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Behavior-related alterations of striatal neurochemistry in a mouse model of stereotyped movement disorder

Michael F. Presti[a], Christopher J. Watson[b], Robert T. Kennedy[b], Mark Yang[c], Mark H. Lewis[a,d,*]

[a]Department of Neuroscience, University of Florida, Gainesville, FL 32610, USA
[b]Department of Chemistry, University of Florida, Gainesville, FL 32610, USA
[c]Department of Statistics, University of Florida, Gainesville, FL 32610, USA
[d]Department of Psychiatry, University of Florida, Gainesville, FL 32610, USA

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Abstract

Motor stereotypy is a common component of several developmental, genetic, and neuropsychiatric disorders. In animals, these behaviors can be induced or attenuated via pharmacological manipulation of specific neural loci comprising cortico basal ganglia–cortical feedback circuits, including the striatum. The present study employed the deer mouse model of spontaneous and persistent stereotypy to assess the involvement of several endogenous neurotransmitters and neuromodulators in mediating the expression of the stereotypic behaviors (i.e., repetitive hindlimb jumping) exhibited by these mice. This was accomplished by employing a microdialysis sampling system coupled on-line to capillary electrophoresis with laser-induced fluorescence (CE–LIF) detection apparatus. Given the 13-s temporal resolution for analyte measurement afforded by this system, discrete behavior-related alterations in striatal neurochemical concentrations were detected. Rearing behavior was found to be associated with significant and selective elevations of striatal glutamate (Glu) and aspartate (Asp) concentrations. Moreover, rearing was found to most frequently precede repetitive jumping. The results also indicated that alterations in striatal serine (Ser) concentrations were involved in the modulation of locomotor activity. The present findings support a role of the striatal glutamatergic system in the mediation of spontaneous stereotypic behavior and suggest a potential neuronal mechanism by which transition to stereotypy occurs in these mice. Moreover, the present findings demonstrate the usefulness of the microdialysis system employed in studying the neurochemical substrates of rapidly transitioning behavior.

Keywords: Stereotypy; Locomotion; Striatum; Glutamate; Serine; Microdialysis; Mouse

1. Introduction

Motor stereotypies are characterized as repetitive, topologically invariant, apparently purposeless behaviors. These abnormal behaviors are commonly manifested as a component of certain developmental, genetic, and neuropsychiatric disorders (Berkson et al., 2001; Symons et al., 1999; Cath et al., 2001) and are associated with environmental restriction (such as laboratory caging) in numerous animal species (Mason, 1991; Bohannon, 2002). Drug-induced stereotyped behaviors have been studied extensively using molecular and pharmacological techniques, yet the neurobiological mechanisms mediating the expression of spontaneous stereotypy remain largely unknown. Several lines of evidence support the hypothesis that stereotypic behaviors are expressed as a consequence of heightened neuronal activity along cortico-basal ganglia–cortical feedback circuits. For instance, studies have shown that pharmacological manipulations of the striatum, an integral locus of the implicated feedback circuitry, can induce, exacerbate, or attenuate stereotypic behaviors (Ernst and Smelik, 1966; Bedingfield et al., 1997; Presti et al., 2003). These studies have focused primarily on the roles of the glutamate (Glu) and dopamine (DA) systems in the mediation of stereotypy and have demonstrated consistently the capacity of both Glu receptor agonists (ionotropic or metabotropic) and DA receptor agonists (D1/D2 or D1-selective) to induce or exacerbate the expression of stereotypic behavior. Similarly, studies have shown that stereotypy induced by systemic

* Corresponding author. Department of Psychiatry, University of Florida, 100 S. Newell Drive, Box 100256, Gainesville, FL 32610, USA. Tel.: +1-352-294-0415; fax: +1-352-294-0425.
E-mail address: mlewis@psychiatry.ufl.edu (M.H. Lewis).

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administration of the indirect DA agonist amphetamine is associated with immediate early gene expression in the rat striatum (Canales and Graybiel, 2000). These findings support the hypothesis that spontaneously emitted abnormal repetitive behavior is associated with alterations of striatal neurochemistry.

To study the neurobiological mediation of spontaneously emitted stereotypy, our lab has adopted a mouse model using *Peromyscus maniculatus* (deer mice). A large majority of these mice exhibits persistent stereotypic behaviors consisting of repetitive jumping, flipping, and patterned running when reared under standard laboratory conditions (Powell et al., 1999). In a previous study, we showed that intrastriatal administration of the noncompetitive *N*-methyl-D-aspartate receptor (NMDAR) antagonist MK-801 or the selective D1R antagonist SCH23390 produced a selective attenuation of stereotyped behavior in these mice (Presti et al., 2003), suggesting that the expression of such spontaneous stereotypy may be associated with heightened corticostriatal signaling. These findings prompted the present study, in which microdialysis sampling was employed to monitor the intrastriatal neurochemistry of freely moving, stereotypic deer mice during episodes of stereotypic and nonstereotypic behavior.

