J. Pharm. Pharmacol. 1995, 47: 852–856
Received March 21, 1994
Accepted February 9, 1995

Comparison of Behavioural Effects of Repeated Treatment with Methamphetamine plus Scopolamine and Methamphetamine Alone on Behavioural Sensitization and Conditioned Response

KUNIO YUI, TAKAO MIURA*, KIMIHITO SUGIYAMA†, MAMORU ONO† AND MORIHARU NAGASE†

*Medical Care Section, Urawa Juvenile Classification Home, Ministry of Justice, Urawa 336, *Department of Psychiatry, Namioka Town Hospital, Namioka, Aomori 036, and †Research Institute of Showa Yakuhin Kako Co., Ltd, Shimonoge 3-13-1, Takatu-ku, Kawasaki 213, Japan*

Abstract

We investigated how repeated treatments with methamphetamine (4·0 mg kg^{-1}, i.p.) plus scopolamine (0·5 mg kg^{-1}, i.p.) and methamphetamine alone effected behavioural sensitization and conditioned response in rats.

Repeated methamphetamine plus scopolamine treatment induced a more progressive and enduring enhancement of focused stereotyped behaviour than repeated methamphetamine treatment. Stereotyped behaviour induced by methamphetamine plus scopolamine was reproduced by challenge injections of methamphetamine plus scopolamine, methamphetamine, and to a lesser extent by scopolamine challenges.

The methamphetamine plus scopolamine-sensitized rats were conditioned to a low frequency tone (300 Hz, 100 dB) associated with the drug state. They exhibited a conditioned response to pairings of the tone (conditioned stimulus) and placebo injections. However, they did not respond to the tone alone or the placebo injections alone.

The methamphetamine-sensitized rats failed to demonstrate any conditioning; only the repeated methamphetamine plus scopolamine treatment induced sensitization to the drug-associated tone. Pairings of exteroceptive conditioned stimulus-interoceptive unconditioned stimulus associations may provide an important source for conditioning to the tone associated with the drug state.

We conclude that behavioural sensitization may operate via a reciprocal balance between the dopaminergic and cholinergic inhibitory systems, in favour of a dopaminergic dominance. Conditioning to the drug-associated tone may be mediated via a reciprocal balance between the two transmitter systems.

Repeated administration of amphetamine or methamphetamine induces behavioural sensitization (Robinson & Becker 1986). Most of the proposed mechanisms focus on functional changes in dopamine systems (Karler et al 1990). However, in studying the neural correlate of amphetamine-induced stereotyped behaviour, stereotyped behaviour has been found to be mediated via a reciprocal balance between dopaminergic and inhibitory cholinergic mechanisms (Arnfred & Randrup 1968; Naylor & Costall 1971; Costall & Naylor 1972; Kokkinidis & Anisman 1980). In this regard, anticholinergics, such as scopolamine hydrobromide (Arnfred & Randrup 1968; Kokkinidis & Anisman 1980), atropine sulphate (Arnfred & Randrup 1968; Costall & Naylor 1972) and orphenadrine (Naylor & Costall 1971) were found to enhance amphetamine-induced stereotyped behaviour. However, there is a relative paucity of data concerning the role of the reciprocal balance between the dopaminergic and inhibitory cholinergic systems in behavioural sensitization. Our preliminary study with rats indicated that repeated methamphetamine (4·0 mg kg^{-1}) plus scopolamine (0·5 mg kg^{-1}) treatment induced robust behavioural sensitization to injections of the two drugs (Yui et al 1988; Yui & Miura 1991). The first purpose of the present study was to evaluate the influence of the dopaminergic-cholinergic balance on behavioural sensitization, by assessing how different drugs induce behavioural sensitization.

Correspondence: K. Yui, Medical Care Section, Urawa Juvenile Classification Home, Ministry of Justice, Takasago 3-16-34-31, Urawa 336, Japan.

