Dopamine D1 receptors involved in locomotor activity and accumbens neural responses to prediction of reward associated with place

Anh Hai Tran*, Ryoi Tamura†, Teruko Uwano†, Tsuneyuki Kobayashi†, Motoya Katsuki‡, and Taketoshi Ono*†§

*Molecular and Integrative Emotional Neuroscience, Graduate School of Medicine, and †Department of Physiology, Faculty of Medicine, Toyama Medical and Pharmaceutical University, Toyama 930-0194, Japan; and ‡National Institute for Basic Biology, Okazaki National Research Institute, Okazaki 444-8585 Aichi, Japan

Communicated by Jan Bureš, Czech Academy of Sciences, Prague, Czech Republic, December 24, 2004 (received for review October 16, 2004)

Predicting reward is essential in learning approach behaviors. Dopaminergic activity has been implicated in reward, movement, and cognitive processes, all essential elements in learning. The nucleus accumbens (NAc) receives converging inputs from corticolimbic information-processing areas and from mesolimbic dopamine neurons originating in the ventral tegmental area. Previously, we reported that in mice, a dopamine D2 receptor knockout (D2R-KO) eliminated the prereward inhibitory response, increased place-field size of NAc neurons, and reduced locomotor activity without marked change in intracranial self-stimulation (ICSS) behavior. The present study investigated the specific contribution of dopamine D1 receptor (D1R) in mediating reward, locomotor activity, and spatial associative processes and in regulating NAc neural responses. In contrast to D2R-KO animals, here we find D1R-KO in mice selectively eliminated the prereward excitatory response and decreased place-field size of NAc neurons. Furthermore, D1R-KO impaired ICSS behavior, seriously reduced locomotor activity, and retarded acquisition of a place learning task. Thus, the present results suggest that D1R may be an important determinant in brain stimulation reward (ICSS) and participates in coding for a type of reward prediction of NAc neurons and in spatial learning.

dopamine receptor | nucleus accumbens | spatial learning

Dopaminergic systems innervate the hippocampal formation (HF), prefrontal cortex, amygdala (AM), and ventral striatum and mediate cognitive processes of working memory and learning (1–6). The nucleus accumbens (NAc) is reliably linked to motivation, locomotion, reward-related processes, and some cognitive functions (1, 3, 7–9). It receives excitatory glutamatergic input from the prefrontal cortex, HF, and AM, as well as a dense converging dopaminergic innervation from the ventral tegmental area (3, 10, 11). Thus, NAc neurons are positioned to recognize context-driven patterns of activation and to relay this information to planning and motor executive systems for appropriate behavioral responses (1, 3, 7, 8, 12). Dopamine has profound effects on behavior as highlighted in previous studies (13–16). Nevertheless, the contribution of dopamine D1 receptor (D1R) in assessing reward information at neural level and its link to behaviors such as spatial associative learning remains to be specified. In the present study, we used knockout mice lacking D1R (D1R-KO) and their wild-type (WT) littermates to examine the contribution of this receptor in mediating reward, locomotion, and spatial learning and in regulating neural responses to prediction of reward. These mice were tested for their ability to perform several spatial tasks, including random reward place search task (RRPST) and place learning task (PLT), by using intracranial self-stimulation (ICSS) as rewards (15). To investigate the involvement of D1R functions in reward processing and spatial associative processes, we recorded neural activity from the NAc of D1R-KO mice and their WT littermates, both of which were well trained in the RRPST and PLT.

Materials and Methods

Subjects. Nine male WT mice (27–35 g) and nine male D1R-KO mice (23–29 g) were used in the present experiment. We obtained the mice from a collaborative laboratory (National Institute for Basic Biology, Okazaki National Research Institute). The experiment was conducted in accordance with guidelines of the National Institutes of Health and Toyama Medical and Pharmaceutical University.

Electrode Implantation and ICSS Training. Mice were implanted bilaterally with monopolar stimulating electrodes for ICSS in the medial forebrain bundle at the level of the posterior lateral hypothalamic area (anteroposterior, −2.3 mm; mediolateral, ±0.70 mm; and dorsoventral, −5.3 mm from the bregma) (17). The recording electrodes assembly was implanted into the dorsal part of the NAc (anteroposterior, +1.42 mm, and mediolateral, ±0.70 mm from the bregma) during the same surgery. This medial region of the NAc exhibits a proportion of neurons that receive converging inputs from both the HF and the AM (10, 11). After recovery from surgery, the efficacy of electrical stimulation was verified in a nose-poking chamber. The mouse was trained daily to self-stimulate in 30- to 60-min sessions for 5–7 days. The current intensity began from 20 μA and was gradually increased by a 10-μA step to determine optimal intensity. After the mouse had learned to make nose-poking responses at stable rates, they were tested at 80% of the optimal intensity with an ascending range of frequencies incremented in ≈0.1 logarithmic units (a 500-ms train of 0.3-ms biphasic square wave, from 16 to 126 Hz, 2 min per episode).

