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Local cerebral glucose utilization in rats exposed to an enriched environment: A comparison to impoverishment

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ABSTRACT

Environmental enrichment and environmental impoverishment have been shown to differentially alter brain function. Here, we investigate the effects of enrichment vs. impoverishment on cerebral use of glucose in rodents. Rats were housed from postnatal day 28 to day 58 in either a socially and environmentally enriched environment or an impoverished environment devoid of other rats or environmental stimuli. Locomotor activity was measured at the end of the enrichment/impoverishment period. Following the duration of the exposure to these environments, cerebral metabolic rate of glucose utilization was determined using quantitative 2-[^{14}C]deoxyglucose autoradiography in 37 brain regions in the cerebral cortex, forebrain, brain stem and thalamus. There were no differences in locomotor activity between the conditions. The nucleus accumbens core and shell had significantly higher rates of glucose utilization in enriched compared to impoverished animals. These data suggest that environment has a significant effect on brain function which may help to explain the beneficial and protective effects of enrichment against drug abuse and addiction.

1. Introduction

Recent research has explored the effects of environmental enrichment on neurochemistry and behavior, from changes in dopaminergic markers (Zakharova et al., 2009; Zhu et al., 2004, 2005), locomotor behavior, (Bowling et al., 1993; Del Arco and Mora, 2008; Del Arco et al., 2007; Hoffmann et al., 2009; Neugebauer et al., 2004; Van Waas and Soffie, 1996) and learning (reviewed in Van Waas and Soffie (1996)), to sensitivities to the effects of drugs (Bardo et al., 2001; Howes et al., 2000; McCool and Chappell, 2009; Solinas et al., 2008). Generally, environmental enrichment is described as "a combination of complex inanimate and social stimulation" (Rosenzweig et al., 1978).

In the case of rodents, enrichment involves rearing animals with peers in large cages with a variety of novel objects and handling the animals daily. Animals reared in an impoverished environment are housed in solitary conditions without regular handling or novel stimuli. It is clear that rearing conditions, either impoverished/isolated or enriched/socially housed, differentially modify aspects of neuronal function and associated behavior. These modifications have implications for an unlimited number of conditions including learning and memory, behavior, psychological disorders, and drug abuse.

Enriched mice and rats display improved learning and memory skills in a variety of tests including the T-maze and water maze (reviewed in van Praag et al. (2000)). These animals also show decreased locomotor levels (Bowling et al., 1993; Del Arco and Mora, 2008; Del Arco et al., 2007; Hoffmann et al., 2009; Neugebauer et al., 2004; Van Waas and Soffie, 1996) which may be explained by the antidepressant effects of enrichment (Brenes et al., 2008), or a decreased response to novelty. As with decreased locomotor behavior, enriched rats that are prenatally exposed to cocaine spend less time following their partners in a social interaction test, while isolated, prenatally cocaine-exposed rats exhibit more play solicitations (Neugebauer et al., 2004). Behavioral differences may be attributed to known alterations in synaptic plasticity and dopaminergic markers associated with rearing rats in enriched or impoverished environments.

Dopamine is heavily implicated in drug abuse and addiction, thus, differences in sensitivity to the effects of drugs and alcohol and associated neural and behavioral changes have been one major focus of environmental enrichment studies. Isolation/impoverishment has been shown to lead to higher levels of self-administration of ethanol (McCool and Chappell, 2009), amphetamine (Bardo et al., 2001), and cocaine (Howes et al., 2000), while enrichment has been shown to decrease self-administration of amphetamine (Bardo et al., 2001; Green et al., 2002) and reduce the effects of other drugs of abuse. These effects may be associated with a reduction in cell surface levels of the dopamine transporter (Zhu et al., 2005) and reduced DA uptake (Zhu et al., 2004) in the mPFC of rats reared in enriched environments compared to those reared in impoverished environments. Additionally, it has been shown that non-contingent cocaine administration raises levels of tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of dopamine, in isolated/impoverished rats, but not in enriched rats, indicating that the

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impoverished rats may have heightened reward sensitivity and vulnerability to drug abuse (Zakharova et al., 2009).

One approach to the analysis of the consequences of environmental enrichment is the use of metabolic mapping with the quantitative autoradiographic 2-[^{14}C]deoxyglucose method (2-DG) for the measurement of rates of local cerebral glucose utilization (Sokoloff et al., 1977). Because of the close coupling between energy metabolism and functional activity in the central nervous system, this method provides a means to identify those brain regions in which functional activity is altered by pharmacological or physiological stimuli or other manipulations (Porrino et al., 1984). Unlike electrophysiology or the measurement of changes in specific protein or mRNA levels, the 2DG method can evaluate effects throughout the entire central nervous system, thus providing a broad visualization of the distribution of alterations in functional activity at all brain levels. Therefore, the purpose of the present study was to map differences in the distribution of rates of cerebral metabolic activity in rats reared in enriched or impoverished environments, in order to determine whether social and environmental housing conditions during development alter patterns of brain activation in adulthood.

