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Ontogeny of Enhanced Striatal Dopamine Release in Rats With Methamphetamine-Induced Behavioral Sensitization

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TSUCHIDA, K., H. UJIKE, A. KANZAKI, Y. FUJIWARA AND K. AKIYAMA. *Ontogeny of enhanced striatal dopamine release in rats with methamphetamine-induced behavioral sensitization.* PHARMACOL BIOCHEM BEHAV **47**(1) 161-169, 1994. – The behavioral sensitization has not been observed in rats under three weeks of age when administration of repeated psychostimulants is started. The aim of our study was to determine the effect of methamphetamine (MAP)-induced behavioral sensitization ontogeny on MAP challenge-induced changes of striatal extracellular concentrations of dopamine (DA) and its metabolites, using in vivo microdialysis. Experimental rats aged 7, 14, 21, 28, and 56 postnatal days (PNDs) were injected IP twice daily with 2 mg/kg MAP for three days, followed by 4 mg/kg for three days. Matched control rats were given equivalent volumes of saline according to the same schedule. Dialysis experiments were carried out 21 days after the last MAP or saline injection. All the rats were injected (IP) with a challenge dose of MAP (4 mg/kg). We reconfirmed that MAP-induced stereotyped behavior was enhanced significantly only when MAP pretreatment was started on PNDs 21, 28, and 56, but not PNDs 7 and 14. Correspondingly, the MAP challenge induced significantly greater increases in striatal extracellular DA concentrations in the MAP-pretreated rats compared with control rats only when MAP pretreatment was initiated on PNDs 21, 28, and 56, but not in younger rats.

Ontogeny Behavioral sensitization Methamphetamine Microdialysis Dopamine

REPEATED administration of amphetamine (AMP) or methamphetamine (MAP) induces progressive augmentation of stereotyped behavior and/or locomotor activity in adult animals (11). This phenomenon, called behavioral sensitization (BS) or reverse tolerance, has become an established animal model of the clinical courses of amphetamine psychosis and paranoid schizophrenia (12,19).

Recent studies using an intracerebral microdialysis technique have revealed that the augmented stereotypy induced by a challenge injection of AMP or MAP in sensitized rats is associated with enhanced dopamine (DA) release from dopaminergic nerve terminals in brain regions such as the striatum and nucleus accumbens (10,18). Kazahaya et al. reported that a challenge injection of MAP induced a significantly greater increase in the extracellular DA concentrations in MAP-pretreated rats than in saline-pretreated control rats (10).

Several pieces of evidence have indicated that BS to the psychostimulants evolves only when subchronic administration is commenced after a certain number of postnatal days (PNDs). In a previous study we found that neonatal rats pretreated with MAP for five days from PNDs 2, 7, 12, and 17 failed to exhibit BS to a challenge dose of this drug administered on PND 35 (6). However, when pretreatment was started on PNDs 22 and 27, BS was observed in response to a challenge dose of MAP on PND 35 (6). Although this finding suggests that MAP-BS occurs after PND 22, the disadvantage of this experimental design is that the abstinence period before the challenge test differed among the groups, since pretreatment was initiated on different PNDs. Kolta et al. maintained a constant interval between the final pretreatment and challenge doses and observed the behavioral responses to a challenge dose of AMP given 15 days after the last dose of the AMP pretreatment started on PNDs 1, 7, 21, and 49 (13). They demonstrated that AMP-induced BS occurred when AMP pretreatment was initiated on PND 49, but no earlier (13). However, they did not give any data between PND 21 and PND 49.

In this study, in addition to behavioral observations, we

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investigated neurochemical mechanisms underlying MAP-BS ontogeny by measuring the extracellular levels of DA and its major metabolites in the striata of rats pretreated with MAP on different PNDs, using in vivo microdialysis.

MATERIALS AND METHODS

Animals and Drug Treatment

Pregnant Sprague-Dawley rats were purchased from Charles River Co. (Japan). The male pups were culled, divided into two subgroups (MAP and saline rats) and housed with their mothers (one family per cage) for three weeks in an environment of constant temperature (24°C), humidity, and lighting (12-h light-dark cycle). The pups were weaned on PND 21 and subsequently were housed four to a cage. The drug pretreatment schedules are shown in Fig. 1. The experimental pups were treated with MAP hydrochloride (Dainippon Co., Japan) for six days, beginning on PND 7 (group 1), PND 14 (group 2), PND 21 (group 3), PND 28 (group 4), and PND 56 (group 5). They were injected (IP) twice daily with 2 mg/kg MAP for three days, followed by 4 mg/kg MAP for three days. Matched control animals were given equivalent volumes of saline (IP) according to the same schedule (Fig. 1).

In Vivo Microdialysis

Dialysis probes which were described previously (10) were used. The dialysis probes were made from ethylene vinyl alcohol plasmapheresis tubing (Evaflex A2, 200 μm diameter; Kurare Co., Osaka, Japan) with a molecular weight cutoff of 75,000. The fiber was bent into a U-shaped loop, inserted into a 21-gauge stainless steel cannula leaving a 6-mm length exposed at each end, which was joined to a 23-gauge cannula with epoxy resin. In vitro experiments showed that recovery of DA from the external medium into the dialysis probe, at a flow rate of 2 μl/min, was approximately 15%. Twenty days after completion of the MAP or saline pretreatment regimens (Fig. 1), each rat was placed on a stereotaxic frame under pentobarbital sodium (50 mg/kg, IP) anesthesia and a dialysis probe was implanted into the left anterior dorsal striatum [coordinates: rostal +2.4 mm, lateral +3.0 mm from the bregma, ventral −6.0 mm from dural surface, according to the atlas of Pellegrino et al. (16)]. The size of brains reaches the adult level by five postnatal weeks when the dialysis experiments were carried out in rats which were treated with MAP beginning on PND 7. Therefore, these coordinates did not need to be adjusted throughout the experiments. We confirmed histologically that the locations of probe tips implanted into the striata did not differ among the rats of various age