Repeated amphetamine treatment can cause the recipient to become conditioned to experimental apparatus associated with the drug state (Schiff 1982; Beninger & Hahn 1983). In man, it is suggested that the high relapse rate seen among patients with a history of amphetamine or methamphetamine psychosis, may largely be the result of conditioning phenomena or excessive incentive learning associated with chronic amphetamine or methamphetamine abuse (Utena 1974; Schiff 1982; Beninger & Hahn 1983). A previous animal study showed that under the influence of dopaminergic hyperactivity, the ability of drug-associated environmental stimuli to elicit a conditioned response was enhanced (Beninger & Hahn 1983). In this regard, environmental stress can act as a precipitant of methamphetamine psychosis following the development of methamphetamine-induced dopaminergic hypersensitivity (Sato et al 1983). In addition, amphetamine sensitization was reported to be interchangeable with stress (Antelman et al 1980). Thus, conditioned response to a tone associated with the drug state following the development of behavioural sensitization might provide useful information regarding reactivity to environmental stimuli. The second purpose of the present study was to assess the ability of co-administration of

methamphetamine and scopolamine to augment the effects of methamphetamine on conditioning, and hence to evaluate the influence of the reciprocal balance between the dopaminergic and cholinergic systems on drug conditioning.

Materials and Methods

Experiment 1

The first experiment was designed to determine the way in which a reciprocal balance between dopaminergic and cholinergic inhibitory systems induces the development of behavioural sensitization.

Animals. Forty-four male Wistar rats, 250–350 g, were housed individually from the 18th day of life and maintained on a reverse 12 h : 12 h dark/light cycle (lights off at 0700 h) with free access to food and water, at a constant environmental temperature (25°C) and relative humidity of 55%. Testing was conducted during the dark cycle.

Drug treatment regimen. Each of the four experimental groups received intraperitoneal injections of methamphetamine (4·0 mg kg^{-1}, Philopon, Dainippon Co., Japan) combined with scopolamine (0·5 mg kg^{-1}, Hysco, Kyorin Co., Japan), methamphetamine (4·0 mg kg^{-1}), scopolamine (0·5 mg kg^{-1}), or control volumes of physiological saline equivalent to the methamphetamine plus scopolamine doses for 14 days (chronic administration period). To determine the potentially different effects of the drugs on behavioural sensitization and the preserved level of behavioural sensitization, methamphetamine plus scopolamine-treated rats were divided randomly into three subgroups at 7 days after the cessation of the chronic treatment. Each of the subgroups, along with the other groups, received five challenge injections of the same doses of the respective regimen that had been given during the chronic administration period, each at 7-day intervals (challenge period).

Behavioural measurement. Rats were placed individually in respective observation cages made of transparent plastic with the same dimensions as the holding cage (33 × 24 × 17 cm high). Red opaque barriers were used to prevent each rat from being influenced by the behaviour of its neighbours. The rats received a 3-h session of habituation to the observation cage for three consecutive days. During the experiment the animals were rated for 5 min at 5, 10, 15, 20, 30, 45, 60, and 120 min after injections by two trained raters, blinded to the treatment groups. The evaluation was

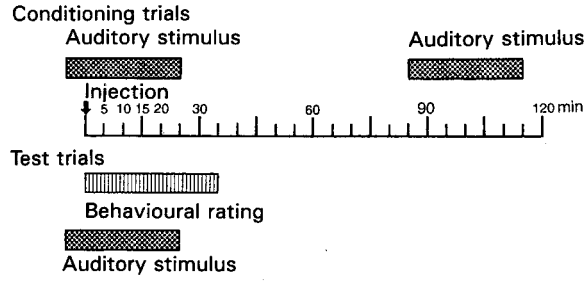

FIG. 1. Graphic presentation of procedures for conditioning and testing for drug conditioning.

based on the following five-point rating scale adapted from the scoring systems of previous reports (Costall & Naylor 1972; Ellinwood & Balster 1974; Sahakian et al 1975; Ujike et al 1990; Paulson et al 1991): 0, animal is asleep or stationary; 1, mild, discontinuous sniffing associated with continuous exploration; 2, burst of sniffing with hyperactivity; 3, continuous sniffing with very brief locomotor activity or rearing; 4, continuous sniffing without rearing and locomotion; 5, continuous, focused sniffing intermingled with gnawing and licking at one place.

Data analysis. The cumulative behavioural score over the 120-min period on each test day was calculated as the average of the eight observations for each rat in each group. Data were analysed using the non-parametric Kruskal-Wallis test followed by the Mann-Whitney U-test. All comparisons were based on two-tailed probabilities.