In vivo intracerebral microdialysis represents a powerful tool with which to characterize the neurochemical mediation of behavior. As a result of recent technological innovations, such as the on-line coupling of microdialysis sampling to capillary electrophoresis with laser-induced fluorescence (CE–LIF) detection systems (for a review, see Kennedy et al., 2002), the temporal resolution of in vivo measurements has improved dramatically. For example, whereas traditional HPLC-based microdialysis techniques can measure intracerebral Glu concentrations with a temporal resolution of approximately 10–30 min (Olive et al., 2000), on-line CE–LIF systems can perform such measurements in as little as 5–20 s (Bowser and Kennedy, 2001). In principle, this enhanced sampling capability enables the detection of dynamic behavior-related alterations in neurochemical signaling.

Moreover, the high-speed multianalyte capability of these devices offers novel opportunities to monitor interactions between neurotransmitter systems. The present study employed microdialysis sampling in freely moving deer mice to characterize the intrastriatal neurochemical milieu associated with stereotypic and nonstereotypic behavioral states in these animals. The study utilized an on-line CE–LIF detection system calibrated for eight neuroactive amines and amino acids, including Glu, aspartate (Asp), γ-aminobutyric acid (GABA), dopamine (DA), taurine (Tau), glutamine (Gln), glycine (GLY), and serine (Ser).

Given the capacity of specific glutamatergic and dopaminergic antagonists to selectively attenuate stereotypy in these mice (Presti et al., 2003) as well as the extensive local modulatory interactions between these two neurotransmitter systems, we hypothesized that relative to states of nonstereotypic motor activity and inactivity, episodes of stereotypic behavior would be associated with elevated Glu and/or DA signaling. To our knowledge, this is the first study to measure the neurochemical substrates of spontaneously emitted abnormal repetitive behavior.

2. Methods

2.1. Animals

We have previously demonstrated that both male and female *P. maniculatus* (deer mice) develop high rates of persistent, spontaneously emitted stereotypy consisting of repetitive vertical jumping, backward somersaulting, and, to a lesser extent, patterned running when housed under standard laboratory conditions (Powell et al., 1999). Mice were group-caged (3–4 same-sex mice/cage) in standard (29 × 18 × 13 cm) laboratory mouse cages. Rodent chow and water were available ad libitum, and temperature was maintained at 24 °C. Mice were maintained on a 15-h light–9-h dark cycle, with lights off at 10:00 a.m. We selected adult (>2 months old) male ($n = 5$) and female ($n = 3$) deer mice demonstrating high levels of repetitive jumping (3000 jumps in 1 h) during an 8-h dark cycle screening session. Mice exhibiting stereotypic somersaulting or patterned running were excluded from the study because these forms of behavior either interfered with the microdialysis sampling apparatus (backward somersaulting) or were more difficult to quantify (patterned running) than repetitive vertical jumping. All procedures were performed in accordance with the guidelines set forth in the NIH Guide for the Care and Use of Laboratory Animals and were approved by the University of Florida Institutional Animal Care and Use Committee.

2.2. Stereotaxic surgery

The mice were anesthetized using a ketamine (100 mg/ml) and acepromazine (10 mg/ml) cocktail administered by subcutaneous injection at the dose of 0.015 ml/g body weight. Using aseptic surgical technique, 24-gauge threaded pedestal guide cannulae were implanted unilaterally into the dorsolateral striatum at the following coordinates: anterior to bregma—0.5 mm; lateral—2.5 mm; ventral—2.5 mm (see Franklin and Paxinos, 1997). The cannulae were fixed in place using ethyl-2-cyanoacrylate glue and dental cement. Animals were then singly housed in a new home cage and were allowed at least 4 days to recover from surgery prior to testing.

2.3. Drugs and reagents

Sodium tetraborate, hydroxypropyl-â-cyclodextrin (HPbCD), *o*-pthaldialdehyde (OPA), â-mercaptoethanol (bME), sodium chloride (NaCl), potassium chloride (KCl),

magnesium sulfate ($MgSO_4$), calcium chloride ($CaCl_2$), sodium hydroxide (NaOH), Glu, Asp, DA, GABA, Tau, Ser, Gly, were purchased from Sigma-Aldrich (Milwaukee, WI). All solutions were prepared in 18.2 MW MilliQ water (Millipore, Molsheim, FR) and filtered through a 0.22-mm MSI Magna Nylon membrane filter (plain; Osmonics, Minnetonka, MN).