2. Methods

2.1. Animals

All animal procedures were performed in accordance with protocols approved by the Wake Forest University School of Medicine Animal Care and Use Committee and were consistent with the NIH *Guide for the Care and Use of Laboratory Animals*. Male Sprague–Dawley rats (n = 22; 28 days old) were obtained from Harlan Laboratories (Indianapolis, IN). All animals were maintained in a temperature- and humidity-controlled vivarium with a12-h light–dark cycle (lights on at 07:00). Food and water were available ad libitum.

2.2. Environmental conditions

Rats were assigned randomly to either an enriched environment group or an impoverished environment group. Enriched rats (n = 10) were housed in standard polycarbonate cages (25.9 × 47.6 × 20.9 cm) in groups of two. The enriched environment contained 4 novel objects that were rotated weekly and the rats were handled daily, for at least 5 min. The impoverished rats (n = 12) were singly housed in standard polycarbonate cages (25.9 × 47.6 × 20.9 cm). Impoverished rats had no objects in their cages and were handled only briefly during cage changes. Rats were housed in these conditions for a period of 30 days at which time they were tested for locomotor activity followed by surgery and cerebral glucose utilization measurement.

2.3. Locomotor activity

At the end of the enrichment period animals were tested for locomotor activity. Locomotor activity was measured in open-field Plexiglas® test chambers (42 × 42 × 30 cm) by electronic counters that detected interruptions of 8 independent infrared photocell beams (Omnitech, Columbus, OH). Photocell counts were recorded and stored at 10-min intervals for a total of 30 min per session. The following measures were calculated: horizontal activity, or the number of total beam interruptions; forward locomotor, or ambulatory activity; vertical activity, or rearing; and stereotypy.

2.4. Surgical procedures

Surgical procedure for the 2-DG studies followed that described by Crane and Porrino (1989). Briefly, rats were lightly anesthetized with a mixture of halothane, nitrous oxide and oxygen. Polyethylene catheters were then inserted into the femoral vein and artery. Catheters ran subcutaneously and exited at the nape of the neck. A minimum of 36 h was allowed prior to initiation of the 2-DG procedure to ensure full recovery from anesthesia.

2.5. 2-[^{14}C]Deoxyglucose method

Local cerebral glucose utilization was measured in the home cages of the animals according to the method of Sokoloff et al. (1977). Rats were initially given an intravenous pulse of 2-[^{14}C]deoxyglucose (specific activity 50–55 mCi/mmol; New England Nuclear, Boston, MA) at a dose of 75 μCi/kg. Timed arterial blood samples were then drawn over the next 45 min. Samples were centrifuged and plasma concentrations were measured for 2[^{14}C]DG and glucose. At the end of the 45-min sampling procedure, animals were sacrificed using 50 mg sodium pentobarbital. Brains were rapidly removed and frozen in isopentane at −45 °C, then stored at −80 °C until sectioning. Coronal sections (20 μm) were cut in a cryostat maintained at −22 °C. Sections were picked up on glass coverslips, dried on a hotplate (60 °C), and then exposed to film (Kodak MRM film, Kodak, Rochester, New York) along with calibrated [^{14}C] standards (Amersham, Arlington Heights, IL) for 12–15 days. Autoradiograms were then analyzed by quantitative densitometry with a computerized image processing system (MCID Imaging Research, Cambridge, England). Optical density measurements for each brain structure were made in a minimum of five sections. Local cerebral glucose utilization was calculated using the operational equation defined by Sokoloff et al. (1977). Rates of glucose utilization were determined in 37 brain structures selected on the basis of previous reports (Whitlow et al., 2002); according to the rat brain atlas (Paxinos and Watson, 1997).

2.6. Statistical analysis

Behavioral data for the treatment groups were analyzed by means of Student's t-test for independent samples. Rates of glucose utilization were analyzed in specific brain region groups (mesocorticolimbic, nigrostriatal, etc.) using Condition (impoverished vs. enriched) × Region ANOVAs with the specific brain areas within the group as a repeated measures variable and treatment as the between subject variable. The Greenhouse–Geisser correction was used if assumptions of sphericity were not met. ANOVAs were conducted for the following brain region groups: mesocorticolimbic (11 areas), nigrostriatal and related areas (8 areas), other limbic regions (8 areas), sensory/motor cortex and thalamus (8 areas), and other areas (2 areas). Where appropriate, post-hoc t-tests were performed on specific regions between condition groups with alpha adjusted for number of tests performed. Data are presented as mean ± SEM μmol/100 g/min.