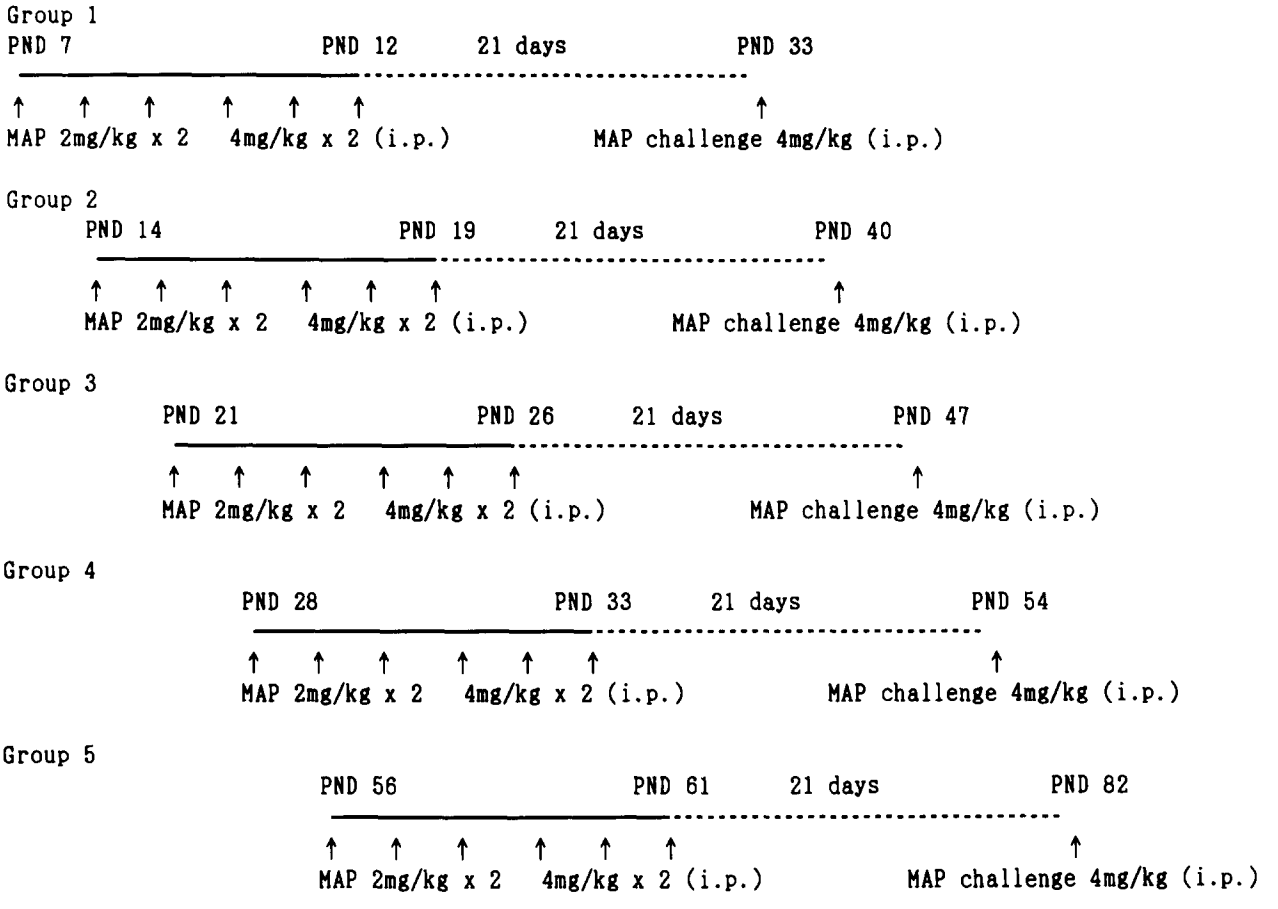

FIG. 1. The drug treatment schedules of methamphetamine-pretreated rats. The experimental pups were treated with MAP hydrochloride for six days (twice daily with 2 mg/kg MAP for three days, followed by 4 mg/kg MAP for three days) beginning on PND 7 (group 1), PND 14 (group 2), PND 21 (group 3), PND 28 (group 4), and PND 56 (group 5). All the rats were injected with a challenge dose of MAP (4 mg/kg, IP) 21 days after the last MAP injection.

groups. The dialysis experiments were carried out the next day (21 days after the last MAP or saline injection). All the rats were injected with a challenge dose of MAP (4 mg/kg, IP). They were conscious during the experiments. The dialysis probe was perfused continuously at 2 μl/min with artificial cerebrospinal fluid (CSF; Na^+, 140 mM; K^+, 3.35 mM; Ca^{2+}, 1.26 mM; Mg^{2+}, 1.15 mM; Cl^-, 151 mM, pH 6.5), and perfusates were collected every 20 min. On completion of the experiments the rats were anesthetized deeply with ether and their brains were perfused transcardially with 10% formalin, removed, and fixed, and the position of each probe was checked histologically.

The perfusates were injected directly onto a reversed-phase high performance liquid chromatography column (Irika Co., Japan) with a coulometric electrochemical detection system (ESA Co., USA; guard electrode = +0.4 V, oxidation elec-