2.4. Microdialysis sampling

Side-by-side microdialysis probes were constructed in-house using a method described previously (Pettit and Justice, 1991). All fused silica capillaries were purchased from Polymicro Technologies (Phoenix, AZ). The dimensions of the capillaries used for probe construction were 40 mm inner diameter (i.d.) by 100 mm outer diameter (o.d.). Briefly, the dialysis probes (200 mm i.d.; 2 mm active length; regenerated cellulose membrane with a 13-kD cut-off) were perfused at a flow rate of 1.0 ml/min for all procedures. The probes were conditioned by placing the probe in artificial cerebral spinal fluid (aCSF; 145 mM NaCl, 2.68 mM KCl, 1.01 mM $MgSO_4$, and 1.22 mM $CaCl_2$) while also perfusing with aCSF using a CMA/102 microsyringe pump (CMA, Acton, MA) for 30 min followed by placement in aCSF for at least 1 h prior to calibration. A three-point calibration curve (peak height vs. concentration) was generated by placing the tip of the probe into three different concentrations of amino acid standards (composed of Glu, Asp, DA, GABA, Tau, Ser, and Gly in aCSF). The standards were maintained at a temperature of 37 °C using a water bath (model 1140-A, VWR Scientific Products, Buffalo Grove, IL).

2.5. Dialysate measurement

A full description of the CE–LIF system as well as the on-line derivatization procedure has been provided previously (Bowser and Kennedy, 2001). Briefly, dialysate was derivatized on-line using a solution of 10 mM OPA, 40 mM BME, 36 mM sodium tetraborate, 0.81 mM HPbCD, and 10% methanol (vol/vol) at pH 9.5. Electrokinetic injections of derivatized dialysate onto the separation capillary (10 mm i.d., 150 mm o.d., and 10.0 cm in length) were performed with the use of a flow-gated interface. Leakage of dialysate onto the separation capillary during a run was prevented through the use of a cross-flow buffer consisting of 10 mM sodium tetraborate with 0.9 mM HPbCD (pH 9.5). The applied voltage for separation corresponded to an electric field of 2.22 kV/cm. Fluorescence detection was performed off-column using a sheath flow system. The sheath flow buffer consisted of 10 mM sodium tetraborate at pH 9.5. Fluorescence was induced with the 351-nm laser line of an argon ion laser (Enterprise 622 argon ion laser; Coherent, Santa Clara, CA), and fluorescence emission (450 nm) was collected orthogonally to the incident beam.

2.6. Experimental design and data analysis

The mice were tested during the dark (active) cycle in their home cages under low-intensity red lights. A test animal was first captured and anesthetized with isofluorane to allow the removal of the obturator and the insertion of a microdialysis probe through the guide cannula. Following recovery from anesthetic (typically less than 1 min), the microdialysis sampling apparatus was inspected and adjusted to ensure the unrestricted mobility of the mouse. Similarly, optical adjustments were made to ensure collection of the maximum fluorescence intensity. The animal was then allowed 90 min to habituate to the testing environment, during which time electropherograms were monitored to ensure stabilization of implantation-induced perturbations to the analyte peaks. Behavioral recordings and analyte measurements were then made over a 2-h testing period. Following completion of the testing session, the subject was sacrificed with a lethal overdose of gaseous anesthetic, and the brain was harvested to allow for histological verification of probe placement. The experimental sessions were videotaped to allow for a computer-assisted encoding of observed behaviors using The Observer software (Noldus). The final 60 min of behavioral data were continuously recorded as mutually exclusive states by a trained observer who had previously established interrater reliability for the recorded behaviors (i.e., jumping, rearing, grooming, burrowing, locomotion, patterned running, and inactivity) at a kappa level of 0.7 or above and who was blinded to analyte concentrations. Analyte measurements were made with a time resolution of approximately 13 s. Electropherograms were acquired, marked, and measured using Labview software (National Instruments), and such measurements were made blind to behavioral data.

The behavioral time series data were synchronized with the corresponding analyte measurements $y(t)$ for each 13-s interval and modeled in an additive manner, where $x_1(t)$, $x_2(t)$,. . ., $x_7(t)$ represent the time engaged in inaction, rearing, burrowing, grooming, jumping, patterned running, and locomotion, respectively, at time interval t; thus $\Sigma_{i=1}{}^{7}$ $x_i(t)=1$. By assuming that neurochemical concentrations vary proportionally to the time engaged in each behavior, the following model was employed:

$$y(t) = \alpha_1 x_1(t) + \alpha_2 x_2(t) + \ldots + \alpha_7 x_7(t) + \varepsilon, \quad (1)$$

where the α_i is the analyte concentration associated with behavior i per unit time and ε represents random variation. To make cross-subject comparisons, neurochemical levels were adjusted by the total mean for each mouse. Thus, $y(t)$ in Eq. (1) represents the level of analyte y at time t divided by this mouse's average y level per 13-s interval. Thus, under the null hypothesis that neurochemical concentrations are not associated with the modulation of behavior, all the αs in Eq. (1) should be 1.00. To compare the analyte concentrations associated with any two particular activities, we