Dose response. Previous studies revealed that with an increasing dose of amphetamine in the dose range of 3–15 mg kg^{-1} (Ellinwood & Balster 1974; Fray et al 1980), stereotypy was gradually intermingled with gnawing and licking. It was reported that with the addition of 3·0 mg kg^{-1} scopolamine to 10·0 mg kg^{-1} amphetamine, intense stereotypy was accompanied by licking and biting (Arnfred & Randrup 1968). Our preliminary dose–effect data indicated that methamphetamine in the dose range of 2·0–10·0 mg kg^{-1}, alone and in combination with 0·5 mg kg^{-1} scopolamine, dose-dependently produced focused stereotypy intermingled with gnawing and licking.

Experiment 2

Experiment 2 was conducted according to conventional drug conditioning (Schiff 1982; Beninger & Hahn 1983; Carey 1991), as follows.

Animals. Thirty-two Wistar rats, 250–350 g, reared in isolation were employed.

Conditioning. Rats were randomly allocated to four groups. Each of the four groups received 14 training trials consisting of daily intraperitoneal injections of methamphetamine (4·0 mg kg^{-1}) plus scopolamine (0·5 mg kg^{-1}), methamphetamine (4·0 mg kg^{-1}), scopolamine (0·5 mg kg^{-1}), or control volumes of physiological saline equal to the methamphetamine plus scopolamine doses, as an unconditioned stimulus. This was paired with a 300 Hz, 100 dB tone as a conditioned stimulus in each respective observation cage. The 300-Hz tone was generated by a CR audiogenerator (Model AG202A, TRIO Co., Japan) situated at the left front of the observation cage. The tone was presented twice for 30 min, 5 min before and 85 min after injections, with an inter-trial interval of 60 min (Fig. 1). At 7 days after the discontinuation of training trials, all four groups of pretreated rats received reconditioning with the same protocol. To ensure the sustainability of conditioning, retraining was repeated five times, at 7-day intervals. The 300-Hz tone was considered to be a sensory exciting stimulus because it elicits a startle response in drug-free rats. Background noise (40 dB) generated by an air conditioning system was constant in the rearing and experimental rooms.

Table 1. The mean stereotypy ratings on the first day of the chronic administration and each test day during the challenge period.

Chronic administration period	Methamphetamine + scopolamine			Methamphetamine	Scopolamine	Saline
1st	2·34 ± 0·11			1·58 ± 0·09	0·38 ± 0·09	0·09 ± 0·15
Challenge period	Methamphetamine + scopolamine	Methamphetamine	Scopolamine	Methamphetamine	Scopolamine	Saline
1st	4·20 ± 0·21	3·75 ± 0·09[a,b,d]	0·98 ± 0·09[e]	3·41 ± 0·15	0·23 ± 0·08	0·06 ± 0·03
2nd	4·29 ± 0·14	4·00 ± 0·11[b,d]	1·58 ± 0·26[e]	3·34 ± 0·19	0·08 ± 0·04	0·03 ± 0·02
3rd	4·34 ± 0·13	4·04 ± 0·15[c,d]	1·10 ± 0·16[e]	2·97 ± 0·30	0·08 ± 0·06	0·03 ± 0·02
4th	4·39 ± 0·10	3·77 ± 0·13[d]	1·35 ± 0·17[e]	3·56 ± 0·13	0·09 ± 0·05	0·02 ± 0·02
5th	4·16 ± 0·26	3·88 ± 0·13[b,d]	1·72 ± 0·18[e]	3·33 ± 0·22	0·19 ± 0·08	0·02 ± 0·02

The results are the mean values ± s.e.m. Each value is the average of 6–8 rats during a 120-min period except for the first injections of methamphetamine plus scopolamine of the chronic administration period which is the average of 20 rats. [a]$P < 0·01$ compared with first injection of methamphetamine plus scopolamine; [b]$P < 0·05$, [c]$P < 0·01$ compared with rats pretreated with methamphetamine and challenged with methamphetamine; [d]$P < 0·01$ compared with rats pretreated with methamphetamine plus scopolamine and challenged with scopolamine; [e]$P < 0·01$ compared with rats pretreated with scopolamine and challenged with scopolamine.