Spatial Task Training. The mice were trained to perform spatial tasks in an open field (80-cm diameter, 25-cm-high wall) that was painted black inside and enclosed by a black curtain. On the first day of training, the cumulative distance traveled in a 10-min trial served as a measure of spontaneous locomotor activity. In the distance movement task (DMT), mice could obtain 50 brain stimulation rewards (BSR) (optimal intensity at 80 Hz) over 10 min for moving a predetermined distance criteria. The distance criteria began at 30 cm and were increased (50, 80 cm). The mice were tested subsequently in the RRPST and PLT. In the RRPST, a reward place (30-cm diameter) was delineated with its center chosen at random within the open field. The mouse was rewarded with BSR when it entered the reward place. In the PLT, there were two reward places (20-cm diameter) located diametrically opposite one another in the open field. The mouse was rewarded in both places when it returned to one reward place

Abbreviations: AM, amygdala; BSR, brain stimulation reward; D1R, dopamine D1 receptor; D1R-KO, D1R knockout; DMT, distance movement task; HF, hippocampal formation; ICSS, intracranial self-stimulation; NAc, nucleus accumbens; PLT, place learning task; RRPST, random reward place search task; I-type, inhibitory type; E-type, excitatory type.

§To whom correspondence should be addressed. E-mail: onotake@ms.toyama-mpu.ac.jp.

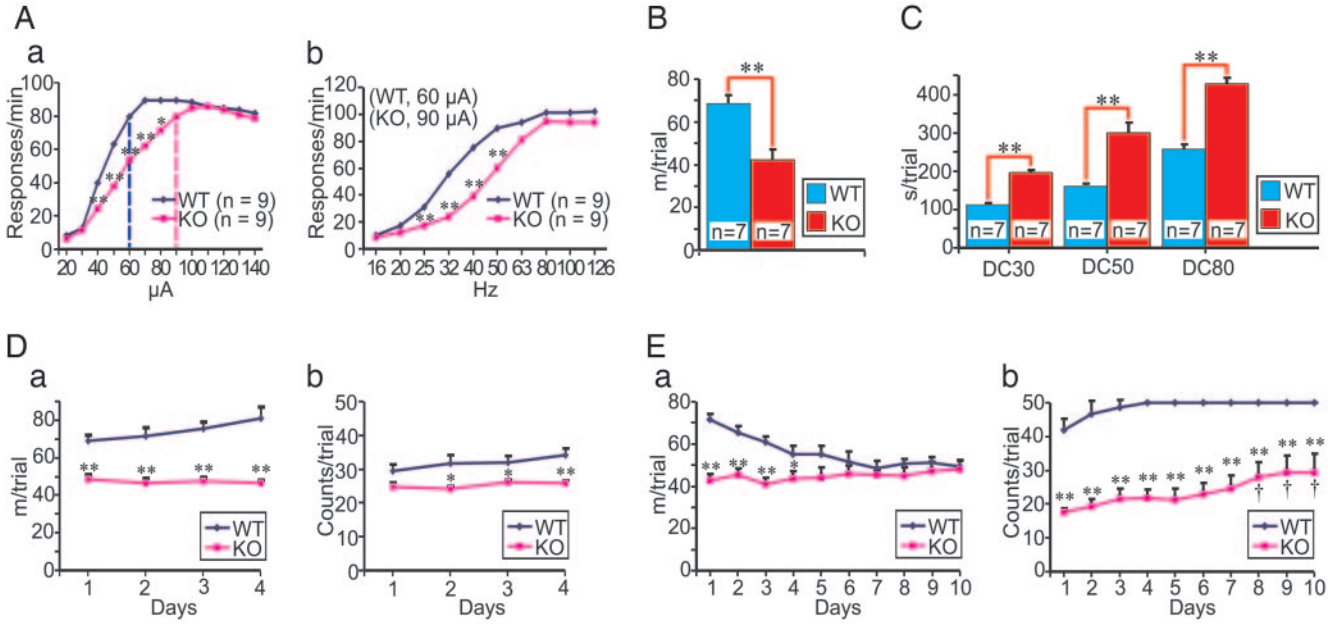

Fig. 1. Comparisons of ICSS behavior, spontaneous locomotor activity, and performance in spatial tasks between WT and D1R-KO mice. (*A*) Self-stimulation screening. (*a*) Intensity–response curve. Vertical dashed bars indicate intensities used for plotting frequency–response curves in *b*. (*b*) Frequency–response curve. (*B*) Spontaneous locomotor activity. (*C*) Performance in DMT. Mean elapsed time per trial in DMT with predetermined distance criteria (DC) of 30 , 50, and 80 cm per reward. (*D* and *E*) Performance in RRPST (*D*) and PLT (*E*). (*a*) Mean distance traveled per trial. (*b*) Mean number of rewards acquired per trial. Note that D1R-KO mice were retarded in acquisition of the PLT. All data are expressed as mean ± SEM. *, $P < 0.05$; **, $P < 0.001$ vs. WT group (Student's *t* test); †, $P < 0.05$ vs. same group on day 1 (Fisher's probable least-squares difference test).

after visiting the other. A trial was terminated when the mouse had received 50 BSR or 10 min had passed, whichever occurred first.