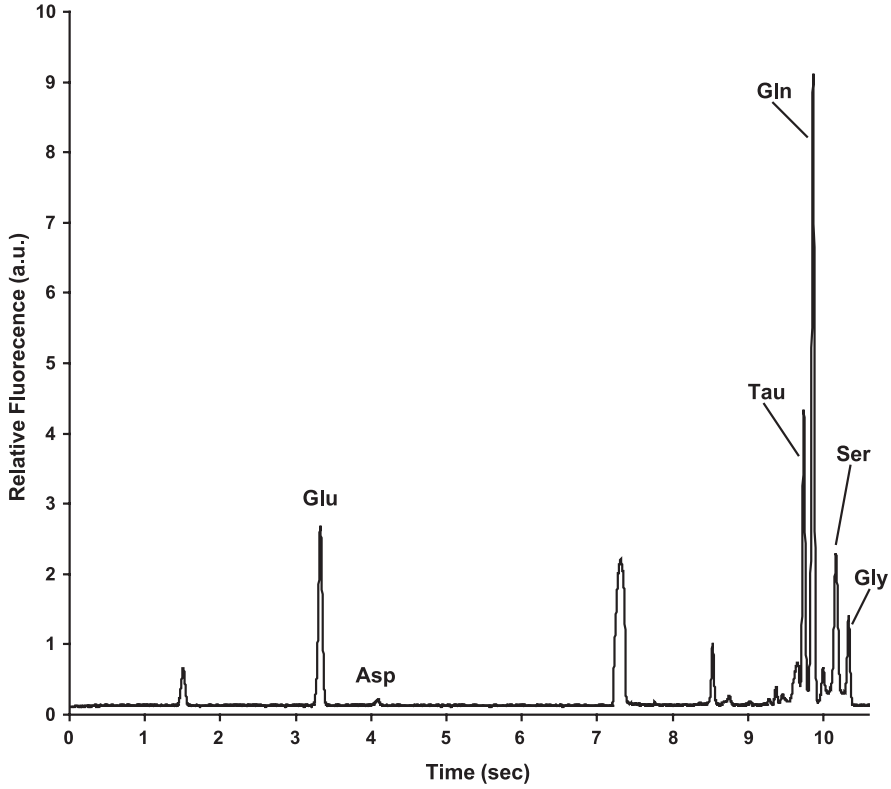

Fig. 1. Representative electropherogram obtained with the described CE–LIF microdialysis system. Peaks reliably detected in each 13-s interval included Glu, Asp, Tau, Gln, Ser, and Gly.

reparametrized Eq. (1) as follows, using a comparison between α_1 and α_2 values as an example.

$$y(t) = (\alpha_1 - \alpha_2)x_1(t) + \alpha_2(x_1(t) + x_2(t)) + \alpha_3 x_3(t) + \ldots + \alpha_7 x_7(t) + \varepsilon \quad (2)$$

Thus, testing the equality of α_1 and α_2 is equivalent to testing whether the first coefficient $\alpha_1 - \alpha_2$ is zero; standard regression analysis was used.

This test was first performed for each individual mouse. When a trend existed among the group (e.g., all $\alpha_i - \alpha_j$ were positive or all were negative), individual mouse data were combined using a multiplicative adjustment; in this case, $y(t)$ was adjusted by the average analyte concentration for each mouse. To protect against a Type I error associated with multiple comparisons, we used the Bonferroni correction to arrive at an adjusted threshold for assigning statistical significance. Inasmuch as there were $(\Sigma_2^7) = 21$ comparisons among the behaviors and there were six amino acids to examine, we claimed statistical significance only when the P value was less than or equal to $.05/(21 \times 6) = .0004$. Inasmuch as Glu was the focus of our primary hypotheses, however, we used a less stringent significance threshold level of .05/21=.0024 for tests involving Glu alterations.

To determine the extent to which stereotypic behaviors were preceded by or followed specific normal motor behaviors, lag sequential analyses were performed using statistical tools available with The Observer software (Noldus).