3. Results

3.1. Locomotor activity

The effects of rearing in impoverished and enriched environments on locomotor behavior are shown in Fig. 1. Housing animals housed in groups of two in an enriched environment produced no significant difference in total distance, horizontal activity or stereotypy when compared to animals in an impoverished environment.

3.2. Cerebral glucose utilization

The rates of local cerebral glucose utilization in enriched and impoverished animals are displayed in Table 1. Cerebral metabolic rates were globally higher in environmentally enriched animals compared to impoverished animals. This pattern was observed in 33 out of the 37 individual brain regions that were measured. Analysis of brain region groups revealed a main effect of region in the mesocorticolimbic group ($F(3.742, 67.36) = 135.5$, $p<0.001$), the nigrostriatal group ($F(3.227, 58.09) = 231.5$, $p<0.001$), the limbic group ($F(3.540, 60.18) = 229.4$,

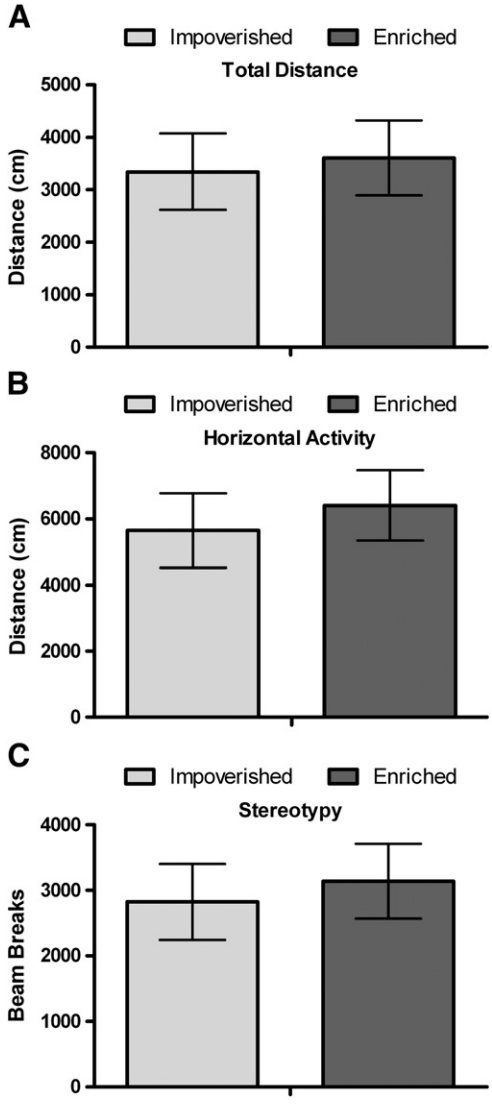

Fig. 1. Effect of environment on spontaneous locomotor activity in rats. Data shown are means ± SEM for cumulative distance or photocell beam breaks during a 30 min test period. Data were analyzed by Student's t-tests.

Table 1
Local glucose utilization in the brains of adult male rats in an impoverished or enriched environment.