Behavioral Analysis. The methods of collection and analysis of behavioral data are described in ref. 15. A computer was programmed to monitor the following: (*i*) the number of nose pokes that occurred in the operant chamber; (*ii*) spontaneous locomotor activity in the open field; and (*iii*) the number of rewards acquired, distance traveled, and duration of each trial in the three spatial tasks. For the number of nose pokes, spontaneous locomotor activity, and trial duration in the DMT, a two-tailed Student *t* test ($P < 0.05$) was performed to determine whether statistically significant differences existed between control and experimental animals. The number of rewards and distance traveled in the RRPST and PLT were analyzed by using two-way ANOVA (animal type, between subjects; day, within subjects). For individual comparisons between subjects, we used the two-tailed Student *t* test; for those within subjects, we used Fisher's probable least-squares difference test ($P < 0.05$).

Electrophysiological Recording. To locate neural activity, the recording electrode assembly was advanced in the NAc at 20–40 μm per day. Activity from each microwire was screened daily while the mouse was in the recording apparatus until unit waveforms of sufficient amplitude yielding signal-to-noise ratio of >3:1 could be isolated. Subsequently, the well isolated unit was recorded while the mice performed the RRPST and PLT.

Analysis of Neuronal Responses to Reward and Location. The averaged firing rate during 4-s bin before the onset of rewards in RRPST trials served as the baseline rate, which was compared with the firing rate in the reward period, by a paired *t* test ($P < 0.05$). Based on responsiveness to BSR in the RRPST, each recorded neuron was classified into the inhibitory (I), excitatory (E), or no response (N) category. Identification of prereward and postreward responses of I-, E-, and N-type neurons were determined in the PLT. Neurons were considered to be prereward inhibitory (I_{pre}), excitatory (E_{pre}), no prediction response (N_{pre}), and postreward inhibitory (I_{post}), excitatory (E_{post}) or no postreward response (N_{post}) if they showed relevant responses in these phases at both of the two rewarding places. Place fields were determined by the data in the RRPST (15). A place field was a cluster of pixels with firing rate exceeding twice the identified mean firing rate, and each place field contained at least nine contiguous pixels.

Results

First, we tested the effect of D1R-KO on ICSS behavior. There was a significant difference in the mean current intensity for ICSS in an operant chamber between the two types of mice (Fig. 1*Aa*). The frequency–response curve for D1R-KO mice shifted rightward (Fig. 1*Ab*), indicating that they had an increased self-stimulation threshold. For ICSS behavior, changes in intensity and frequency of the stimulation are thought to produce parallel shifts in spatial and temporal summation, respectively, of the induced neural activity at synapses (18). Thus, in the D1R-KO mice, the rightward shift in either or both curves implies that more current is required to produce an equivalent reward as measured by the rate of operant responding.

In tests of forward locomotion over extended periods, the D1R-KO mice showed a significant reduction in activity compared with their WT littermates (Fig. 1*B*). We found differences in the elapsed time per trial between the two groups when various distance criteria were used in a DMT (Fig. 1*C*). This result demonstrates that the D1R-KO mice moved more slowly than the WT mice. This reduced locomotion was also evident during RRPST training over consecutive days (Fig. 1*Da*) and paralleled the fewer rewards that the mice acquired in this task (Fig. 1*Db*).