2.7. Histology

Following the completion of the in vivo microdialysis experiment, the mouse brains were harvested and snap frozen. Brain tissue was sectioned on a cryostat into 20-μm slices, slide mounted, and examined under a microscope. The

Table 1

	Inactive	Jumping	Grooming	Digging	Locomotion	Rearing
Rearing	Glu ↑ * Asp ↑ *	Glu ↑ * Asp ↑ *	Glu ↑ * Asp ↑ *	Glu ↑ * Asp ↑ *	Glu ↑ (.01) Asp ↑ (.001)	N/A
Inactive	N/A	Gln ↑ *	Gln ↑ *	Gln ↑ (0.03)	Unchanged	Gln ↑ *
Locomotion	Ser ↑ (.002)	Ser ↑ (.02)	Ser ↑ *	Unchanged	N/A	Ser ↑ (.02)

Summary of significant (*=P<.0004) and trended (P values indicated in parentheses) behaviorally-related alterations in striatal neurochemical concentrations. For example, Glu and Asp concentrations are significantly elevated during rearing states as compared to states of inactivity.

Table 2

Amino acid	Coefficients	Estimated difference ± S.E.	Overall P value
Glu	$\alpha_r - \alpha_i$	0.086 ± 0.011	.0001
Glu	$\alpha_r - \alpha_d$	0.133 ± 0.033	.0001
Glu	$\alpha_r - \alpha_g$	0.069 ± 0.015	.0001
Glu	$\alpha_r - \alpha_j$	0.075 ± 0.012	.0001
Glu	$\alpha_r - \alpha_p$	0.101 ± 0.029	.0001
Asp	$\alpha_r - \alpha_i$	0.134 ± 0.027	.0001
Asp	$\alpha_r - \alpha_d$	0.398 ± 0.106	.0002
Asp	$\alpha_r - \alpha_l$	0.199 ± 0.061	.0010
Asp	$\alpha_r - \alpha_g$	0.159 ± 0.035	.0001
Gln	$\alpha_i - \alpha_g$	0.063 ± 0.016	.0001
Gln	$\alpha_i - \alpha_j$	0.033 ± 0.010	.0009
Ser	$\alpha_l - \alpha_g$	0.129 ± 0.035	.0003
Ser	$\alpha_r - \alpha_g$	0.045 ± 0.018	.0117

The first column indicates the amino acid evaluated. In the second column, αs are the coefficients defined in Eq. (1), and the subscripts are d—digging, g—grooming, i—inaction, j—jumping, l—locomotion, p—patterned running, and r—rearing. The third column is the estimated difference given by Eq. (2) with the standard error of the estimate, and Column 4 indicates the overall P value for combined group data.

appropriate sections were placed in register with a stereotaxic brain atlas to verify the coordinates of probe placement.

3. Results

3.1. Analyses of behavior-related striatal neurochemistry

Overall, the present findings provide strong support for the utility of the described CE–LIF microdialysis sampling system in investigations addressing the neurochemical mediation of behavior. Unfortunately, GABA and DA concentrations were not reliably detected (see Fig. 1 for a representative electropherogram); however, the results of the present study support a role of the striatal glutamatergic system in the mediation of spontaneous stereotypic behavior and suggest a potential neuronal mechanism by which transition to stereotypy occurs in these mice. Specifically, pairwise comparisons revealed that rearing behavior was associated with a statistically significant ($P < .0004$) elevation of intrastriatal concentrations of the excitatory amino acid neurotransmitters Glu and Asp as compared to the concentration of these neurotransmitters associated with all other recorded behavioral states except locomotion. Compared to locomotion, rearing was associated with increased intrastriatal Glu ($P = .01$) and Asp ($P = .001$) concentrations, although these differences were not statistically significant given the stringent alpha employed. Furthermore, states of inactivity were associated with elevated concentrations of striatal Gln. These differences were statistically significant ($P < .0004$) in comparison to the Gln concentrations associated with rearing, jumping, and grooming behaviors. Increased Gln during inactivity was also observed when compared to digging, although this difference did not meet our criterion for statistical significance ($P = .03$). Finally, locomotion was associated with a generalized increase in striatal Ser concentrations. A statistically significant ($P < .0004$) increase in Ser concentrations during locomotion was observed in comparison to Ser concentrations associated with grooming behavior but not to striatal Ser concentrations associated with rearing ($P = .02$), jumping ($P = .01$), and inactivity ($P = .002$). These findings are summarized in Tables 1 and 2. No other statistically significant