Region	Impoverished (n = 12)	Enriched (n = 10)	% Diff
Mesocorticolimbic system			
Cingulate cortex, area 3	91.1 ± 3.2	95.5 ± 3.9	4.9%
Infralimbic cortex	71.3 ± 2.6	73.9 ± 2.7	3.7%
Agranular insular cortex	82.1 ± 2.7	88.2 ± 3.8	7.4%
Anterior cingulate cortex	99.9 ± 3.4	109.3 ± 3.6	9.4%
Anterior nucleus accumbens	86.2 ± 2.7	90.0 ± 3.3	4.4%
Nucleus accumbens, core	75.8 ± 2.4	84.3 ± 1.9*	11.1%
Nucleus accumbens, shell	73.1 ± 3.2	85.4 ± 3.6*	16.9%
Basolateral amygdala	77.9 ± 3.0	86.2 ± 3.5	10.7%
Central nucleus, amygdala	41.1 ± 1.4	43.1 ± 1.3	4.7%
Median forebrain bundle	63.2 ± 1.5	65.4 ± 1.6	3.6%
Ventral tegmental area	74.8 ± 3.8	71.5 ± 2.9	−4.5%
Nigrostriatal system and related areas			
Dorsolateral caudate	108.5 ± 4.1	120.2 ± 4.9	10.7%
Dorsomedial caudate	92.9 ± 4.1	100.6 ± 3.9	8.3%
Ventral caudate	97.6 ± 3.3	103.4 ± 3.2	6.0%
Globus pallidus	61.1 ± 2.8	63.3 ± 2.9	3.6%
Medial habenula	70.8 ± 3.1	71.8 ± 2.6	1.5%
Lateral habenula	96.7 ± 3.5	104.5 ± 3.6	8.1%
Substantia nigra, pars compacta	72.0 ± 2.6	74.1 ± 1.7	3.0%
Substantia nigra, pars reticulata	58.7 ± 2.8	63.0 ± 2.7	8.3%
Other limbic areas			
Medial thalamus	107.2 ± 4.5	118.5 ± 5.0	10.5%
Lateral thalamus	92.8 ± 3.0	96.7 ± 3.8	4.2%
Hippocampus CA1	64.3 ± 2.7	69.8 ± 2.6	8.4%
Hippocampus CA3	69.7 ± 3.0	76.7 ± 2.4	10.0%
Hippocampus dentate gyrus	54.5 ± 2.2	58.4 ± 2.3	7.2%
Ventromedial hypothalamus	50.0 ± 2.0	49.7 ± 2.0	−0.7%
Dorsal raphe	72.6 ± 3.3	72.9 ± 5.0	0.3%
Median raphe	96.9 ± 3.8	95.6 ± 4.3	−1.4%
Sensory/motor cortex and thalamus			
Motor cortex	96.5 ± 3.6	105.4 ± 4.0	9.2%
Auditory cortex	127.7 ± 4.2	133.1 ± 4.1	4.2%
Visual cortex	97.8 ± 3.3	106.7 ± 4.6	9.1%
Corpus collosum	34.1 ± 1.8	37.3 ± 1.9	9.4%
Medial geniculate	107.1 ± 3.8	109.1 ± 4.5	1.8%
Lateral geniculate	87.4 ± 3.2	91.6 ± 3.2	4.8%
Superior colliculus	89.6 ± 3.8	98.6 ± 3.1	10.1%
Inferior colliculus	114.3 ± 5.3	128.0 ± 6.7	12.0%
Other areas			
Locus coeruleus	64.5 ± 3.0	62.9 ± 2.3	−2.6%
Cerebellum	73.4 ± 3.5	76.1 ± 4.1	3.7%

Values are means ± SEM of the number of animals in parentheses, expressed as μmol/100 g/min.
*P < 0.05 difference between impoverished and enriched animals, post-hoc Student's t-test.

$p < 0.001$), the sensory/motor group ($F(3.983, 67.72) = 170.2$, $p < 0.001$) and the "other" group ($F(1, 16) = 29.19$, $p < 0.001$). Subsequently there was a significant interaction of Condition × Region in the mesocorticolimbic group ($F(3.742, 67.36) = 2.663$, $p = 0.043$). Based on evident differences between 2-DG means in the condition groups, two post-hoc t-tests were performed on the nucleus accumbens core and shell. Both the nucleus accumbens core ($p = 0.01$) and shell ($p = 0.02$) showed a significant difference between impoverished and enriched conditions. Significant interactions were not found in any other brain regions.

4. Discussion

The results of the present study demonstrate that pair housing and environmental enrichment produce alterations in functional activity, as measured by higher rates of glucose consumption, in the nucleus accumbens core and shell. In addition, while not significant, this pattern was observed in the majority of discrete brain regions that were measured.

The nucleus accumbens is a brain region that is heavily innervated by dopamine neurons and highly implicated in reward processing and the reinforcing properties of drugs of abuse. Our finding that impoverishment and enrichment differentially affect glucose utilization is consistent with previous reports of alterations in this region and dopaminergic differences due to enrichment or impoverishment. Greater functional activity may reflect increases in dendritic spine density in the nucleus accumbens that have been reported with environmental enrichment (Comery et al., 1996; Kolb et al., 2003). There is also evidence that basal levels of dopamine are reduced in the nucleus accumbens of mice reared in isolation (Eells et al., 2006).