Post-test for conditioned effects. Residual drug effects such as amphetamine metabolite (*p*-hydroxy-noradrenaline), and unexcreted methamphetamine can effect test results. Since the amphetamine metabolite is no longer detectable after 6 days (Browne & Segal 1977), a test for conditioned response was given 6 days after each weekly retraining period. Physiological saline (placebo) was substituted for the respective drugs. We assessed the effects of pairing the exteroceptive tone cue and interoceptive drug cue by comparing it with alternative conditions. We tested the tone with a placebo injection, the tone alone and the placebo alone at 7-day intervals according to a Latin-square design. Animals were rated for 5 min at 5, 10, 15, 20 and 30 min by two trained raters blinded to the treatment (Fig. 1). Because amphetamine or methamphetamine can induce conditioning of stereotypy (Ellinwood 1971; Robbins 1976), we employed the 0–5 point rating scale used in experiment 1 to assess the conditioned response.

Results

Behavioural Responses to the Drugs

Repeated treatment with methamphetamine plus scopolamine induced significantly augmented behavioural responses as compared with repeated methamphetamine treatment ($U = 10·00–42·50$, $Z = 1·92–3·58$, $P < 0·01$ or $P < 0·05$). As shown in Table 1, challenge response to methamphetamine in the methamphetamine plus scopolamine-pretreated rat was significantly greater than that exhibited after the first injections of methamphetamine plus scopolamine ($U = 116·00$, $Z = 3·42$, $P < 0·01$). Stereotyped behaviour induced by methamphetamine plus scopolamine was reproduced by challenge injections of methamphetamine plus scopolamine and methamphetamine to about the same degree, and to a lesser extent by the scopolamine challenges as compared with scopolamine-pretreated rats ($U = 0·00–0·50$, $Z = 3·07–3·23$, $P < 0·01$).

Table 2. Mean conditioned response and time course of conditioned response to the tone conditioned stimulus-placebo pairing, placebo alone and tone alone.

		Methamphetamine + scopolamine	Methamphetamine	Scopolamine	Saline
Tone–placebo pairing		1·10 ± 0·28[a,c,f,h]	0·25 ± 0·09	0·28 ± 0·05	0·17 ± 0·06
Time	5 min	0·63 ± 0·16[e,g]	0·18 ± 0·06	0·18 ± 0·06	0·09 ± 0·04
	10 min	0·28 ± 0·06[b,d,f,g]	0·00 ± 0·00	0·03 ± 0·03	0·03 ± 0·03
	15 min	0·15 ± 0·04[a,c,e,g]	0·03 ± 0·03	0·03 ± 0·03	0·00 ± 0·00
	20 min	0·05 ± 0·09	0·00 ± 0·00	0·00 ± 0·00	0·00 ± 0·00
	30 min	0·03 ± 0·06	0·05 ± 0·03	0·05 ± 0·03	0·03 ± 0·03
Placebo		0·60 ± 0·17	0·38 ± 0·09	0·43 ± 0·16	0·23 ± 0·07
Time	5 min	0·28 ± 0·11	0·33 ± 0·08	0·18 ± 0·07	0·15 ± 0·08
	10 min	0·20 ± 0·08	0·10 ± 0·05	0·13 ± 0·05	0·03 ± 0·03
	15 min	0·10 ± 0·05	0·03 ± 0·03	0·13 ± 0·08	0·03 ± 0·03
	20 min	0·00 ± 0·00	0·00 ± 0·00	0·00 ± 0·00	0·00 ± 0·00
	30 min	0·03 ± 0·03	0·00 ± 0·00	0·03 ± 0·03	0·00 ± 0·00
Tone		0·23 ± 0·08	0·18 ± 0·07	0·18 ± 0·05	0·11 ± 0·04
Time	5 min	0·13 ± 0·04	0·05 ± 0·03	0·05 ± 0·03	0·03 ± 0·03
	10 min	0·05 ± 0·03	0·05 ± 0·03	0·05 ± 0·03	0·03 ± 0·03
	15 min	0·03 ± 0·03	0·05 ± 0·03	0·05 ± 0·03	0·00 ± 0·00
	20 min	0·00 ± 0·00	0·00 ± 0·00	0·03 ± 0·03	0·03 ± 0·03
	30 min	0·00 ± 0·00	0·00 ± 0·00	0·03 ± 0·03	0·03 ± 0·03

The results are the mean ± s.e.m. Each data point is calculated as the average of eight rats of five test days in the respective treatment groups. [a]$P < 0·05$, [b]$P < 0·01$ compared with methamphetamine-sensitized data; [c]$P < 0·05$, [d]$P < 0·01$ compared with scopolamine-pretreated rats; [e]$P < 0·05$, [f]$P < 0·01$ compared with saline-pretreated controls. To examine an important source for drug conditioning, conditioned response to the tone–placebo pairing, the tone alone and placebo alone were compared with each other in the respective treatment groups. [g]$P < 0·05$, [h]$P < 0·01$ compared with conditioned response to tone alone.