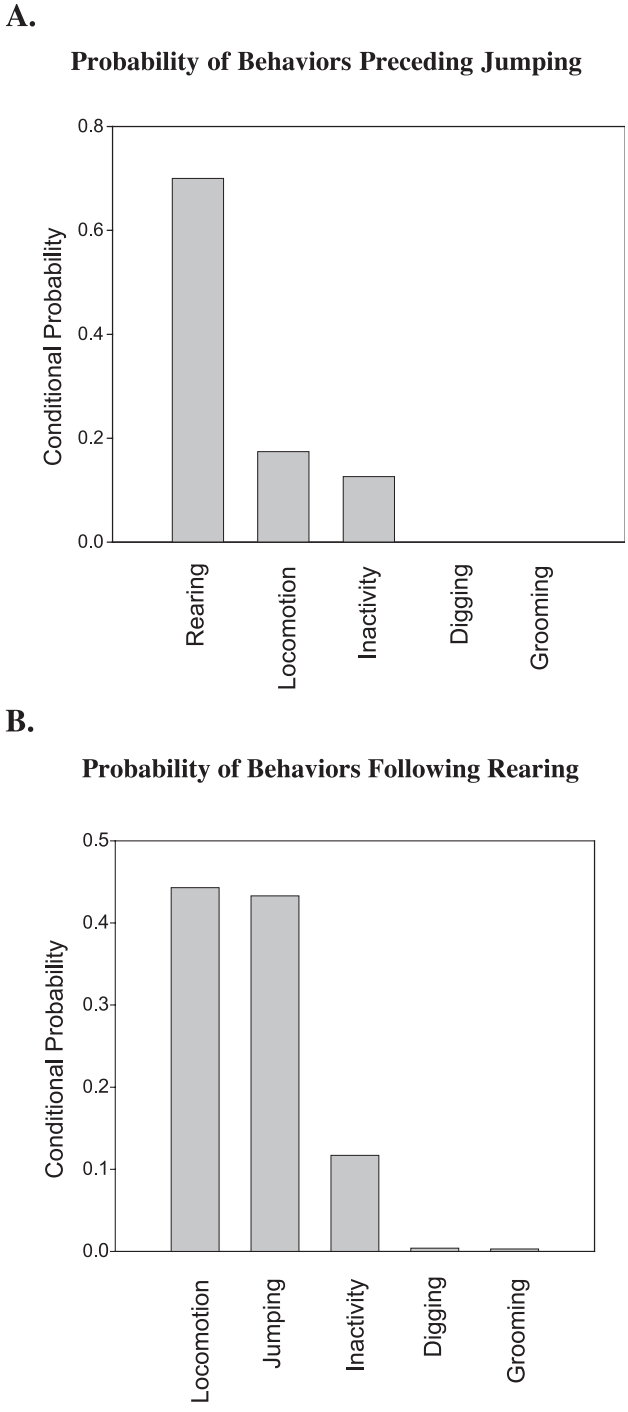

Fig. 2. Lag sequential analyses were performed to determine the conditional probability with which (A) behaviors preceded jumping stereotypy and (B) behaviors followed jumping stereotypy.

differences were detected among any of the remaining pairwise comparisons between behavior-related neurochemical concentrations.

3.2. Lag sequential analyses of transition between behavioral states

Given the robust and exclusive interaction between rearing behavior and intrastriatal excitatory neurotransmitter levels, and the potential importance of hindlimb rearing in the organization of the jumping stereotypy exhibited by deer mice, lag sequential analyses were performed to determine the conditional probability with which transitions were made between behavioral states. Specifically, the probabilities of behavioral states to either precede a bout of stereotypic jumping or to follow an episode of rearing were determined. The results indicate that jumping behavior was most likely to be immediately preceded by rearing (69.5%). There was a 17.4% and 12.6% probability that jumping was preceded by locomotion and inactivity, respectively. Furthermore, rearing was most likely to be immediately followed by locomotion (45.0%) or stereotypic jumping behavior (43.3%). There was an 11.1% probability that rearing was followed by inactivity. These conditional probabilities are presented graphically in Fig. 2.

3.3. Verification of probe coordinates

All of the coronal sections examined revealed microdialysis probe placement in the striatum. Although the lateral striatum was targeted, some placements were found in more medial striatal positions. The anteroposterior range of placement was 0.8 to 1.2 mm anterior to bregma. Probe positions are depicted in Fig. 3.