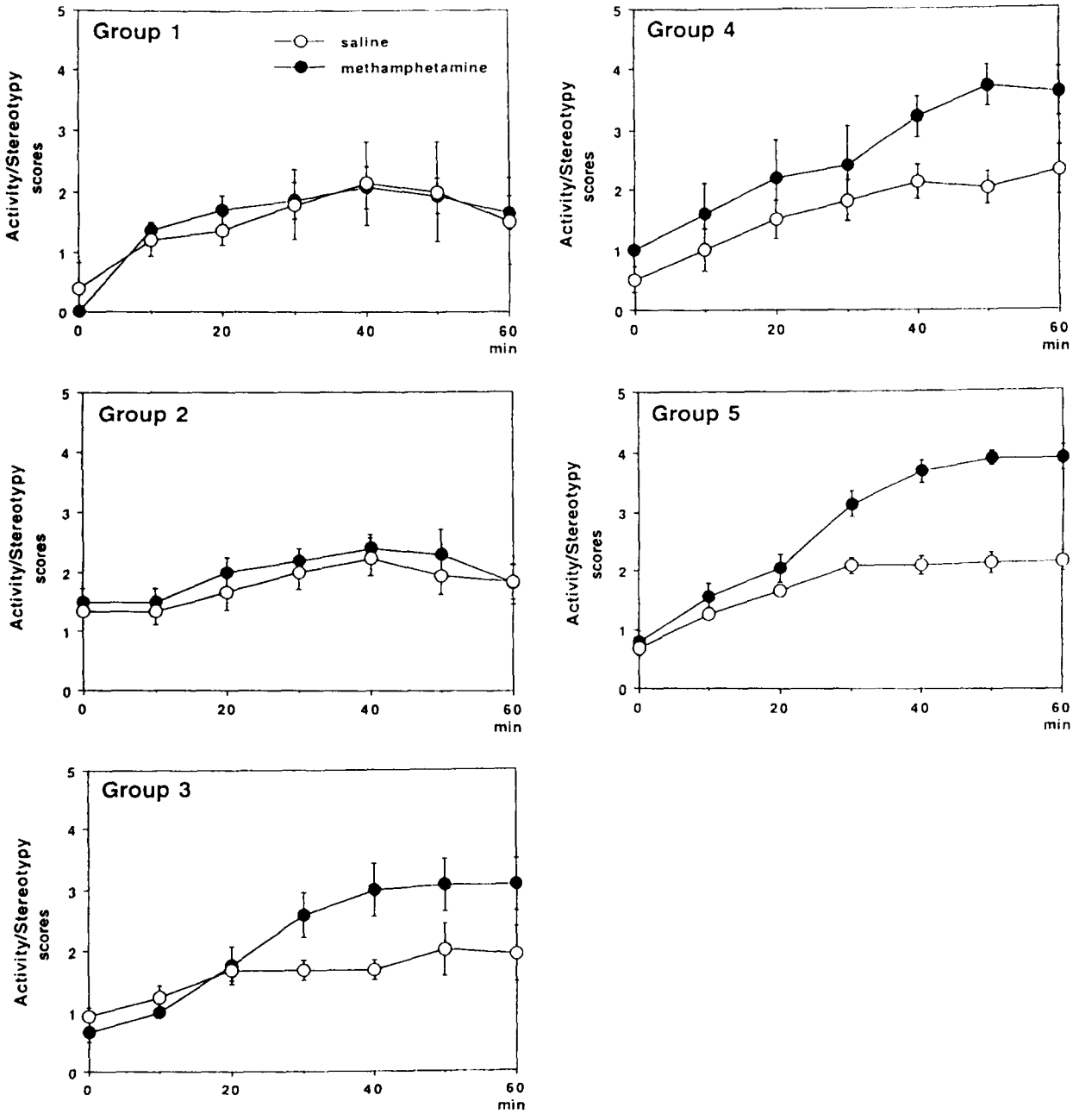

FIG. 2. Time course of activity and stereotypy induced by methamphetamine (MAP, 4 mg/kg) in rats 21 days after withdrawal from MAP (●, twice-daily IP injections of 2 mg/kg for three days, followed by 4 mg/kg for three days) or normal saline (○). The activity/stereotypy scores were significantly higher in the MAP-pretreated rats than in the saline-pretreated control rats in group 3 ($P < 0.01$), group 4 ($P < 0.01$), and group 5 ($P < 0.05$), but not in group 1 and group 2; groups 1–4 two-way ANOVA, group 5 Scheffe's method.

trode = +0.05 V, reduction electrode = −0.35 V) to measure the DA, 3,4-dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA) concentrations. The DA, DOPAC, and HVA were separated at 27°C by ion-pair reversed-phase chromatography using Cosmosil ODS-C18 5-μm resin (Nakarai Co., Japan), and the mobile phase comprised 0.05 M sodium dihydrogen phosphate buffer (pH 4.3) containing EDTA (0.05 mM), octanesulfonic acid (1 mM), 5% methanol, and 5% acetone. When the values of three samples were stable, the challenge of MAP injection was administered immediately (their mean was regarded as the zero time value), and measurements were continued for 3 h thereafter.

Behavioral Observation

Behavioral observations were conducted in parallel with the striatal perfusate collections in rats which were pretreated and subjected to MAP challenge as described above. Each rat was videotaped for 60 s every 10 min for 60 min after the MAP challenge. Their behavior was scored by a single trained rater, who was unaware of the pretreatment conditions, according to the following activity/stereotypy rating system (23): 0 = asleep or still, 1 = locomotion with normal exploration and normal sniffing and head movement pattern, 2 = increased sniffing and head movement rate associated with hyperlocomotion and rearing, 3 = sporadic stereotyped sniffing and stereotyped up–down head movements with periodic locomotion activity, 4 = almost continuous stereotyped sniffing and head movements occasionally interrupted by brief periods of locomotion, and 5 = continuous and intense stereotyped sniffing and repetitive head movements at one location.

Statistical Analysis

The differences in the mean dialysate baseline concentrations of DA and its metabolites between the MAP- and corresponding saline-pretreated rats of each group and in those among MAP- or saline-pretreated rats of different groups were analyzed using one-way analysis of variance (ANOVA). The changes in the extracellular concentrations of DA and its metabolites and activity/stereotypy scores that occurred in the MAP- and corresponding saline-pretreated rats of each group were compared using two-way ANOVA. When two-way ANOVA revealed the significant interaction between pretreatment and time, data were analyzed by using multiple comparison of Scheffe's method. Differences at $P < 0.05$ were considered to be significant.

RESULTS

Behavioral Observation

The behavioral data are presented in Fig. 2. Even in the youngest group 1 rats (they were PND 33 when the experiments were carried out), the challenge dose of MAP showed apparent motor stimulating effects. In fact, it induced a significant increase in activity/stereotypy scores, $F(5, 72) = 2.97$, $P < 0.02$.