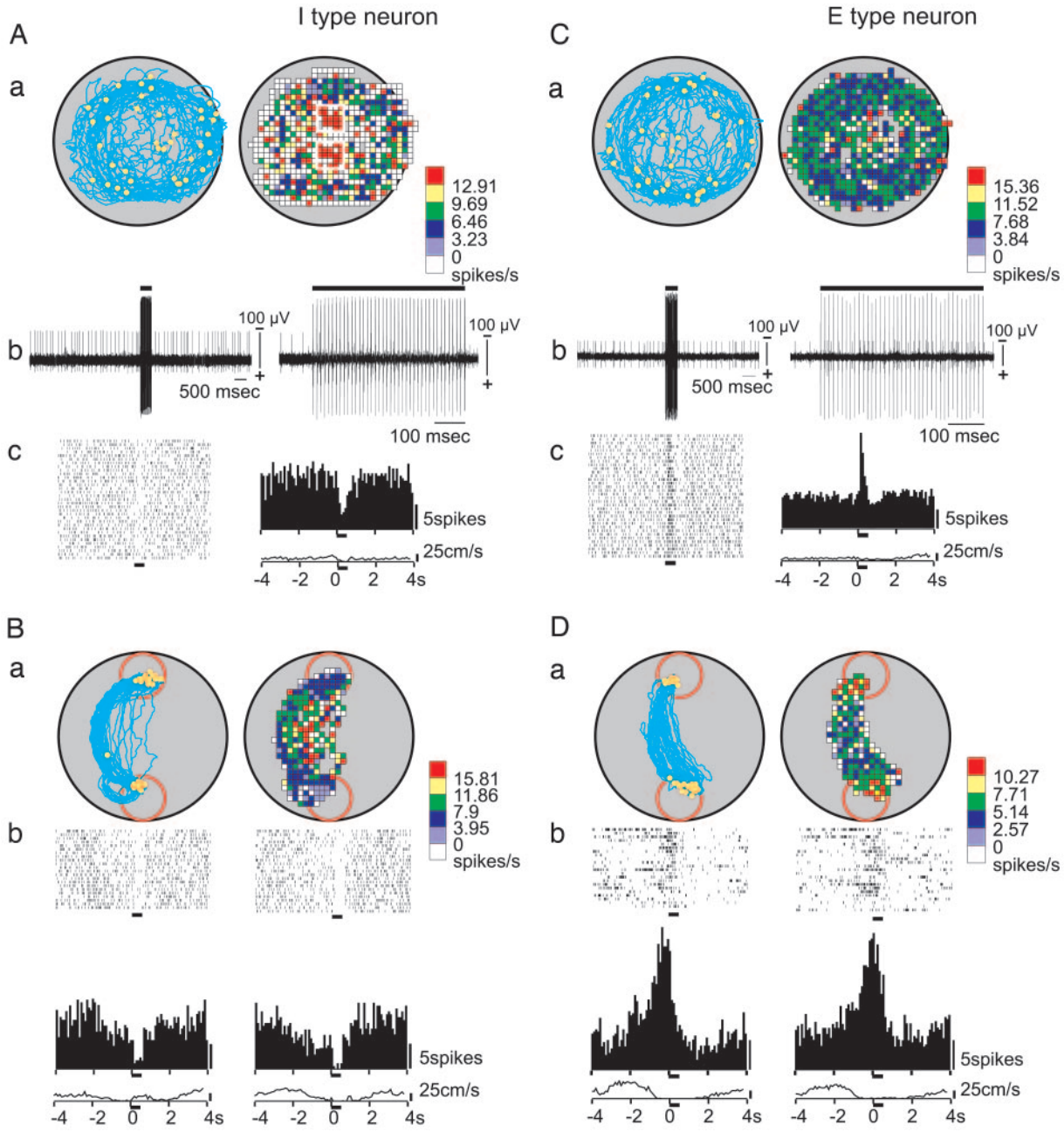

Fig. 2. Examples of accumbens neurons showing correlations with reward and place during RRPST and PLT in WT mice. (*A* and *C*) Performance of mice and neural responses in RRPST. (*a*) Trail of mouse (*Left*) and firing rate map (*Right*). Yellow dots in trail map indicate locations of reward delivery. (*b*) Single sweep of responses to BSR (*Left*) and its expanded display (*Right*). The bars above the sweeps indicate BSR period. (*c*) Rastergrams (*Left*), histograms of firing (*Right Upper*), and curve of averaged locomotion speed (*Right Lower*). (*B* and *D*) Performance of mice and neural responses in PLT. (*a*) Trail of mouse (*Left*) and firing rate map (*Right*). (*b*) Rastergram (*Left Upper*), histogram of firing (*Left Middle*), and curve of averaged locomotion speed (*Left Bottom*) corresponding to data recorded at upper red circled place. (*Right*) Rastergram, histogram, and curve of averaged speed corresponding to data recorded at lower red circled place. Note that the activity of this I-type neuron was not correlated with movement speed. Horizontal bars below rastergrams, histograms, and speed curves indicate BSR period. Color scale tables to the right of the firing maps indicate calibration for firing rate. The white open rectangles in the firing rate maps delineate place fields.

For testing spatial learning ability, we trained the mice in the PLT. The D1R-KO mice clearly were retarded in the acquisition of the PLT (Fig. 1*E*). They traveled less than the WT mice during the first 4 days (Fig. 1*Ea*) but obtained fewer rewards throughout 10 days of training (Fig. 1*Eb*). Although the D1R-KO mice increased the number of rewards they obtained over the course of training, they never reached the performance of the WT mice. Examination on the trails observed in the PLT revealed that, whereas the WT mice shuttled between two fixed rewarding places efficiently (Fig. 2 *Ba* and *Da*), the D1R-KO mice traveled in circles (Fig. 3 *Ba* and *Da*).