Alterations in glucose utilization in the nucleus accumbens may be associated with the protective effects of enrichment against drug abuse and addiction (for review see Stairs and Bardo (2009)). Isolation/impoverishment leads rodents to self-administer greater amounts of ethanol (Deehan et al., 2007; McCool and Chappell, 2009), while enrichment has been shown to reduce the motivational properties of ethanol (de Carvalho et al., 2010). Rodents that have been reared in an enriched environment are less likely to self-administer low doses of amphetamine (Bardo et al., 2001; Green et al., 2002) and cocaine (Howes et al., 2000). While they are more sensitive to the acute

locomotor stimulating effects of amphetamine, enriched rats are resistant to sensitization after repeated injections (Bowling and Bardo, 1994; Bowling et al., 1993). Amphetamine has also been shown to increase levels of glutamate in the nucleus accumbens to a much greater extent in enriched animals than in impoverished animals (Rahman and Bardo, 2008). In addition to reducing reward sensitivity in drug-naïve animals, environmental enrichment decreases the negative effects of prenatal and juvenile cocaine exposure (Neugebauer et al., 2004) and prevents the reinstatement of a previously established cocaine-induced conditioned place preference (Solinas et al., 2008). These results are supported by data showing that rats reared in isolation show greater reward sensitivity, even to sucrose, than socially housed, enriched rats (Brenes et al., 2008).

The 2-DG method is most often used to measure changes in task related functional activity as reflected by changes in rates of local cerebral metabolism. However, it can also be used to assess baseline differences in brain glucose metabolism associated with different states or phenotypes. Task-related changes generally occur over a relatively short time frame usually in the range of seconds and minutes, whereas basal rates of glucose utilization generally have longer time lines (hours, days and weeks) and reflect intrinsic ongoing brain activity. There are numerous processes in the brain that require energy including the restoration and maintenance of chemical gradients, protein synthesis and trafficking, transcription, neurotransmitter synthesis and processing, intracellular signaling, axonal transport, etc. (Ames, 2000). The differences in rates of glucose utilization observed here between rats raised in impoverished and enriched conditions undoubtedly are differences in intrinsic brain activity, and are not directly related to a task or to a response to external stimuli. More likely, the differences reflect the accumulation of an animal's metabolic history and may be amplified in its interactions with the external world.

The data presented here show no differences in locomotor activity between the impoverished and enriched animals. This is in contrast to previous studies which suggest that environmentally enriched animals have decreased locomotor activity compared to animals housed in an impoverished environment (Brenes et al., 2008, 2009; Elliott and Grunberg, 2005; Green et al., 2003; Smith et al., 2009; Van Waas and Soffie, 1996; Zaias et al., 2008). The discrepancy between these results may be due to differences in the number of animals in socially housed groups. For each of the previously mentioned studies, enriched animals were housed in groups of three to twelve per cage, whereas animals in the current study were housed only in pairs. Therefore, the lack of locomotor differences observed here may be due to more limited social interaction in our enriched groups. If this paradigm had been extended with additional social stimuli, it is plausible that overt behavioral changes would have appeared.

Another possible explanation for the discrepancy between this and other reports is the age at testing. Other evidence suggests that the benefits of enrichment and social housing are more robust in adolescent animals (Zakharova et al., 2009) although this is not a consistent finding (Bowling and Bardo, 1994). Since the animals in the present study were adult at the time of testing, this may have contributed to the lack of locomotor differences between the enriched and impoverished groups. Despite the lack of behavioral differences, there were apparent differences in brain function in reward-related areas. Thus, these data suggest that brain changes due to enrichment occur before there are any overt behavioral changes. Furthermore, it is apparent that small changes in environment are sufficient to produce alterations in brain function, even in the absence of significant changes in behavior.

In addition to the significant difference in glucose metabolism observed in the nucleus accumbens, there was also a trend for higher glucose utilization in the cingulate cortex, dorsolateral caudate, basolateral amygdala, and the CA3 region of the hippocampus of enriched animals. These trends are consistent with literature on other changes associated with enrichment. For example, enrichment has been shown to benefit certain neurological disorders such as Huntington's disease (van Dellen et al., 2000), which is known to degenerate the caudate, an area associated with cognition and motor function (Douaud et al., 2006; Hedreen and Folstein, 1995). Environmental enrichment also decreases stress related neuronal activity in the amygdala (Abraham and Kovacs, 2000). Lastly, environmental enrichment has been shown to improve hippocampal dependent memory (Duffy et al., 2001), and lead to increases in cerebral glucose utilization in the nucleus accumbens of Tryon rats, a strain bred for their ability to learn (Gonzalez-Lima et al., 1994). While our measures of metabolism in these regions were not statistically significant they are measurements of basal levels of metabolism and are therefore resting state. On this note, the trends we observed in these regions may have been significantly different if metabolism had been measured during a task.

In summary, the present findings confirm that environmental enrichment affects glucose metabolism in the nucleus accumbens, a brain region known to be an integral part of drug addiction. In addition, the paradigm of enrichment used in this study was not sufficient to produce locomotor effects in these animals. These results may reflect mechanisms underlying the reported behavioral benefits of environmental enrichment.

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