The MAP challenge induced significantly higher activity/stereotypy scores in the MAP-pretreated rats than in the saline-pretreated control rats in group 3, $F(1, 60) = 14.4$, $P < 0.01$, and group 4, $F(1, 48) = 16.6$, $P < 0.01$, but not in group 1, $F(1, 72) = 0.435$, NS) and group 2, $F(1, 54) = 1.376$, NS). In group 5, since interaction between pretreatment and time was significant, the data were analyzed by using multiple comparison of Scheffe's method. It demonstrated that the MAP-pretreated rats in group 5 showed significant higher intensity of activity/stereotypy scores than corresponding saline-pretreated rats at 40, 50, and 60 min after MAP challenges ($P < 0.05$).

TABLE 1

CONCENTRATION IN STRIATAL PERFUSATE (fmol/μl) (MEAN ± SEM)

Group	*n*	DA	DOPAC	HVA
1				
Controls	7	3.69 ± 0.34	567 ± 110	523 ± 61.5
MAP	7	4.05 ± 0.59	689 ± 107	500 ± 59.9
2				
Controls	6	5.99 ± 0.97	528 ± 37.7	690 ± 46.1
MAP	5	5.94 ± 0.91	615 ± 118	642 ± 68.5
3				
Controls	6	5.19 ± 1.07	663 ± 118	666 ± 54.1
MAP	6	4.80 ± 0.91	799 ± 149	674 ± 76.4
4				
Controls	5	3.10 ± 0.44	556 ± 109	642 ± 77.5
MAP	5	2.57 ± 0.11	699 ± 126	710 ± 76.4
5				
Controls	12	5.49 ± 0.49	758 ± 77.2	642 ± 52.1
MAP	12	5.35 ± 0.47	790 ± 93.1	682 ± 53.1

Baseline striatal levels of extracellular DA, DOPAC and HVA. The values shown are the mean ± SEM. Baseline striatal perfusate concentrations of DA, DOPAC and HVA in rats 21 days after withdrawal from MAP (twice daily IP injections of 2 mg/kg for 3 days followed by 4 mg/kg for 3 days) or normal saline. There were no significant differences in the levels of DA, DOPAC and HVA between the MAP-pretreated and saline-pretreated control rats (one-way ANOVA). There were neither significant differences in the basal levels of DA, DOPAC and HVA among the MAP-pretreated groups nor among the saline-pretreated groups (one-way ANOVA).

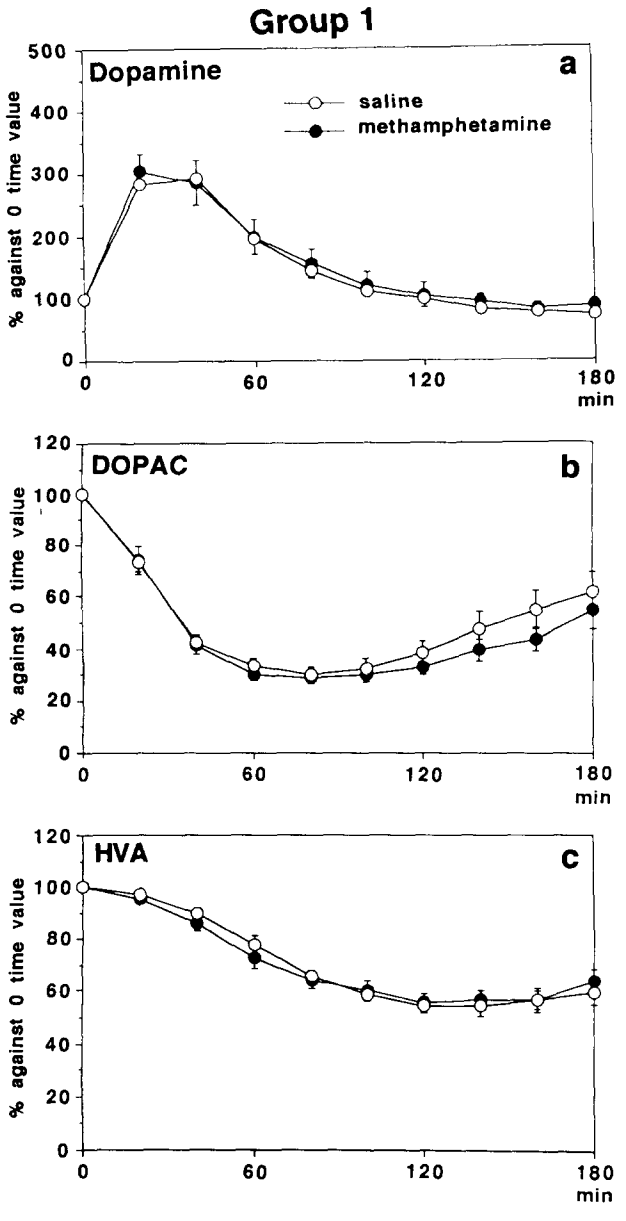

FIG. 3. Group 1. Effect of methamphetamine (MAP, 4 mg/kg) on (a) DA, (b) DOPAC, and (c) HVA concentrations in striatal perfusates of rats 21 days after withdrawal from MAP (●, twice-daily IP injections of 2 mg/kg for three days, followed by 4 mg/kg for three days, n = 7) or normal saline (○, n = 7) started on PND 7. The data are expressed as percent (mean ± SE) of the zero time value. There were no significant differences in the respective levels of DA, DOPAC, and HVA between the MAP- and saline-pretreated rats (two-way ANOVA).

Microdialysis Study

Baseline levels of extracellular DA, DOPAC, and HVA in the striatum. There were no significant differences in the basal levels of DA, DOPAC, and HVA between the MAP- and matched saline-pretreated control rats of each group. Neither were there significant differences in the baseline concentrations of DA and its metabolites among the MAP- or the saline-pretreated rats of different groups. The baseline concentrations of these compounds in the striatal perfusates are summarized in Table 1.