We next investigated how the D1R influences neural responses in the NAc during these behavioral tests. Typical examples of I- and E-type neural responses recorded from the WT mice during the RRPST are shown in Fig. 2 *A* and *C*, respectively. During the BSR period, suppression in firing of the I-type neurons ranged from 34% to 90% (Fig. 2*A b* and *c*), and facilitation of the E-type ranged from 60% to 500% (Fig. 2*C b*

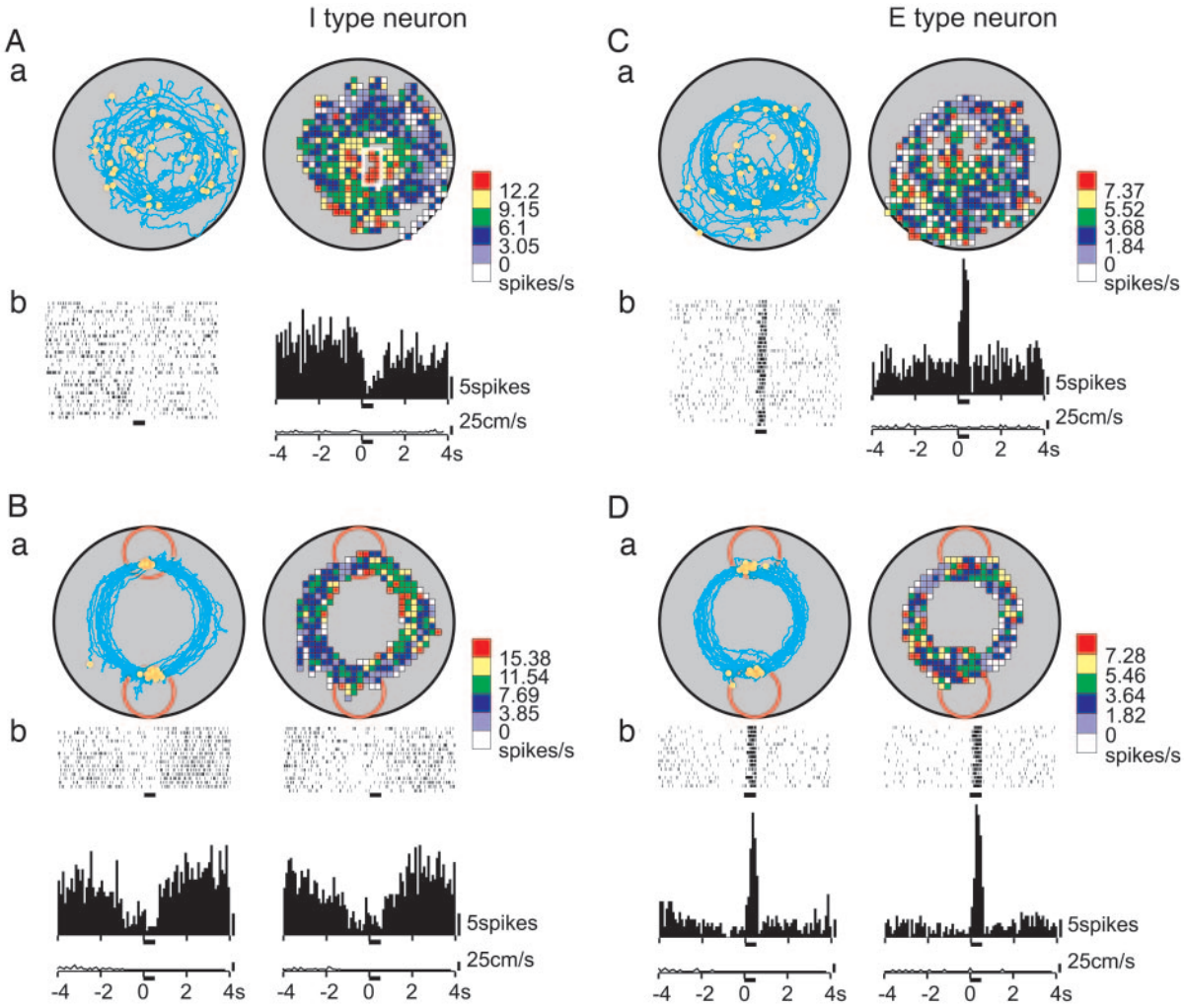

Fig. 3. Examples of accumbens neurons showing correlations with reward and place during RRPST and PLT in D1R-KO mice. (*A* and *C*) Performance of mice and neural responses in RRPST. (*a*) Trail of mouse, reward locations (*Left*), and firing rate map (*Right*). (*b*) Rastergrams (*Left*), histograms of firing (*Right Upper*), and curves of averaged locomotion speed (*Right Lower*). (*B* and *D*) Performance of mice and neural responses in PLT. Other notations were the same as for those in Fig. 2. Note that prereward excitation is absent in E-type neuron (*Db*), whereas I-type neurons still display prereward inhibition (*Bb*).

