METHAMPHETAMINE-INDUCED BEHAVIORAL EFFECTS AND RELEASES OF BRAIN CATECHOLAMINES AND BRAIN CONCENTRATIONS OF METHAMPHETAMINE IN MICE

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Abstract—The characteristic behavioral effect of methamphetamine (MA) at 2.5 mg/kg was enhanced locomotor activity which lasted over 2.5 hr. At 10.0 mg/kg MA, stereotyped behavior was predominant and lasted over 3 hr. The behavioral effect of 5.0 mg/kg MA was of the mixed type. MA at 5.0 and 10.0 mg/kg lowered the brain NE level from 2 hr after drug treatment, while the accumulation of MHPG-SO₄ was increased over 2 hr at 2.5 and 5.0 mg/kg MA. The accumulation of HVA was significantly increased at 10.0 mg/kg MA over 3 hr. Accordingly, the behavioral effects of MA at the earlier period were compatible with the biochemical effects of MA. The behavioral effects during the 2- to 4-hr period, however, seem to be unrelated to the actions on brain catecholamines. Measurement of brain MA concentrations revealed that approx. 2 μg/g in the brain may be necessary to produce enhanced locomotor activity and the increased accumulation of brain MHPG-SO₄. It appeared that approx. 8 to 9 μg/g MA in the brain was required to produce characteristic stereotyped behavior and the increased accumulation of HVA. Therefore, the behavioral and biochemical effects of MA were correlated with the brain MA concentrations.

There have been many correlative behavioral and biochemical studies of amphetamine, but few studies have been made of methamphetamine. Amphetamine produced two types of behavioral effects in rats that may be related to brain catecholamines: enhanced locomotor activity and stereotyped behavior. Similar dose-related behavioral effects by methamphetamine have been observed in mice (1). It is now generally assumed that the behavioral effects of amphetamine resulted from the ability of these drugs to release catecholamines from nerve terminals in the central nervous system (2–5). Recent evidence suggests that the stereotyped behavior evoked by amphetamine involves striatal dopaminergic neurons (6, 7). The enhanced locomotor activity elicited by amphetamine is thought to be mediated by noradrenergic neurons in the brain (8), although subsequent studies revealed that this effect involves brain dopamine (9–12). Little effort, however, has been made to study the relationship between brain catecholamines and the type and magnitude of methamphetamine-induced behavior. Also, no research has been conducted on the time-courses of behavioral and biochemical effects of methamphetamine and brain methamphetamine concentrations over 3 hr. It has been suggested that the best estimation of catecholamine turnover may be provided by measuring the accumulation of major endogenous metabolic end products of catecholamines in the brain (13). The sulfate conjugate of 3-methoxy-4-hydroxy-
phenylethyneglycol (MHPG-S04) has been identified as the major metabolite of nor
epinephrine in rat brain (14). The metabolic pathways of dopamine to homovanillic acid
(HVA) have also been well established (15). In the present study, we investigated the
effects of methamphetamine on locomotor activity and on stereotyped behavior in mice,
as well as brain catecholamine levels and the accumulation of endogenous MHPG-S04
and HVA. The present study was also designed to determine if there are correlations
between methamphetamine-induced behavioral and biochemical effects and brain
methamphetamine concentrations.

Materials and Methods

Animals: Male ddY-strain mice weighing approx. 25 g were used in all experiments.

Materials: Methamphetamine hydrochloride (MA) was obtained from Dainippon
Seiyaku Co. Norepinephrine hydrochloride (NE), dopamine hydrochloride (DA), and
homovanillic acid (HVA) were purchased from the Sigma Chemical Co. (3-Methoxy-4
sulfonyloxyphenyl)-glycol Kaliumsalz (MHPG-S04) was obtained from Fluka AG.

Behavioral rating: The behavior of each mouse was rated using the method of Peachey
et al. (1) over a 4 hr period following the i.p. administration of saline, 2.5, 5.0 and 10.0
mg/kg MA. MA was injected at 10:00 a.m. Mice were placed in individual activity cages
1 hr before MA treatment. The following 2 behavioral parameters were quantitated:
activity (locomotor activity in any direction) and stereotyped behavior (gnawing, licking
or sniffing). Ten ratings were made over a 90-sec period at exactly 10-sec intervals.
Each rating consisted of noting the presence or absence of each type of behavior using a
score of 1 or 0, respectively. The maximum possible rating score for each parameter at
every 15 min interval was 10.