Striatal DA and metabolites following injection of MAP challenge. The group 1 data are shown in Fig. 3. The MAP challenge enhanced the extracellular DA concentrations. In the MAP-pretreated rats started on PND 7, the mean extracellular DA concentration peaked (307 ± 25.4% [mean ± SE]

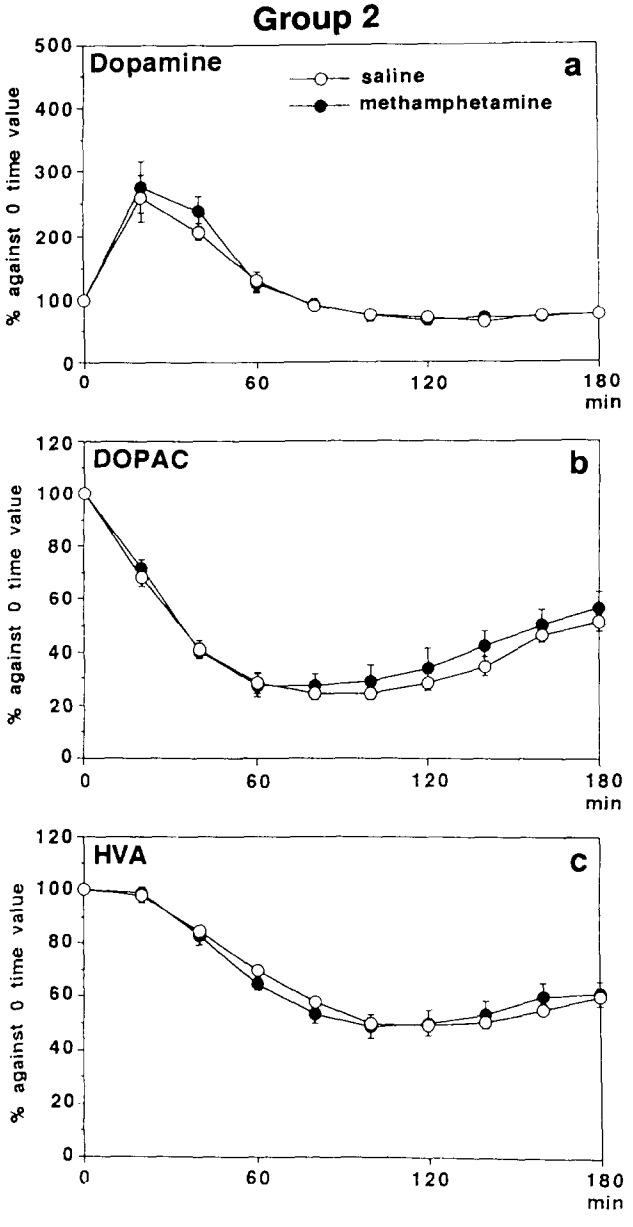

FIG. 4. Group 2. Effect of methamphetamine (MAP, 4 mg/kg) on (a) DA, (b) DOPAC, and (c) HVA concentrations in striatal perfusates of rats 21 days after withdrawal from MAP (●, twice-daily IP injections of 2 mg/kg for three days, followed by 4 mg/kg for three days, n = 5) or normal saline (○, n = 6) started on PND 14. The data are expressed as percent (mean ± SE) of the zero time value. There were no significant differences in the respective levels of DA, DOPAC, and HVA between the MAP- and saline-pretreated rats (two-way ANOVA).

of the zero time value, $n = 7$) during the first 20 min following the challenge MAP injection. In the saline-pretreated control rats, it peaked (294 ± 31.0%, $n = 7$) 20–40 min after the challenge MAP injection. These mean concentrations did not differ significantly, $F(1, 108) = 0.695$, NS). The MAP challenge also reduced the extracellular DOPAC and HVA concentrations, and their respective values between MAP- and saline-pretreated rats of this group did not differ significantly.