and *c*). These I- and E-type neurons in the RRPST also showed prereward inhibitory (Fig. 2*Bb*) or excitatory (Fig. 2*Db*) responses in the PLT, respectively. In the WT mice, most of the I- and E-type neurons showed their respective responses of 1–1.5 s preceding the reward delivery, with I-type neurons showing decreases in prereward firing from 32% to 73% and E-type neurons showing prereward excitatory with increases in firing from 40% to 300%. Postreward responses lasted for 0.5–1.5 s, with decreases in firing from 32% to 85% or increases in firing from 42% to 250%.

Fig. 3 *A* and *C* shows typical I- and E-type neurons recorded from the D1R-KO mice in the RRPST. In the PLT, the prereward inhibitory response appeared normally (Fig. 3*Bb*) in the I-type neuron, which also displayed an inhibitory response in the reward and postreward phases. Conversely, the prereward excitatory response was absent in the E-type neuron (Fig. 3*Db*). In fact, this E-type neuron displayed prereward inhibitory response.

The activity of 67 and 61 neurons was recorded from the medial core part of the NAc of the WT and D1R-KO mice, respectively, during the RRPST and PLT tests. Table 1 compares the response characteristics of neurons from the WT and D1R-KO mice. Consistent with our previous studies using rats (19) and mice (15), in WT mice, the number of neurons with prereward excitatory responses (9 of 67, 13.5%) was roughly equal to those with inhibitory responses (11 of 67, 16.3%). In the D1R-KO mice, in contrast, there were no neurons with prereward excitatory responses (0 of 61, 0%), whereas the number of prereward inhibitory neurons (9 of 61, 14.8%) was comparable with that of the WT mice. Interestingly, although the number of I-type neurons with prereward inhibitory responses did not differ between the WT and D1R-KO mice, there were a few E-type neurons having prereward inhibitory responses in the D1R-KO mice (3 of 61, 4.9%), but none in the WT mice. The total number of responding neurons in the reward and postreward phases did not differ significantly between the two groups.

The average place-field size of place-related neurons (i.e., neurons that increased their activity when the mouse was at a specific location in the open field) in the D1R-KO mice was about half that of the WT mice (Table 1) (D1R-KO, 172 ± 21 cm^2, 3.4% of recording arena; WT, 350 ± 52 cm^2, 7% of recording arena; $P < 0.05$). Fig. 2*A* shows an example of a place-related neuron in the WT mice, with a place field located at the center of the open field. An I-type neuron from a D1R-KO mouse with a smaller place field is illustrated in Fig. 3*A*.

Table 1. Accumbens neural responses in the WT and D1R-KO mice

		Prereward			Postreward			Place-related	
Mice	No. (%)	I_{pre}, no. (%)	E_{pre}, no. (%)	N_{pre}, no. (%)	I_{post}, no. (%)	E_{post}, no. (%)	N_{post}, no. (%)	No. (%)	Size, cm^2 (ratio vs. WT)
WT									
I	21 (31.3)	7 (10.3)	2 (3.0)	12 (18.0)	5 (7.4)	3 (4.5)	13 (19.4)	2 (3.0)	350 ± 52 (1)
E	8 (12.0)	0 (0.0)	4 (6.0)	4 (6.0)	2 (3.0)	2 (3.0)	4 (6.0)	2 (3.0)	
N	38 (56.7)	4 (6.0)	3 (4.5)	31 (46.2)	4 (6.0)	1 (1.5)	33 (49.2)	2 (3.0)	
Total	67 (100)	11 (16.3)	9 (13.5)	47 (70.2)	11 (16.4)	6 (9.0)	50 (74.6)	6 (9.0)	
D1R-KO									
I	17 (27.9)	4 (6.6)	0 (0.0)	13 (21.3)	5 (8.2)	3 (4.9)	9 (14.8)	3 (4.9)	172 ± 21† (0.49/1)
E	8 (13.1)	3 (4.9)	0 (0.0)	5 (8.2)	2 (3.3)	1 (1.6)	5 (8.2)	2 (3.3)	
N	36 (59.0)	2 (3.3)	0 (0.0)	34 (55.7)	4 (6.6)	1 (1.6)	31 (50.8)	2 (3.3)	
Total	61 (100)	9 (14.8)	0* (0.0)	52 (85.2)	11 (18.1)	5 (8.1)	45 (73.8)	7 (11.5)	

Neurons recorded from the WT and D1R-KO mice were classified as inhibitory (I), excitatory (E), or no response (N) according to their responses to BSR in the RRPST. The responses of classified neurons before (pre) and after (post) reward were examined in the PLT. Place field sizes were measured in the RRPST.
*$P < 0.01$ (χ^2 test).
†$P < 0.05$ (*t* test).