Conditioned activity

The methamphetamine plus scopolamine-sensitized rats showed significantly augmented behavioural response to the tone–placebo pairings as compared with the methamphetamine-sensitized rats (mean sum, $U = 7{\cdot}50$, $Z = 2{\cdot}61$, $P < 0{\cdot}01$; time point values, $U = 4{\cdot}00$–$12{\cdot}00$, $Z = 2{\cdot}44$–$3{\cdot}27$, $P < 0{\cdot}01$ or $P < 0{\cdot}05$), the scopolamine-pretreated rats (mean sum, $U = 7{\cdot}50$, $Z = 2{\cdot}60$, $P < 0{\cdot}01$; time point values, $U = 6{\cdot}50$–$12{\cdot}00$, $Z = 2{\cdot}44$–$2{\cdot}91$, $P < 0{\cdot}01$ or $P < 0{\cdot}05$), and the saline-treated controls (mean sum, $U = 5{\cdot}50$, $Z = 2{\cdot}63$, $P < 0{\cdot}01$; time point values, $U = 6{\cdot}00$–$8{\cdot}00$, $Z = 2{\cdot}40$–$2{\cdot}86$, $P < 0{\cdot}01$ or $P < 0{\cdot}05$). The effects of the tone alone and placebo alone showed no significant differences among the four treatment groups. Interestingly, only methamphetamine plus scopolamine-sensitized rats showed a significant acquisition of conditioned response to the tone–placebo pairing compared with the tone alone (mean sum, $U = 7{\cdot}00$, $Z = 2{\cdot}65$, $P < 0{\cdot}01$; time point values, $U = 9{\cdot}0$–$12{\cdot}0$, $Z = 2{\cdot}28$–$2{\cdot}60$, $P < 0{\cdot}05$) (Table 2).

Discussion

Numerous previous studies on amphetamine- or methamphetamine-induced stereotyped behaviour have been conducted using similar uni-dimensional rating scales to those used in the present study. Individual types of response were ranked in order of progression from normal to the most intense of behavioural acts including gnawing and licking (Costall & Naylor 1972; Ellinwood & Balster 1974; Karler et al 1990). All rating scales have the inherent limitation of the stereotypy rating scale, in assuming an underlying continuum of behavioural response categories; however, this limitation should not detract from the understanding of the behavioural effects of methamphetamine (Fray et al 1980).

Sensitization effects of methamphetamine plus scopolamine on stereotyped behaviour

The administration of amphetamine in combination with anticholinergic agents can inhibit cholinergic systems following the exhaustion of the latent compensatory effects, resulting in a further enhancement of the effects of dopaminergic stimulation (Costall & Naylor 1972). Thus, treatment with methamphetamine alone would not induce a dopaminergic–cholinergic imbalance; therefore, we used methamphetamine plus scopolamine-pretreated rats.

We found that stereotyped behaviour induced by methamphetamine plus scopolamine was reproduced to a similar extent by challenge injections of methamphetamine plus scopolamine and methamphetamine, and to a lesser degree by scopolamine challenges. The findings suggest that behavioural sensitization might operate via the reciprocal balance between the dopaminergic and inhibitory cholinergic systems in favour of a dopaminergic dominance.

Conditioned response of methamphetamine plus scopolamine-sensitized rats

Previous studies with rats have reported that amphetamine in the dose range $0{\cdot}5$–$5{\cdot}0\,mg\,kg^{-1}$ (Herz & Beninger 1987) or at dose of $2{\cdot}5\,mg\,kg^{-1}$ (Beninger & Hahn 1983) induced conditioned locomotor activity in a novel environment. Amphetamine at doses of 0·8, 2·6 and $4{\cdot}7\,mg\,kg^{-1}$ paired with a tone and placement in a novel observation cage induced conditioned sniffing, rearing and locomotor activity (Schiff 1982). In the present study, methamphetamine-sensitized rats failed to display a conditioned response. Our previous study showed that rats with repeated methamphetamine plus scopolamine treatment exhibited progressively augmented reactivity to the 300 Hz tone, resulting in a significant attenuation of their intense stereotypy, as compared with methamphetamine-treated rats (Yui et al 1994). Therefore, methamphetamine-sensitized rats may fail to acquire conditioning due to a low sensitivity to the 300 Hz tone.