The group 2 data are shown in Fig. 4. The MAP challenge

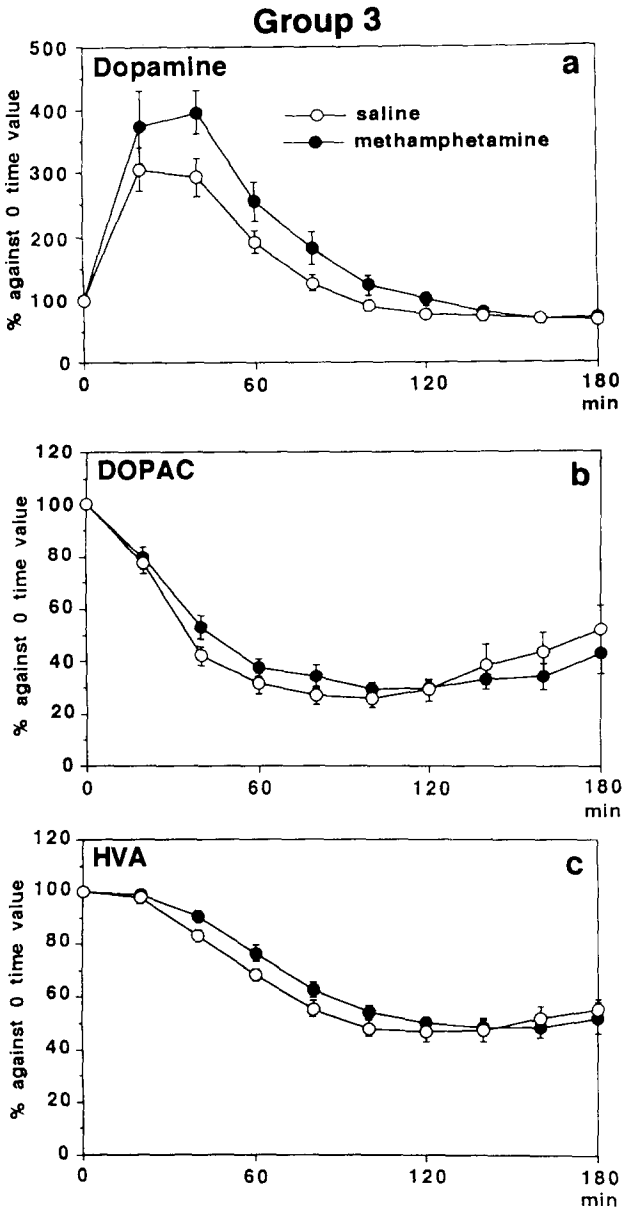

FIG. 5. Group 3. Effect of methamphetamine (MAP, 4 mg/kg) on (a) DA, (b) DOPAC, and (c) HVA concentrations in striatal perfusates of rats 21 days after withdrawal from MAP (●, twice-daily IP injections of 2 mg/kg for three days, followed by 4 mg/kg for three days, $n = 6$) or normal saline (○, $n = 6$) started on PND 21. The data are expressed as percent (mean ± SE) of the zero time value. The DA concentration was significantly higher in the MAP-pretreated rats than in the saline-pretreated control rats ($P < 0.01$), and there were no differences in the respective concentrations of DOPAC and HVA between the MAP- and saline-pretreated rats (two-way ANOVA).

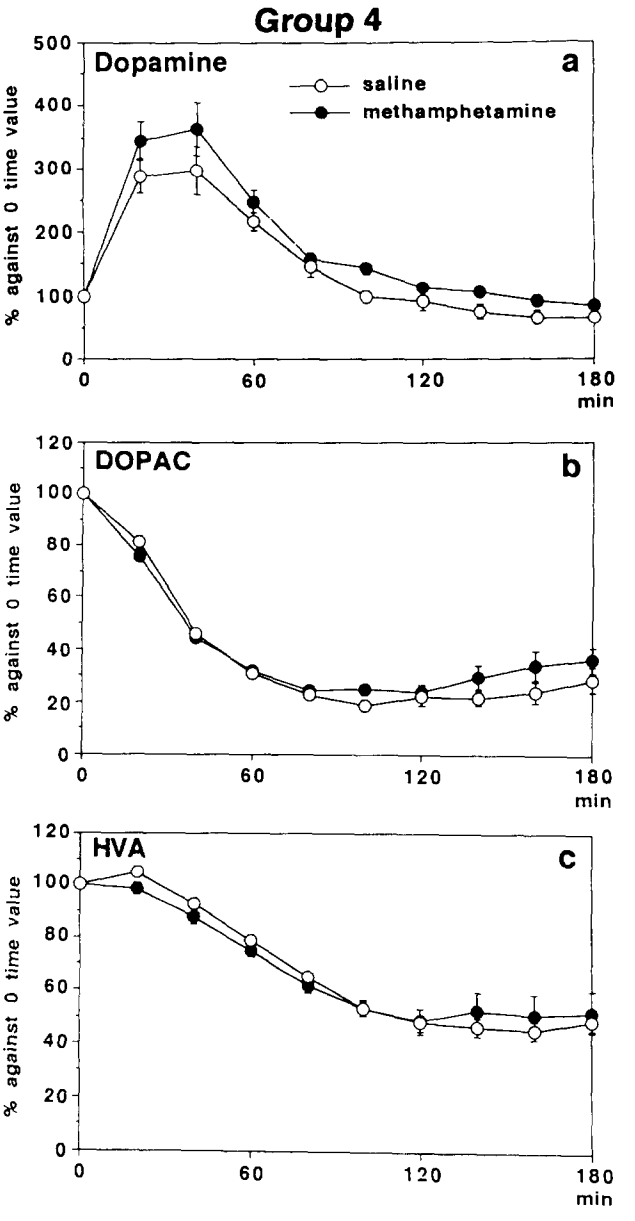

FIG. 6. Group 4. Effect of methamphetamine (MAP, 4 mg/kg) on (a) DA, (b) DOPAC, and (c) HVA concentrations in striatal perfusates of rats 21 days after withdrawal from MAP (●, twice-daily IP injections of 2 mg/kg for three days, followed by 4 mg/kg for three days, $n = 5$) or normal saline (○, $n = 5$) started on PND 28. The data are expressed as percent (mean ± SE) of the zero time value. The DA concentration was significantly higher in the MAP-pretreated rats than in the saline-pretreated control rats ($P < 0.01$), and there were no differences in the respective concentrations of DOPAC and HVA between the MAP- and saline-pretreated rats (two-way ANOVA).

enhanced the extracellular DA concentrations. In the MAP-pretreated rats started on PND 14, the extracellular DA concentration peaked (277 ± 40.2%, n = 5) during the first 20 min following the challenge MAP injection, as did that in the saline-pretreated control rats (255 ± 50.9%, n = 6); these values did not differ significantly, $F(1, 81) = 0.347$, NS). The MAP challenge reduced the extracellular levels of DOPAC and HVA, and the magnitudes of their decreases between the MAP- and saline-pretreated rats did not differ significantly.