Discussion

Major neural systems of the brain use dopamine as a principal neurotransmitter to mediate locomotor (nigrostriatal system), motivated behavior (mesolimbic system), and learning and memory (mesocortical system). Impairments in the nigrostriatal pathway contribute to dysfunctional movement, a common symptom in Parkinson's disease. Therefore, the reduced locomotor activity observed in the D1R-KO mice may have resulted from changes in the D1R system in the nigrostriatal system. Previously, we have shown that D2R-KO also resulted in a reduction of locomotor activity (15), but milder than that of the D1R-KO mice. Thus, both D1R and D2R are involved in control of locomotor behavior, and they function in a synergistic interaction manner (20–22). The mesolimbic and mesocortical pathways, arising mainly from the ventral tegmental area and innervating the mesial parts of the limbic system, including the NAc, AM, HF, and prefrontal cortex, function in incentive motivational processes (1, 7–9). It has been reported that reward information is processed in the prefrontal cortex, AM, and ventral tegmental area (3, 23–28), and spatial information is processed in the HF (5, 29, 30), both of which then converge on NAc neurons (10, 11, 15, 19). The D1R-KO eliminated the prereward excitatory response in the NAc of mice, whereas the response during and after reward was unchanged. The D1R facilitates synaptic excitatory responses induced by activation of *N*-methyl-D-aspartate receptors (11, 31). Based on our observations, we suggest that the D1R plays a critical role in coding the prereward excitatory response of NAc dopaminoceptive neurons during the incentive phase, but not in the rewarding (consummatory) or postreward phases of motivated behavior. Alteration in neural responses in incentive phase in the D1R-KO mice could reflect the essential contribution of the D1R in predictive response of NAc neurons. However, it also might reflect dysfunction of the D1R in the structures providing reward information to the NAc, such as the AM. Action of dopamine expressed via the D1R and D2R in the NAc and its afferent sources may interact with glutamatergic action through NMDA receptors (11, 20–22, 31), which then affect learning (5, 32) or other conditions such as drug sensitization (33). Depletion of dopamine, and lesions of the NAc or its afferent pathways, such as damage to the HF, cause changes in spatial performance (2, 5, 34, 35). A blockade of D1-like receptors caused a decrease in stability of hippocampal place fields (36), which in turn could influence spatial task performance. In the D1R-KO mice, therefore, the impairment of spatial learning in parallel with changes in the NAc place-related activity could be attributed to hippocampal dysfunction due to the lack of D1R.

Information about the location of a reward and predicting its availability is important for establishing approach behavior (3). Previously, we found that the D2R-KO failed to exhibit a prereward inhibitory response but that its prereward excitatory response was unchanged. These mice and their WT controls also performed the PLT comparably (15). In contrast, NAc neurons in the D1R-KO mice reported here lacked prereward excitatory responses, and these mice performed poorly in the PLT. Based on the data from both types of KOs, we suggest that the prereward excitatory response in NAc neurons depends on the D1R, and it might partly contribute to perform spatial tasks based on memory of a place associated with reward (e.g., the PLT). The prereward inhibitory response, conversely, appears to depend on the D2R (15). It was unchanged in the I-type cells or even increased in the E-type cells of D1R-KO mice but clearly was insufficient to permit normal performance of the PLT. Thus, we have demonstrated that lacking of the D1R resulted in the spatial learning deficit and selective incentive alterations in the NAc neural response, suggesting an important contribution of D1R in neural mechanism for spatial associative learning at neural and behavioral levels.

This work was supported in part by a Ministry of Education, Culture, Sports, Science and Technology (Japan) Grant-in-Aid for Scientific Research on Priority Areas (C), Advanced Brain Science Project.