Catecholamine assay: Brain NE and DA were determined by high performance liquid
chromatography over 3 hr following the i.p. administration of 2.5, 5.0 and 10.0 mg/kg
MA. The mice were sacrificed at 3:00 p.m. Brain tissues were homogenized in 3 ml of
0.4 N perchloric acid containing 0.1 mg/ml EDTANa2. The supernatant was transferred
into a glass stoppered centrifuge tube containing 1.2 g of KCl and mixed. The super
natant was adjusted to pH 8.4 and placed on a 0.2 g alumina column. The effluent
was decanted. The column was washed twice with 2 ml of distilled water, and
catecholamines were eluted with 2 ml of 0.2 N acetic acid. Then, 250 x1 of the eluate
was injected into the chromatograph equipped with a Model VL-611 injector, a 4.6 x 250
mm Finepak SIL C18 column, a Model FP-550 A spectrofluorometer with a micro flow
cell and a Twinkle solvent delivery system (Japan Spectroscopic Co.). The flow rate of
the mobile phase of 0.1 M KH2PO4, pH 2.0, containing 0.1 mM EDTANa2 was 0.7 ml/
min. The fluorescence was measured at 280 nm for the excitation wave length and 313 nm
for the emission wave length. Retention
times for NE and DA were 5.5 and 11 min,
respectively. At least 50 ng/g and 200 ng/g
brain tissue for NE and DA were detectable
in this method.

MHPG-S04 and HVA assay: After mice
were pretreated i.p. with 200 mg/kg of
probenecid, brain MHPG-S04 and HVA of
1-hr accumulation at each hr were assayed by
the method of Meek and Neff (16) and by the
method of Murphy et al. (17) over 3 hr
following the i.p. injection of 2.5 and 5.0 mg/
kg MA, respectively. When 10.0 mg/kg MA
was given, the levels were assayed over 4 hr,
since enhanced locomotor activity reappeared
at 4 hr after drug treatment. The mice were
sacrificed at 3:00 p.m. Probenecid was
pretreated 10 min prior to each experimental
period so that the value of 1-hr accumulation
was the value at the period of 1 hr and 10 min.
minus the value at 10 min after pretreatment with probenecid.

**Methamphetamine assay:** Brain concentrations of methamphetamine and its metabolite, amphetamine (A), were determined by gas-liquid chromatography over 3 hr following the i.p. administration of 2.5, 5.0 and 10.0 mg/kg MA. Brain tissues were homogenized in 4 volumes of 0.4 N perchloric acid. To 1 ml of the homogenate, 1 ml of 5 N NaOH saturated with NaCl and 6 ml of n-pentane were added. After 15-min of shaking, 5 ml of n-pentane phase was transferred into a 10 ml glass-stoppered test tube containing 0.1 ml of trifluoroacetic acid. After heating at 60°C for 30 min, the mixture was dried under nitrogen. The residue was reconstituted in 0.1 ml of acetone. One µl of the acetone phase was injected into the gas chromatograph (GC-7A, Shimadzu) equipped with a flame-thermionic detector and a 1.6 m x 3 mm glass column packed with 2% OV-17 on Uniport HP. The chromatographic conditions were as follows: column temperature, 150°C; injection port temperature, 200°C; helium flow rate, 40 ml/min; hydrogen flow rate, 3.5 ml/min; air flow rate, 150 ml/min. Under above conditions, retention times for MA and A were 1.16 and 2.05 min, respectively. The concentrations of MA and A in each brain sample were determined by interpolation on the individual aqueous standard curves for MA and A. At least 100 ng/g brain tissue for both MA and A was detectable in this method. The half-life values of MA in brain were calculated by determining the disappearance rate constant (k) using regression analysis and by using the equation: $t_{1/2} = 0.693/k$.

**Statistical analysis:** Statistical comparisons of the MA-induced behavioral and biochemical effects with the effects of saline-treated mice were conducted for each drug dosage using the *t*-test for independent groups.