It is important to note that the present results, indicating the establishment of conditioning to a tone associated with the methamphetamine plus scopolamine state in the methamphetamine plus scopolamine-sensitized rats, suggests acquisition of a conditioned response to the pairing of the exteroceptive tone cue and the interoceptive drug cues, following the establishment of behavioural sensitization. In other words, there existed a link between an exteroceptive conditioned stimulus and an interoceptive unconditioned stimulus, which can be formed in the course of the conditioning trial (MacMahon et al 1981). Thus, co-administration of methamphetamine and scopolamine can augment the effects of methamphetamine on drug conditioning. In light of the findings of the first experiment that methamphetamine plus scopolamine induced vigorous sensitization effects, it is suggested that robust behavioural sensitization induced by methamphetamine plus scopolamine may lead to an enhanced conditioning to the tone–placebo pairing. As previously proposed (Segal & Mandell 1974), conditioning is difficult to explain as a single process of a drug's behavioural effect. Nor can a conditioned stimulus simply be limited to a tone, as it must include all stimuli impingeing upon an animal before and after the drug injection (Schiff 1982).

Administration of scopolamine has been reported to disrupt classical conditioning (Harvey et al 1983; Salvatierra & Berry 1989), or retard the rate of acquisition to a tone-conditioned stimulus by blocking the unconditioned and conditioned excitatory properties of tone stimuli (Harvey et al 1983). Accordingly, it is suggested that scopolamine can disrupt conditioned response to the exteroceptive tone-conditioned stimulus associated with the drug state by impairing the transfer of experience from the training session to the test session (Warburton & Groves 1969). However, the present results demonstrate that although scopolamine and methamphetamine, when administered separately, are ineffective in producing a conditioned response, the addition of scopolamine to methamphetamine with repeated treatment is effective. Conditioning was dependent on the co-administration of scopolamine and methamphetamine.

According to previous studies, the establishment of drug conditioning to amphetamine-associated environments involves a dopaminergic action (Schiff 1982; Beninger & Hahn 1983; Herz & Beninger 1987). Conditioning to a tone in association with methamphetamine plus scopolamine treatment supports the possibility that the reciprocal balance between the dopaminergic and cholinergic systems

may be involved in drug conditioning in which the effects of methamphetamine are enhanced by anticholinergics such as scopolamine.

In conclusion, these findings indicate that behavioural sensitization may operate via the reciprocal balance between the dopaminergic and inhibitory cholinergic systems in favour of a dopaminergic dominance, and that conditioning to methamphetamine plus scopolamine paired with a tone-conditioned stimulus might be mediated via the reciprocal balance between the two transmitter systems. It is suggested that methamphetamine plus scopolamine induced a robust behavioural sensitization to the 300-Hz tone, which may have led to conditioning by the tone-placebo pairing. It is of importance to note that exteroceptive conditioned stimulus-interoceptive unconditioned stimulus associations may provide an important source to explain the conditioning effects of drugs.

Acknowledgement

We thank Dr H. Kuribara (Behavioural Research Institute, School of Medicine, Gunma University) for his review and helpful comments.

References

Antelman, S. M., Eichler, A. J., Black, C. A., Kocan, D. (1980) Interchangeability of stress and amphetamine in sensitization. Science 207: 329–331

Arnfred, T., Randrup, A. (1968) Cholinergic mechanism in brain inhibiting amphetamine-induced stereotyped behaviour. Acta Pharmacol. Toxicol. 26: 384–394

Beninger, R. J., Hahn, B. L. (1983) Pimozide blocks establishment but not expression of amphetamine-produced environment-specific conditioning. Science 220: 1304–1306

Browne, R. G., Segal, D. S. (1977) Metabolic and experimental factors in the behavioral response to repeated amphetamine. Pharmacol. Biochem. Behav. 6: 545–552

Carey, R. J. (1991) Pavlovian conditioning between co-administered drugs: elicitation of an apomorphine-induced antiparkinsonian response by scopolamine. Psychopharmacology 104: 463–469

Costall, B., Naylor, R. J. (1972) Modification of amphetamine effects by intracerebrally administered anticholinergic agents. Life Sci. 11: 239–253