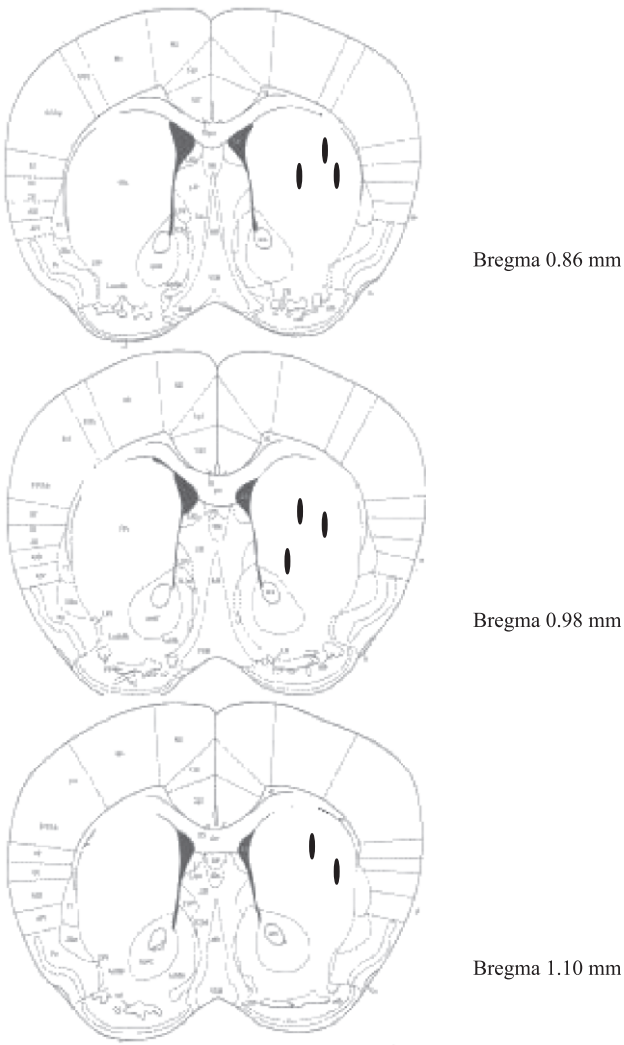

Fig. 3. Diagrammatic representation of the microdialysis probe placements. All probe positions were within the striatum in the anteroposterior range of 0.5 to 1.5 mm anterior to bregma.

4. Discussion

The present study demonstrated that dynamic behavior-related changes in striatal neurochemistry can be detected in a spontaneously stereotypic mouse model by employing microdialysis sampling coupled on-line to a capillary CE–LIF detection system. Specifically, the results demonstrate that rearing behavior was associated with significant and selective elevations of striatal excitatory amino acid concentrations. This finding is consistent with reports of heightened intrastriatal Glu concentrations in rats during generalized open-field activity consisting of rearing, locomotion, and grooming (Bland et al., 1999). As a result of the poor (10-min) temporal resolution afforded by the HPLC separation system used in this study, however, the authors were able to conclude only that rearing and/or locomotion were associated with the heightened Glu release. Given the increased (13-s) sampling resolution of the present CE–LIF system, the influences of these and other behaviors on striatal glutamatergic tone were determined independently, demonstrating that the movement-related increase in extracellular Glu concentration is most powerfully associated with rearing behavior. Thus, these findings support the utility of the employed microdialysis sampling and detection system in studies of behavioral neurochemistry.

Further support for the capacity of the described microdialysis system to detect endogenous behavior-related alterations in neurochemical concentrations stems from the present findings related to inactivity. Specifically, states of inactivity were associated with significantly higher concentrations of striatal Gln than those measured during most motor activities, including jumping, rearing, and grooming. Given the dependence of these motor behaviors on striatal glutamatergic signaling, the movement-related decrease in striatal Gln concentrations may represent acute activation of the Gln cycle, which functions to replenish neuronal Glu stores through transmembrane uptake and conversion processes (Nicklas et al., 1987), during states of motor activity.

Thus, the observed elevation in extracellular Gln during states of inactivity is consistent with the theorized process whereby expression of Glu-dependent behavior is associated with the transformation of synaptic Gln into intracellular Glu in neurons responsible for maintenance of the given behavior.

Another salient finding of the present study relates to the observed serinergic involvement in the mediation of locomotor activity. Specifically, elevated dialysate concentrations of Ser were detected during locomotive states relative to all other behaviors except digging. Although only the difference between locomotion and grooming-related Ser measurements was found to be statistically significant ($P < .0004$), a trend toward heightened locomotor-related Ser release was detected relative to Ser levels associated with rearing ($P = .02$), jumping ($P = .01$), and inactivity ($P = .002$). This finding is consistent with reports that drug-induced hyperlocomotion is potentiated following intrastriatal administration of a D-serine analog (Kretschmer et al., 1992) and thus provides additional support for the validity of behavior-related neurochemical data obtained through the use of the described microdialysis sampling and detection system. Given the role of Ser in regulating the conductive properties of NMDARs via activation of the modulatory Gly-binding site, the observed increase in locomotion-related Ser signaling may represent a neuronal mechanism for the differentiation of NMDAR activity-dependent behaviors.