**Results**

Behavioral effects of MA in mice: The time courses of behavioral effects of MA are shown in Fig. 1. In the saline group, locomotor

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![Fig. 1. Time course of methamphetamine-induced behavioral effects in mice. Mice were placed in individual cages and MA-induced behavioral effects were scored as described in Methods. Each point represents the mean±S.E. of 9 determinations.](image-url)
activity was sporadic and its scores varied in the range from 0 to 0.75±0.49. Stereotyped behavior was not observed. At 0.64 mg/kg MA, locomotor activity was slightly increased over 2 hr with the peak effect of 2.3±0.8 point, but this increase was not significant. Stereotyped behavior was not observed. The dose of 2.5 mg/kg MA markedly enhanced locomotor activity over 2.5 hr with the peak effect of 8.0±0.8 points occurring within 30 min. Stereotyped behavior was slightly observed, but this incidence was not significant. At 5.0 mg/kg MA, significantly enhanced locomotor activity occurred over 3 hr with almost the maximum rating score within 30 min. Stereotyped behavior began at 30 min after MA was given and lasted for about 2 hr with its peak incidence of 7.3±0.7 points at 1.25 hr. Accordingly, the behavioral effect of 5.0 mg/kg MA was of the mixed type of enhanced locomotor activity and stereotyped behavior. At 10.0 mg/kg MA, locomotor activity markedly enhanced at the first 15 min with the peak effect of 8.6±0.8 points. This enhanced activity, however, was gradually diminished to the rating score of 0.8±0.5 points at 1 hr, and then the locomotor activity was slowly increased, reaching the rating score of 6.3±1.2 points at 4 hr. Stereotyped behavior already began at the first 15 min with the rating score of 5.3±1.3 points and reached the maximum effect at 30 min. This maximum effect lasted for 2 hr and then gradually subsided. At 4 hr, stereotyped behavior almost disappeared. Accordingly, both enhanced locomotor activity and stereotyped behavior simultaneously occurred at 10 mg/kg MA. Since stereotyped behavior is predominant at this dose, enhanced locomotor activity may reappear at 3 to 4 hr after drug treatment when stereotyped behavior subsided.

Effects of MA on NE and DA levels in mouse brain: The time courses of the steady-state levels of NE and DA over 3 hr are shown in Table 1. No significant change in the level of NE was observed over 3 hr at 2.5 mg/kg MA. The doses of 5.0 and 10.0 mg/kg, however, caused the slight depletion of NE with values of approx. 17 to 32% of the control at 2 to 3 hr. The level of DA was slightly elevated at 1 to 3 hr from 112 to 118% of the control value. However, the doses of 5.0 and 10.0 mg/kg generally caused no change in the DA level over 3 hr.

Effects of MA on the accumulation of MHPG-SO₄ and HVA in mouse brain: Effects of MA on the 1-hr accumulation of

| MA (mg/kg) | Control | 0 min | 15 min | 30 min | 1 hr | 2 hr | 3 hr |
|------------|---------|-------|--------|--------|------|------|------|
| 2.5        | 100±3   | 104±4 | 103±3  | 98±3   | 91±3 | 92±3 |
| 5.0        | 0.289±0.008a | 100±3 | 106±3  | 102±5  | 84±4* | 83±5 | 78±6* |
| 10.0       | 100±3   | 110±3 | 100±4  | 92±4   | 78±4* | 69±3* |

| MA (mg/kg) | Control | 0 min | 15 min | 30 min | 1 hr | 2 hr | 3 hr |
|------------|---------|-------|--------|--------|------|------|------|
| 2.5        | 100±3   | 104±4 | 109±1  | 118±3* | 117±3* | 112±3* |
| 5.0        | 0.758±0.019a | 100±3 | 109±4  | 112±5  | 104±6 | 108±7 | 103±4 |
| 10.0       | 100±3   | 112±2* | 104±4  | 105±2  | 101±5 | 100±5 |

Catecholamines are expressed as a percentage of the control values±S.E. of 6 determinations. *μg/g brain tissue±S.E. of 12 determinations. **Significantly different from the control at P<0.05.
MHPG-\textsubscript{SO4} and HVA after probenecid (200 mg/kg i.p.) are shown in Table 2. The accumulation of MHPG-\textsubscript{SO4} was significantly increased at the periods of 0–1 hr and 1–2 hr by treatment with 2.5 and 5.0 mg/kg MA (2.9- to 5.0-fold of the control), but its increase at 10.0 mg/kg MA was not statistically significant. At a period of 2–3 hr, however, no significant increase was observed at either dose of MA. On the contrary, the accumulation of HVA was significantly increased at a period of 0–1 hr at a dose of 5.0 mg/kg (1.5-fold of the control) and over 3 hr at a dose of 10.0 mg/kg (approx. double-fold). At the period of 3–4 hr, however, no increase was observed even at 10.0 mg/kg MA.