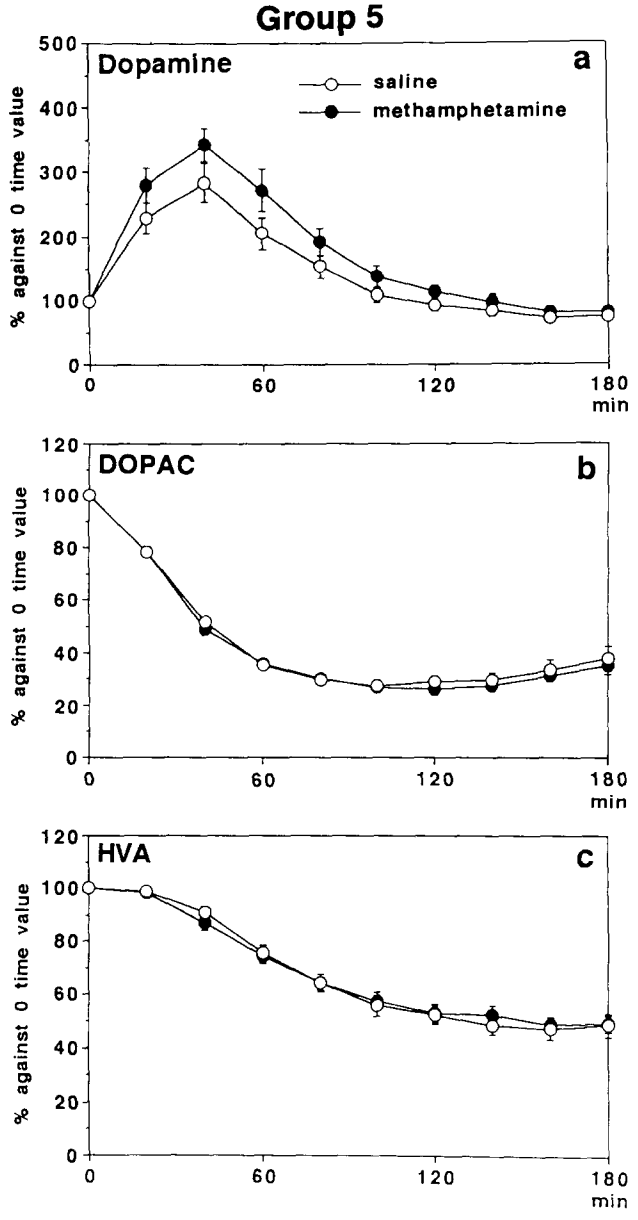

FIG. 7. Group 5. Effect of methamphetamine (MAP, 4 mg/kg) on (a) DA, (b) DOPAC, and (c) HVA concentrations in striatal perfusates of rats 21 days after withdrawal from MAP (●, twice-daily IP injections of 2 mg/kg for three days, followed by 4 mg/kg for three days, n = 5) or normal saline (○, n = 5) started on PND 56. The data are expressed as percent (mean ± SE) of the zero time value. The DA concentration was significantly higher in the MAP-pretreated rats than in the saline-pretreated control rats ($P < 0.01$), and there were no differences in the respective concentrations of DOPAC and HVA between the MAP- and saline-pretreated rats (two-way ANOVA).

The group 3 data are shown in Fig. 5. The MAP challenge enhanced extracellular DA concentrations. In the MAP-pretreated rats started on PND 21, the extracellular DA concentration peaked (397 ± 35.2%, n = 6) 20–40 min after the injection of MAP, while in the saline control rats it peaked (306 ± 34.5%, n = 6) during the first 20 min following the challenge MAP injection. The extracellular DA concentrations increased significantly more in the MAP-pretreated rats than in the saline-pretreated control rats, $F(1, 90) = 11.3$, $P < 0.01$). The challenge MAP injection reduced the extracellular concentrations of DOPAC and HVA; their respective amounts between the MAP- and saline-pretreated rats did not differ significantly.

The group 4 data are shown in Fig. 6. The MAP challenge enhanced extracellular DA concentrations. In the MAP-pretreated rats started on PND 28, the extracellular DA concentration peaked (364 ± 42.8%, n = 5) 20–40 min after the MAP challenge injection, as did that in the saline control rats (298 ± 37.0%, n = 5). The extracellular DA concentrations increased significantly more in the MAP-pretreated rats than in the saline-pretreated control rats, $F(1, 72) = 11.5$, $P < 0.01$. The MAP injection reduced the extracellular levels of DOPAC and HVA; their respective levels between MAP- and saline-pretreated rats did not differ significantly.

The group 5 data are shown in Fig. 7. The MAP challenge enhanced extracellular DA concentrations. In the MAP-pretreated rats started on PND 56 the extracellular DA concentration peaked (343 ± 24.7%, n = 12) 20–40 min after the MAP challenge injection, as did that in the saline controls (284 ± 31.6%, n = 12). The extracellular DA concentrations increased significantly more in the MAP-pretreated rats than in the saline-pretreated rats, $F(1, 198) = 12.5$, $P < 0.01$. The MAP injection reduced the extracellular concentrations of DOPAC and HVA; their respective levels between MAP- and saline-pretreated rats did not differ significantly.

DISCUSSION

The behavioral patterns induced by acute administration of psychostimulants to developing and adult animals differ. It has been reported that although pups exhibit increased locomotor activity in response to AMP as early as PND 10 (4), adult-like stereotypy does not occur until PNDs 18–21 (14). Such ontogeny of AMP-induced stereotypy is consistent with the behavioral data of the present study showing that the final MAP challenge induced intense stereotypy even in the group 1 rats on PND 33.

It is well known that subchronic intermittent administration of MAP or AMP induces BS in adult animals, which endures after withdrawal of pretreatment. Of several factors that influence BS establishment, a postnatal stage appears to be critical for this form of persistent neural plasticity. Indeed, several pieces of evidence have suggested that BS development is ontogenic. We first reported that MAP-BS occurred only when subchronic administration was initiated on about PND 22 (6). Similarly, Kolta et al. reported that AMP-induced BS occurs in animals in which AMP pretreatment was initiated on PND 49, but not PND 21 (13). These two studies differ in the timing of the withdrawal period between the last pretreat-

ment and the challenge doses; the challenge dose was given on PND 35, regardless of the first pretreatment day, in our previous study (6), whereas it was administered 15 days after the last pretreatment day in the study of Kolta et al. (13). Despite the different experimental designs, the results of both studies concur, and suggest that PND 21 and the subsequent few days are critical for the development of BS.

Although the neurochemical mechanism underlying BS remains to be elucidated, several studies (10,18), including one from our department (10), have demonstrated that the expression of an augmented behavioral response to a challenge dose of a psychostimulant is associated with enhanced DA release from nigrostriatal or mesolimbic dopaminergic neuronal terminals.