Ellinwood, E. H. (1971) "Accidental conditioning" with chronic methamphetamine intoxication: implication for a theory of drug habituation. Psychopharmacologia 21: 131–138

Ellinwood, E. H., Balster, R. L. (1974) Rating the behavioral effects of amphetamine. Eur. J. Pharmacol. 28: 35–41

Fray, P. J., Sahakian, B. J., Robbins, T. W., Koob, G. F., Iversen, S. D. (1980) An observational method for quantifying the behavioural effects of dopamine agonists: contrasting effects of *d*-amphetamine and apomorphine. Psychopharmacology 69: 253–259

Harvey, J. A., Gormezano, I., Cool-Hauser, V. A. (1983) Effects of scopolamine and methylscopolamine on classical conditioning of the rabbit nictitating membrane response. J. Pharmacol. Exp. Ther. 225: 42–49

Herz, R. S., Beninger, R. J. (1987) Comparison of the ability of (+)-amphetamine and caffeine to produce environment-specific conditioning. Psychopharmacology 92:365–370

Karler, R., Chaudhry, I. A., Calder, L. D., Turkanis, S. A. (1990) Amphetamine behavioral sensitization and the excitatory amino acids. Brain Res. 537: 76–82

Kokkinidis, L., Anisman, H. (1980) Amphetamine models of paranoid schizophrenia: an overview and elaboration of animal experimentation. Psychol. Bull. 88: 551–579

MacMahon, S. W., Blampied, N. M., Hughes, R. N. (1981) Aversive stimulus properties of scopolamine. Pharmacol. Biochem. Behav. 15: 389–392

Naylor, R. J., Costall, B. (1971) The relationship between the inhibition of dopamine uptake and the enhancement of amphetamine stereotypy. Life Sci. 10: 909–915

Paulson, P. E., Camp, D. M., Robinson, T. E. (1991) Time course of transient behavioral depression and persistent behavioral sensitization in relation to regional brain monoamine concentrations during amphetamine withdrawal in rats. Psychopharmacology 103: 480–492

Robinson, T., Becker, J. B. (1986) Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. Brain Res. Rev. 11: 157–198

Sahakian, B. J., Robbins, T. W., Morgan, M. J., Iversen, S. D. (1975) The effects of psychomotor stimulants on stereotypy and locomotor activity in socially-deprived and control rats. Brain Res. 84: 195–205

Salvatierra, A. T., Berry, S. D. (1989) Scopolamine disruption of septo-hippocampal activity and classical conditioning. Behav. Neurosci. 103: 715–721

Sato, M., Chen, C.-C., Akiyama, K., Otsuki, S. (1983) Acute exacerbation of paranoid state after long-term abstinence in patients with previous methamphetamine psychosis. Biol. Psychiatry 18: 429–440

Schiff, S. R. (1982) Conditioned dopaminergic activity. Biol. Psychiatry 17: 135–154

Segal, D. S., Mandell, A. J. (1974) Long-term administration of d-amphetamine: progressive augmentation of motor activity and stereotypy. Pharmacol. Biochem. Behav. 2: 249–255

Ujike, H., Akiyama, K., Otsuki, S. (1990) D-2 but not D-1 dopamine agonists produce augmented behavioral response in rats after subchronic treatment with methamphetamine or cocaine. Psychopharmacology 102: 459–464

Utena, H. (1974) On relapse-liability: schizophrenia, amphetamine psychosis and animal model. In: Mitsuda, H., Fukuda, T. (eds) Biological Mechanisms of Schizophrenia and Schizophrenia-like Psychosis. Igakushoin, Tokyo, pp 285–287

Warburton, D. M., Groves, P. M. (1969) The effects of scopolamine on habituation of acoustic startle in rats. Commun. Behav. Biol. 3: 289–293

Yui, K., Miura, T. (1991) Cholinergic modulation on stereotyped behaviors and behavioral hypersensitivity (reverse tolerance) in rats. Jpn. J. Psychopharmacol. 11: 141–156

Yui, K., Miura, T., Fukushima, T. (1988) Behavioral responses induced by methamphetamine administration in combination with scopolamine. Psychopharmacology 96: 167

Yui, K., Miura, T., Sugiyama, K., Ono, M., Nagase, M. (1994) Stereotyped behavioral responses to an auditory stimulus in the course of repeated treatment with methamphetamine plus scopolamine and methamphetamine in rats. Jpn. J. Psychopharmacol. 14: 169–178