**Relationship between pharmacological and biochemical effects and brain levels of MA and A:** At 2.5 mg/kg MA, the peak MA brain concentration was 2.63±0.27 \(\mu\)g/g at 15 min after drug administration. The brain MA concentration declined to 0.35±0.05 \(\mu\)g/g at 3 hr and the half-life of brain MA was 56.0

### Table 2. Effects of methamphetamine on the levels of MHPG-\textsubscript{SO4} and HVA in mouse brain

| MA    | MHPG-\textsubscript{SO4} level (pmol/g) | HVA level (\(\mu\)g/g) |
|-------|----------------------------------------|-------------------------|
|       | 0–1 hr | 1–2 hr | 2–3 hr | 3–4 hr | 0–1 hr | 1–2 hr | 2–3 hr | 3–4 hr |
| Control | 77.2±21.4 |         |         |         | 0.151±0.012 |         |         |         |
| 2.5 mg/kg | 271.1±71.0* | 226.1±43.3* | 177.8±45.5* | 207.2±65.5 | 0.173±0.020 | 0.156±0.020 | 0.140±0.009 | 0.299±0.008* |
| 5.0 mg/kg | 383.7±59.1* | 271.4±45.3* | 115.0±36.9 | 99.9±33.9 | 0.227±0.016 | 0.159±0.021 | 0.168±0.016 | 0.272±0.036* |
| 10.0 mg/kg | 240.7±74.3 | 207.2±65.5 | 99.9±33.9 | 90.0±21.7 | 0.299±0.008* | 0.272±0.036* | 0.279±0.027 | 0.151±0.018 |

Values are expressed as the means±S.E. of 6 determinations. *Significantly different from the control at \(P<0.05\).

### Table 3. Brain methamphetamine and amphetamine levels in mice given methamphetamine

| MA    | 15 min | 30 min | 1 hr | 2 hr | 3 hr | \(t_{1/2}\) |
|-------|--------|--------|------|------|------|---------|
| 2.5 mg/kg | 2.63±0.27 | 2.10±0.32 | 1.39±0.18 | 0.51±0.09 | 0.35±0.05 | 56.0 min |
| 5.0 mg/kg | 4.52±0.38 | 4.96±0.35 | 3.72±0.22 | 1.53±0.16 | 0.84±0.10 | 56.7 min |
| 10.0 mg/kg | 8.10±0.31 | 8.90±0.40 | 6.63±0.43 | 3.02±0.37 | 1.91±0.35 | 68.7 min |

| Amphetamine level | |
|-------|--------|--------|------|------|------|
| 2.5 mg/kg | 0.11±0.02 | 0.11±0.04 | 0.16±0.04 | 0.13±0.01 | 0.15±0.02 |
| 5.0 mg/kg | 0.20±0.03 | 0.45±0.04 | 0.78±0.12 | 0.64±0.10 | 0.47±0.11 |
| 10.0 mg/kg | 0.43±0.06 | 1.31±0.09 | 1.59±0.15 | 1.20±0.13 | 1.21±0.19 |

Each value represents the mean±S.E. of 4 determinations. Levels are expressed as \(\mu\)g/g brain tissue.
min. The brain A concentration was 0.11–0.16 μg/g (Table 3). Enhanced locomotor activity was predominant and lasted over 2.5 hr. The accumulation of brain MHPG-SO₄ was increased over 2 hr; however, accumulation of brain HVA was not observed. At 5.0 mg/kg MA, the behavioral effect was of the mixed type. The peak MA brain concentration was 4.96±0.35 μg/g at 30 min after drug administration and then declined to 0.84±0.10 μg/g at 3 hr with an apparent half-life value of 56.7 min. The brain A concentration appeared to reach a plateau (0.45–0.78 μg/g) from 30 min till 3 hr (Table 3). The accumulation of brain MHPG-SO₄ was increased over 2 hr, and that of brain HVA was also increased at the first 1-hr period. At 10.0 mg/kg MA, stereotyped behavior was predominant and lasted over 3 hr. The peak MA brain concentration was 8.90±0.04 μg/g at 30 min and then declined to 1.91±0.35 μg/g at 3 hr with an apparent half-life value of 68.7 min. The brain A concentration appeared to reach a plateau (1.20–1.59 μg/g) from 30 min till 3 hr (Table 3). The accumulation of brain HVA was increased over 3 hr, whereas the accumulation of brain MHPG-SO₄ was not significantly altered. At 4 hr after drug administration, enhanced locomotor activity moderately reappeared, while the accumulation of brain MHPG-SO₄ or HVA was not altered.