1. Everitt, B. J. & Wolf, M. E. (2002) *J. Neurosci.* **22,** 3312–3320.
2. Gasbarri, A., Sulli, A., Innocenzi, R., Pacitti, C. & Brioni, J. D. (1996) *Neuroscience* **74,** 1037–1044.
3. Schultz, W. (1998) *J. Neurophysiol.* **80,** 1–27.
4. Waelti, P., Dickinson, A. & Schultz, W. (2001) *Nature* **412,** 43–48.
5. Wilkerson, A. & Levin, E. D. (1999) *Neuroscience* **89,** 743–749.
6. Williams, G. V. & Goldman-Rakic, P. S. (1995) *Nature* **376,** 572–575.
7. Ikemoto, S. & Panksepp, J. (1999) *Brain Res. Brain Res. Rev.* **31,** 6–41.
8. Kalivas, P. W. & Nakamura, M. (1999) *Curr. Opin. Neurobiol.* **9,** 223–227.
9. Robbins, T. W. & Everitt, B. J. (1996) *Curr. Opin. Neurobiol.* **6,** 228–236.
10. Finch, D. M. (1996) *Hippocampus* **6,** 495–512.
11. Floresco, S. B., Blaha, C. D., Yang, C. R. & Phillips, A. G. (2001) *J. Neurosci.* **21,** 2851–2860.
12. LeDoux, J. (2002) *Synaptic Self: How Our Brains Become Who We Are* (Viking Penguin, New York).
13. Drago, J., Gerfen, C. R., Lachowicz, J. E., Steiner, H., Hollon, T. R., Love, P. E., Ooi, G. T., Grinberg, A., Lee, E. J., Huang, S. H., *et al.* (1994) *Proc. Natl. Acad. Sci. USA* **91,** 12564–12568.
14. Glickstein, S. B. & Schmauss, C. (2001) *Pharmacol. Ther.* **91,** 63–83.
15. Tran, A. H., Tamura, R., Uwano, T., Kobayashi, T., Katsuki, M., Matsumoto, G. & Ono, T. (2002) *Proc. Natl. Acad. Sci. USA* **99,** 8986–8991.

16. Xu, M., Moratalla, R., Gold, L. H., Hiroi, N., Koob, G. F., Graybiel, A. M. & Tonegawa, S. (1994) *Cell* **79,** 729–742.
17. Franklin, K. B. J. & Paxinos, G. (1997). *The Mouse Brain in Stereotaxic Coordinates* (Academic, San Diego).
18. Gallistel C. R. (1976) in *Brain-Stimulation Reward*, eds. Wauquier, A. & Rolls, E. T. (North–Holland, Amsterdam), pp. 97–99.
19. Martin, P. D. & Ono, T. (2000) *Behav. Brain Res.* **116,** 23–38.
20. David, H. N. & Abraini, J. H. (2002) *Eur. J. Neurosci.* **15,** 869–875.
21. Mele, A., Castellano, C., Felici, A., Cabib, S., Caccia, S. & Oliverio, A. (1996) *Eur. J. Pharmacol.* **308,** 1–12.
22. Tomiyama, K., McNamara, F. N., Clifford, J. J., Kinsella, A., Koshikawa, N. & Waddington, J. L. (2001) *Eur. J. Pharmacol.* **418,** 47–54.
23. Baeg, E. H., Kim, Y. B., Huh, K., Mook-Jung, I., Kim, H. T. & Jung, M. W. (2003) *Neuron* **40,** 177–188.
24. Schoenbaum, G., Chiba, A. A. & Gallagher, M. (1998) *Nature Neurosci.* **1,** 155–159.
25. Schoenbaum, G., Setlow, B., Saddoris, M. P. & Gallagher, M. (2003) *Neuron* **39,** 855–867.
26. Watanabe, M. (1996) *Nature* **382,** 629–632.
27. Yamatani, K., Ono, T., Nishijo, H. & Takaku, A. (1990) *Behav. Neurosci.* **104,** 503–531.
28. Ono, T., Nishijo, H. & Uwano, T. (1995) *Prog. Neurobiol.* **46,** 401–422.
29. Kobayashi, T., Nishijo, H., Fukuda, M., Bures, J. & Ono, T. (1997) *J. Neurophysiol.* **78,** 597–613.
30. Kobayashi, T., Tran, A. H., Nishijo, H., Ono, T. & Matsumoto, G. (2003) *Neuroscience* **117,** 1025–1035.
31. Levine, M. S., Altemus, K. L., Cepeda, C., Cromwell, H. C., Crawford, C., Ariano, M. A., Drago, J., Sibley, D. R. & Westphal, H. (1996) *J. Neurosci.* **16,** 5870–5882.
32. Smith-Roe, S. L. & Kelley, A. E. (2000) *J. Neurosci.* **20,** 7737–7742.
33. Capper-Loup, C., Canales, J. J., Kadaba, N. & Graybiel, A. M. (2002) *J. Neurosci.* **22,** 6218–6227.
34. Floresco, S. B., Braaksma, D. & Phillips A. G. (1999) *J. Neurosci.* **19,** 11061–11071.
35. Morris, R. G. M., Garrud, P., Rawlins, J. N. P. & O'Keefe, J. O. (1982) *Nature* **297,** 681–683.
36. Kentros, C. G., Agnihotri, N. T., Streater, S., Hawkins, R. D. & Kandel, E. R. (2004) *Neuron* **42,** 283–295.