Finally, the present findings provide information about the neurobiological mediation of spontaneous stereotypic behavior. Although no acute alterations of striatal neurochemistry were detected during bouts of stereotypic jumping, results of the lag sequential analyses indicate that rearing, which was associated with significantly elevated striatal excitatory amino acid concentrations, was by far the most probable antecedent to jumping. Inasmuch as rearing, which was associated with increased striatal Glu and Asp concentrations, was typically followed by stereotypy, the present findings may be interpreted to reflect a novel "priming mechanism" whereby a rearing-induced elevation in excitatory neurotransmitter release could serve to disinhibit neuronal processes mediating the expression of stereotypic behavior in these mice. Specifically, given the dependence of these stereotypies on striatal NMDAR activation (Presti et al., 2003), we propose that elevated striatal Glu concentrations associated with "preparatory" rearing may produce a depolarizing influence on medium spiny neurons sufficient to remove the magnesium block imposed on NMDARs during subthreshold membrane potentials, thereby enabling the activation of these receptors. It is hypothesized that this priming mechanism may underlie sustained NMDAR activity and transition to stereotypic behavior.

Taken together, the results of the present study provide strong support for the utility of microdialysis sampling techniques coupled on-line to capillary CE–LIF detection systems in investigations of the neurochemical mediation of natural (non-drug-induced) behavior. The system employed yielded results that confirmed and elaborated the findings of other microdialysis and pharmacological studies, and provided novel insights related to the neurobiological mediation of abnormal repetitive behavior. Efforts to improve the temporal resolution of the system through optimization of the separation capillary to a narrower field of analytes will permit future experiments to test the hypothesized priming-related transition to stereotypy by focusing solely on differences between Glu concentrations associated with normal and preparatory rearing behavior.

References

Bedingfield JB, Calder LD, Thai DK, Karler R. The role of the striatum in the mouse in behavioral sensitization to amphetamine. Pharmacol Biochem Behav 1997;56:305–10.

Berkson G, Andriacchi T, Sherman L. More information on the nature of stereotyped body-rocking. Am J Ment Retard 2001;106:205–8.

Bland ST, Gonzale RA, Schallert RT. Movement-related glutamate levels in rat hippocampus, striatum, and sensorimotor cortex. Neurosci Lett 1999;277:119–22.

Bohannon J. Can a mouse be standardized? Science 2002;298:2320–1.

Bowser MT, Kennedy RT. In vivo monitoring of amine neurotransmitters using microdialysis with on-line capillary electrophoresis. Electrophoresis 2001;22:3668–76.

Canales JJ, Graybiel AM. A measure of striatal function predicts motor stereotypy. Nat Neurosci 2000;3:377–83.

Cath DC, Spinhoven P, Hoogduin CA, Landman AD, van-Woerkom TC, van-de-Wetering BJ, et al. Repetitive behaviors in Tourette's syndrome and OCD with and without tics: what are the differences? Psychiatry Res 2001;101:171–85.

Ernst AM, Smelik PG. Site of action of dopamine and apomorphine on compulsive gnawing behavior in rats. Experientia 1996;22:837–8.

Franklin KJB, Paxinos G. The mouse brain: in stereotaxic coordinates. New York: Academic Press, 1997.

Kennedy RT, Watson CJ, Haskins WE, Powell DH, Strecker RE. In vivo neurochemical monitoring by microdialysis and capillary separations. Curr Opin Chem Biol 2002;6:659–65.

Kretschmer BD, Zadow B, Volz TL, Volz L, Schmidt WJ. The contribution of the different binding sites of the *N*-methyl-D-aspartate (NMDA) receptor to the expression of behavior. J Neural Transm Gen Sect 1992;87:23–35.

Mason G. Stereotypies: a critical review. Anim Behav 1991;41:1015–37.

Nicklas WJ, Zeevalk G, Hyndman A. Interactions between neurons and glia in glutamate/glutamine compartmentation. Biochem Soc Trans 1987; 15:208–10.

Olive MF, Mehmert KK, Hodge CW. Microdialysis in the mouse nucleus accumbens: a method for detection of monoamine and amino acid neurotransmitters with simultaneous assessment oflocomotor activity. Brain Res Brain Res Protoc 2000;5:16–24.

Pettit HO, Justice JB. Effect of dose on cocaine self-administration behavior and dopamine levels in the nucleus accumbens. Brain Res 1991; 539:94–102.

Powell SB, Newman HA, Pendergast J, Lewis MH. A rodent model of spontaneous stereotypy: initial characterization of developmental, environmental, and neurobiological factors. Physiol Behav 1999;66: 355–63.

Presti MF, Mikes HM, Lewis MH. Selective blockade of spontaneous motor stereotypy via intrastriatal pharmacological manipulation. Pharmacol Biochem Behav 2003;74:833–9.

Symons FJ, Butler MG, Sanders MD, Feurer ID, Thompson T. Self-injurious behavior and Prader–Willi syndrome: behavioral forms and body locations. Am J Ment Retard 1999;104:260–9.