rectifying K^+ channels by various antidepressant drugs. Neuropsychopharacology **29**: 1841-1851.

19. North, R. A. 1989. Drug receptors and the inhibition of nerve cells. Br. J. Pharmacol. **98**: 13-28.

20. Ikeda, K., T. Kobayashi, T. Ichikawa, *et al.* 1995. Functional couplings of the δ- and the κ-opioid receptors with the G-protein-activated K^+ channel. Biochem. Biophys. Res. Commun. **208**: 302-308.

21. Ikeda, K., T. Kobayashi, T. Ichikawa, *et al.* 1996. Comparison of the three mouse G-protein-activated K^+ (GIRK) channels and functional couplings of the opioid receptors with the GIRK1 channel. Ann. N. Y. Acad. Sci. **801**: 95-109.

22. Ikeda, K., K. Kobayashi, T. Kobayashi, *et al.* 1997. Functional coupling of the nociceptin /orphanin FQ receptor with the G-protein-activated K^+ (GIRK) channel. Mol. Brain. Res. **45**: 117-126.

23. Reuveny, E., P. A. Slesinger, J. Inglese, *et al.* 1994. Activation of the cloned muscarinic potassium channel by G protein βγ subunits. Nature **370**: 143-146.

24. Kobayashi, T., K. Ikeda, H. Kojima, *et al.* 1999. Ethanol opens G-protein-activated inwardly rectifying K^+ channels. Nat. Neurosci. **2**: 1091-1097.

25. Lewohl, J. M., W. R. Wilson, R. D. Mayfield, *et al.* 1999. G-protein-coupled inwardly rectifying potassium channels are targets of alcohol action. Nat. Neurosci. **2**: 1084-1090.

26. Kobayashi, T., K. Washiyama & K. Ikeda. 2006. Inhibition of G protein-activated inwardly rectifying K^+ channels by ifenprodil. Neuropsychopharmacology **31**: 516-524.

27. Suzuki, T., H. Kato, M. Tsuda, *et al.* 1999. Effects of the non-competitive NMDA receptor antagonist ifenprodil on the morphine-induced place preference in mice. Life. Sci. **64**:

PL151-PL156.

28. Morgan, A. D., M. E. Carroll, A. K. Loth, *et al.* 2003. Decreased cocaine self-administration in Kir3 potassium channel subunit knockout mice. Neuropsychopharacology **28**: 932-938.

29. Ago, Y., T. Harasawa, S. Itoh, *et al.* 2005. Antidepressant-like effect of coadministration of sulpiride and fluvoxamine in mice. Eur. J. Pharmacol. **520**: 86-90.

Figure legends

FIGURE 1. Effects of paroxetine on CPP for METH in mice. (A) Reduction of METH CPP by paroxetine (Px) pretreatment. Mice were pretreated with saline (S) in both the conditioning and CPP test phases (S-S), paroxetine only in the CPP test phase (S-Px), paroxetine only in the conditioning phase (Px-S), and paroxetine in both the conditioning and the CPP test phases (Px-Px). The CPP score was defined as the time spent in the drug-paired compartment during the CPP test phase (Day 9) minus the time spent in the same compartment during the preconditioning phase (Day 2). The CPP score of the Px-Px group was significantly lower than that of the S-S group ($^{\#}P < 0.05$). (B) Comparison of time spent in the conditioned compartment before and after conditioning in the four groups. There was a significant CPP in the S-S and Px-S groups, but not in the S-Px and Px-Px groups (when paroxetine was administered in the CPP test phase). $^{***}P < 0.001$, $^{*}P < 0.05$, ns: not significant ($P > 0.05$).