Discussion

In the present experiments, the characteristic behavioral effect of MA at 2.5 mg/kg was enhanced locomotor activity, but stereotyped behavior was predominant at 10 mg/kg MA. MA at 5.0 and 10.0 mg/kg lowered the brain NE level from 2 hr after drug treatment, while the accumulation of MHPG-SO₄ by probenecid was increased over 2 hr at 2.5 and 5.0 mg/kg MA. The accumulation of HVA by probenecid was significantly increased at 10.0 mg/kg MA over 3 hr. These results are compatible with those of Taylor and Snyder who proposed that amphetamine-induced stimulation of motor activity is the result of an action on noradrenergic neurons, whereas stereotyped behavior is associated with dopaminergic nerve activity (8). Cook et al. (18) reported similar results. MA at 5.0 mg/kg lowered endogenous levels of NE at 3 hr, inhibited uptake of norepinephrine at 0.5 and 1 hr and markedly increased normetanephrine levels at 0.5 hr. They concluded that a high correlation was found between the changes in behavior and normetanephrine levels. Although it is suggested that amphetamine can release both “stored” and “newly synthesized” catecholamines (19), it may act by selectively releasing “newly synthesized” amines since reserpine, which destroys the granular “storage pool” of brain amines, does not alter amphetamine stimulation; whereas α-methyltyrosine which disrupts catecholamine synthesis can block the central stimulant actions of amphetamine (2, 20). Accordingly, the behavioral effects of MA at the earlier period appeared to be compatible with the biochemical effects of MA which may mainly reflect the effect on “stored” catecholamines. However, the behavioral effects at the 2- to 4-hr period seem to be unrelated to the actions on brain catecholamines. Subsequent studies revealed that stimulation of locomotor activity and stereotyped behavior were associated with dopaminergic nerve activity of the nucleus accumbens and the striatum, respectively (9, 12). In our experiments, however, the increased accumulation of HVA by 2.5 mg/kg MA, which predominantly enhanced locomotor activity, was not observed.

Our studies on the relationship between the brain MA concentration and magnitude of drug-induced behavior or brain catecholamines yielded some interesting findings. The values of brain MA concentrations and magnitude of drug-induced behavior are
similar to those reported by Brien et al. (21) who, however, only reported the values of the 90-min observation period. The half-life value of brain MA at either dose was approx. 1 hr which was also similar to their value. For 2.5 mg/kg MA, the peak magnitude of enhanced locomotor activity was observed within 30 min, and a peak concentration of 2.63 μg/g was attained at 15 min. The accumulation of brain MHPG-SO₄ was increased over 2 hr. Therefore, approx. 2 μg/g MA may be necessary to produce enhanced locomotor activity and the increased accumulation of brain MHPG-SO₄. For 5.0 mg/kg MA, the behavioral effect was of the mixed type. Peak incidence of stereotyped behavior was attained within 1.25 hr. A peak MA concentration of 4.96 μg/g was attained at 30 min, and the accumulation of HVA was increased at the first 1-hr period. It has been reported that the enhanced locomotor activity found with 2.5 mg/kg MA is consistent with similar findings in the mouse following the acute administration of 2.0 mg/kg amphetamine (22). Therefore, more than 5 μg/g MA plus A may be necessary to produce stereotyped behavior and the increased accumulation of HVA. This concentration, however, caused the mixed type of behavioral effects. For 10.0 mg/kg MA, stereotyped behavior and the increased accumulation of HVA were predominant over 3 hr. The peak MA brain concentration was 8.90 μg/g at 30 min. Hence it appeared that approx. 8 to 9 μg/g MA was required to produce characteristic stereotyped behavior. Peak incidences of behavioral and biochemical effects of MA, however, were reached about 0.5 to 1 hr later than the time at which peak MA concentration was reached, and these effects may remain for an appreciable period of time. At 3 hr after drug treatment, the concentration of MA plus A was approx. 3 μg/g which may be sufficient to produce enhanced locomotor activity. This may account for the fact that enhanced locomotor activity moderately reappeared at 4 hr after drug administration. Therefore, the behavioral and biochemical effects of MA were correlated with the brain MA concentrations.