The aim of this study was to determine whether the ontogeny of MAP-induced BS is associated with changes in DA release, using an in vivo microdialysis technique in addition to behavioral observations. In agreement with our previous report (6), MAP-induced stereotyped behavior was enhanced significantly only when MAP pretreatment was started on PNDs 21, 28, and 56, not on PNDs 7 and 14. Correspondingly, a challenge dose of MAP induced a significantly greater increase in striatal extracellular DA concentrations in the MAP-pretreated rats in groups 3, 4 and 5 (pretreatment initiated on PNDs 21, 28, and 56, respectively) compared with the corresponding controls. These results show clearly that the MAP challenge-induced DA release from the nigrostriatal dopaminergic terminals was significantly greater in MAP-pretreated rats than in saline-pretreated control rats after PND 21. Therefore, MAP-BS and the accompanying enhanced DA release appear to have been established in the rats in which MAP pretreatment was initiated on PND 21 or later, but not earlier.

Although the reason why MAP does not induce BS in younger pups remains to be elucidated, the development of central dopaminergic neurons may provide a clue to identifying factors that contribute to the development of BS in the critical period. For example, it has been reported that the striatal DA concentration and activity of tyrosine hydroxylase (5), the initial and rate-limiting enzyme of the DA synthetic pathway, in rats reached 75% of the adult level by four weeks postpartum.

Postnatal development of DA uptake sites may account for the MAP-BS ontogeny. Two pieces of evidence have implicated dopamine uptake sites in DA release in MAP-BS. First, the presence of functional DA uptake sites is essential for MAP and AMP to evoke DA release, whereas the predominant pharmacological property of cocaine is inhibition of DA reuptake (1). The cross-behavioral sensitization and accompanying enhanced DA release observed between cocaine and MAP may be related to altered function of the DA transporter (1). Second, the transmembrane Na^+ gradient, which is maintained by Na^+,K^+-adenosinetriphosphatase (ATPase), is important for the operation of the DA transporter. An intrastriatal infusion of ouabain, a selective inhibitor of Na^+,K^+-ATPase, resulted in a greater release of DA in MAP-pretreated rats than in saline control rats (9). The ontogeny of specific binding of DA uptake sites has been investigated in the rat striatum during the early postnatal period using [^{3}H]GBR 12783, a selective ligand for the dopamine transporter (2). The number of striatal [^{3}H]GBR 12783 specific binding sites increased from PND 1 to PND 40, when it reached the adult level. Other investigators demonstrated that striatal binding of [^{3}H]mazindol to DA uptake sites increased twofold from PND 10 to PND 16 in rats (17). These data suggest that the DA uptake sites mature during the postnatal period from PND 16 to PND 40. In light of the report that nomifensine, a selective inhibitor of DA uptake, attenuated AMP-induced DA release (3), it appears likely that the low numbers of DA transporters during the ontogenic process are inefficacious at releasing DA and subsequently do not induce MAP-BS.

Other factors which are subject to postnatal developmental changes and have been implicated in the establishment of MAP-BS include DA receptors. Several pieces of evidence have indicated that stimulation of D_1 receptors in the substantia nigra pars reticulata (SNr) by somatodendritically released DA is essential for the initiation of BS (8,20). We demonstrated a lasting increase in the number of DA D_1 receptors in the SNr after subchronic MAP administration and suggested that the enhanced stimulation of SNr D_1 receptors by MAP—probably by somatodendritically released DA—observed in rats with MAP-BS resulted in altered modulation of dopaminergic neurons by a striatonigral feedback pathway (22). The number of SNr D_1 receptors has been reported to increase dramatically from PND 10 to PND 16 (17). Taken together, these results suggest that the ontogeny of SNr D_1 receptors plays a crucial role in the development of MAP-BS.

The numbers of striatal D_1 (26) and D_2 receptors (15) also have been reported to increase postnatally up to about PND 21, when they reached adult levels. A substantial number of D_1 and D_2 receptors are located on striatal neurons which project to the SNr as feedback pathways. We found that blockade of either D_1 or D_2 receptors by systemic administration of respective receptor antagonists prior to each MAP injection prevented the development of MAP-BS (24) and, in parallel, the enhancement of DA release elicited by a MAP challenge alone (7). Therefore, blockade of either subtype of postsynaptic DA receptors during chronic MAP administration suppressed the development of presynaptic mechanisms that are involved in DA release. The finding that the number of striatal D_1 and D_2 receptors reached adult levels by about PND 21 appears to concur with our result that the critical point for establishment of BS is on or around PND 21.

Finally, the interaction of nigral afferents and dopaminergic neuronal activity in the substantia nigra pars compacta (SNc) per se should be discussed. In a recent review, Kalivas and Stewert suggest that the initiation of BS involves D_1 receptors on the terminals of the nigral afferents and D_2-subtype autoreceptors on the SNc neurons (8). Stimulation of somatodendritic D_2 receptors on adult nigrostriatal dopaminergic neurons results in membrane hyperpolarization and inhibition of spontaneous activity. The effect of apomorphine (a mixed D_1/D_2 receptor agonist) and quinpirole (a selective D_2 receptor agonist) administration on the neuronal activity of nigrostriatal DA neurons was examined using extracellular iontophoretic techniques in two- and four-week-old pups and adult rats (25). The result showed that the sensitivities to the inhibitory effects of apomorphine and quinpirole were similar in all the age groups. These results suggest that adult-like somatodendritic D_2 autoreceptor sensitivity is exhibited as early as the second postnatal week of development. Therefore, although somatodendritic D_2 autoreceptors have been reported to contribute to the initiation of BS (8), somatodendritic DA autoreceptor sensitivity may not differ significantly at different postnatal developmental stages (25). On the other hand, nigrostriatal dopamine-containing neurons from two-week-old rats were less sensitive to the inhibitory effects of cumulative IP

(21) or IV (27) amphetamine doses than adult rats. Taking into consideration that DA autoreceptor sensitivity in two-week-old rats appears to be similar to that of adults (25), it is likely that the striatonigral feedback pathways and/or the dopamine transporter in the early postnatal stage differ from those of adult rats.

In conclusion, although it remains to be investigated which factor in the dopaminergic system is essential for the development of MAP-BS, the maturation of the entire dopaminergic neurotransmission system—namely, DA synthesis, DA transporter, SNr D_1 receptors, and postsynaptic D_1 and D_2 receptors—is likely to play a pivotal role.

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