption in adulthood? A similar fashion of shifting is found with respect to responses to stress: early handling induces long-lasting behavioral and stress-related hormonal changes, although these are not stable throughout life, being detectable mostly after puberty [38].

Interestingly, hetero-oligomerization of adenosine and dopamine receptors (A2A/D2) may be involved in the psychostimulant-induced behavioral sensitization [39], and neonatally handled rats are less prone to develop such a state of sensitization [40]. In addition, this early-life intervention is also associated with a reduced D3 dopamine receptor binding and mRNA levels in the nucleus accumbens-shell [40], and there is evidence of functional A2A/D3 heteromeric complexes [41]. Therefore, the decreased 5′-nucleotidase activity observed in this study and,

consequently, a decrease in adenosine levels, may help to explain other behavioral and neurochemical findings presented by neonatally handled rats.

Some neurochemical alterations occur during periadolescence in the nucleus accumbens [42–44]. There have been descriptions of changes in nucleotide-metabolizing enzymes in the central nervous system as a function of the developmental stage [45–47]. Since neonatally handled rats present a diminished level of 5′-nucleotidase in adulthood, these effects could be related to the behavioral effects observed. It is known that adenosine modulation occurs only after puberty [48]; therefore, the effects of dopamine modulation by adenosine (and the effects on feeding behavior) are possibly observed only in adulthood.

Although there were no differences concerning body weight, it remains to be determined if the preference for palatable food in the neonatally handled group is related to an increased vulnerability to obesity. As already demonstrated [7], these animals eat the same amount of lab chow than do controls. The increased consumption is specific for palatable food, and only a continuous exposure to this type of food could answer the question above, which is out of the scope of this study. In addition, it is possible that differences in body weight appear between the groups in older rats.

In summary, neonatal handling leads to persistent behavioral and neurochemical alterations in adulthood, which appear only after puberty. An increased ingestion of sweet food, if associated with a differential accumbens function, may mean an increased vulnerability to compulsive eating [49] and its consequences, such as obesity and its correlates.

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