References

1) Peachey, J.E., Rogers, B., Brien, J.F., Maclean, A. and Rogers, D.: Measurement of acute and chronic behavioral effects of methamphetamine in the mouse. Psychopharmacologia (Berlin) 48, 271–275 (1976)
2) Weissman, A., Koe, B.K. and Tenen, S.S.: Antiamphetamine effects following inhibition of tyrosine hydroxylase. J. Pharmacol. Exp. Ther. 151, 339–352 (1966)
3) Randrup, A. and Munkvad, I.: Role of catecholamines in the amphetamine excitatory response. Nature 211, 540 (1966)
4) Hanson, L.C.F.: Evidence that the central action of (+)-amphetamine is mediated via catecholamines. Psychopharmacologia (Berlin) 10, 289–297 (1967)
5) Sulser, F., Owens, M.L., Norwich, M.R. and Dingell, J.V.: The relative role of storage and synthesis of brain norepinephrine in the psychomotor stimulation evoked by amphetamine or by desipramine and tetrabenazine. Psychopharmacologia (Berlin) 12, 322–332 (1968)
6) Ernst, A.M.: Mode of action of apomorphine and dexamphetamine on gnawing compulsion in rats. Psychopharmacologia (Berlin) 10, 316–323 (1967)
7) Scheel-Kruger, J. and Randrup, A.: Stereotype hyperactive behaviour produced by dopamine in the absence of noradrenaline. Life Sci. 6, 1389–1398 (1967)
8) Taylor, K.M. and Snyder, S.H.: Differential effects of D- and L-amphetamine on behavior and on catecholamine disposition in dopamine and norepinephrine containing neurons of rat brain. Brain Res. 28, 295–309 (1971)
9) Pijnenburg, A.J.J. and Van Rossum, J.M.: Stimulation of locomotor activity following injection of dopamine into the nucleus accumbens. J. Pharm. Pharmacol. 25, 1003–1005 (1973)
10) Thornburg, J.E. and Moor, K.E.: The relative importance of dopaminergic and noradrenergic neuronal systems for the stimulation of locomotor activity induced by amphetamine and other drugs. Neuropharmacology 12, 853–866
11) Jackson, D.M., Anden, N.-E. and Dahlstrom, A.: A functional effect of dopamine in the nucleus accumbens and in some other dopamine-rich parts of the rat brain. Psychopharmacologia (Berlin) 45, 139–149 (1975)

12) Kelly, P.H., Seviour, P.W. and Iversen, S.D.: Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. Brain Res. 94, 507–522 (1975)

13) Meek, J.L. and Neff, N.H.: The rate of formation of 3-methoxy-4-hydroxyphenylethanol sulfate in brain as an estimate of the rate of formation of norepinephrine. J. Pharmacol. Exp. Ther. 184, 570–575 (1973)

14) Schanberg, S.M., Schildkraut, J.J., Breese, G.R. and Kopin, I.J.: Metabolism of normetanephrine-1H in rat brain—Identification of conjugated 3-methoxy-4-hydroxyphenylglycol as the major metabolite. Biochem. Pharmacol. 17, 247–254 (1968)

15) Hornykiewicz, O.: Dopamine (3-hydroxytyramine) and brain function. Pharmacol. Rev. 18, 925–964 (1966)

16) Meek, J.K. and Neff, N.H.: Fluorometric estimation of 4-hydroxy-3-methoxyphenylethanol sulfate in brain. Br. J. Pharmacol. 45, 435–441 (1972)

17) Murphy, G.F., Robinson, D. and Sharman, D.F.: The effect of tropolone on the formation of 3,4-dihydroxyphenylacetic acid and 4-hydroxy-3-methoxyphenylacetic acid in the brain of the mouse. Br. J. Pharmacol. 35, 107–115 (1969)

18) Cook, J.D. and Schanberg, S.M.: The effects of methamphetamine on behavior and on the uptake, release and metabolism of norepinephrine. Biochem. Pharmacol. 19, 1165–1179 (1970)

19) Chiueh, C.C. and Moore, K.E.: d-Amphetamine-induced release of "newly synthesized" and "stored" dopamine from the caudate nucleus in vivo. J. Pharmacol. Exp. Ther. 192, 642–653 (1975)

20) Rech, R.H., Carr, L.A. and Moore, K.E.: Behavioral effects of α-methyltyrosine after prior depletion of brain catecholamines. J. Pharmacol. Exp. Ther. 160, 326–335 (1968)

21) Brien, J.F., Kitney, J.C., Peachey, J.E. and Rogers, B.J.: Methamphetamine-induced behavioral effects and brain concentrations of methamphetamine and its metabolite amphetamine in mice. Res. Commun. Chem. Pathol. Pharmacol. 22, 313–328 (1978)

22) Dominic, J.A. and Moore, K.E.: Acute effects of α-methyltyrosine on brain catecholamine levels and on spontaneous and amphetamine stimulated motor activity in mice. Arch. Int. Pharmacodyn. Ther. 178, 166–176 (1969)