FIGURE 2. Effects of fluvoxamine on CPP for METH and on transitions between compartments. (A) Lack of a significant effect of fluvoxamine (Fv) on METH CPP. Mice were pretreated with saline in both the conditioning and the CPP test phases (S-S), fluvoxamine only in the CPP test phase (S-Fv), fluvoxamine only in the conditioning phase (Fv-S), and fluvoxamine in both the conditioning and the CPP test phases (Fv-Fv). There was a significant CPP in all groups. Fluvoxamine pretreatment in the conditioning phase and/or the CPP test phase failed to inhibit METH CPP (pre- and post-conditioning preference test results were analyzed with paired *t*-tests, $^{***}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$). (B) Decreases in transitions between the compartments by fluvoxamine pretreatment. There were significant decreases in transitions in the S-Fv, Fv-S,

and Fv-Fv groups, but not in the S-S group [number of transitions in the pre- and post-conditioning phases was analyzed with paired *t*-tests, $***P < 0.001$, $**P < 0.01$, ns: not significant ($P > 0.05$)]. The transition score was defined as the number of transitions during the CPP test phase (Day 9) minus the number of transitions during the preconditioning phase (Day 2).

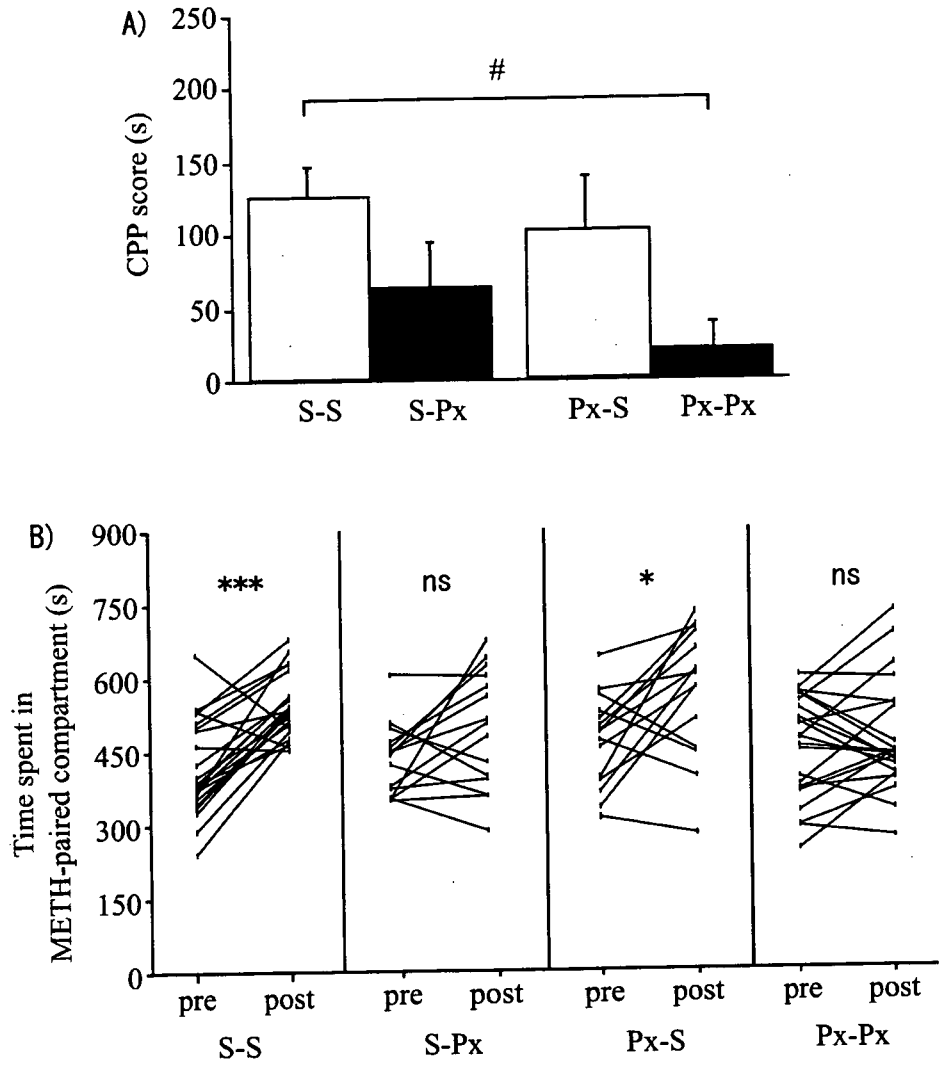


FIGURE 1. Effects of paroxetine on CPP for METH in mice. (A) Reduction of METH CPP by paroxetine (Px) pretreatment. Mice were pretreated with saline (S) in both the conditioning and CPP test phases (S-S), paroxetine only in the CPP test phase (S-Px), paroxetine only in the conditioning phase (Px-S), and paroxetine in both the conditioning and the CPP test phases (Px-Px). The CPP score was defined as the time spent in the drug-paired compartment during the CPP test phase (Day 9) minus the time spent in the same compartment during the preconditioning phase (Day 2). The CPP score of the Px-Px group was significantly lower than that of the S-S group (#P < 0.05). (B) Comparison of time spent in the conditioned compartment before and after conditioning in the four groups. There was a significant CPP in the S-S and Px-S groups, but not in the S-Px and Px-Px groups (when paroxetine was administered in the CPP test phase). ***P < 0.001, *P < 0.05, ns: not significant (P > 0.05).

129x149mm (600 x 600 DPI)

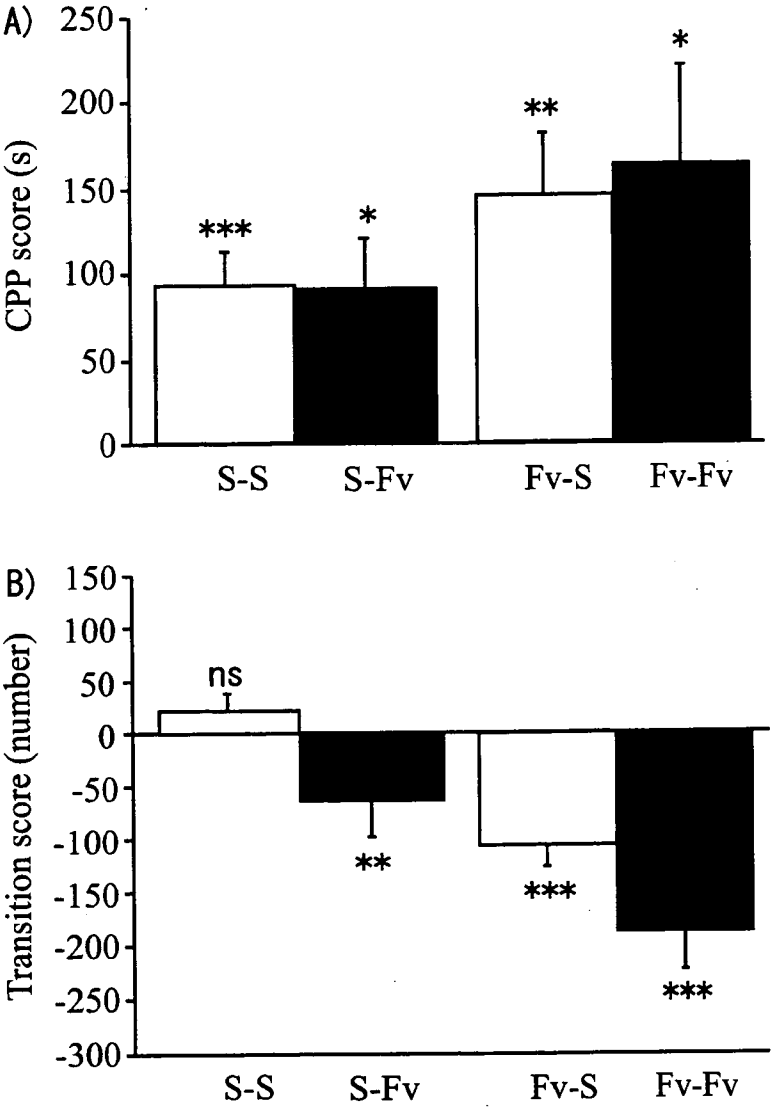


FIGURE 2. Effects of fluvoxamine on CPP for METH and on transitions between compartments. (A) Lack of a significant effect of fluvoxamine (Fv) on METH CPP. Mice were pretreated with saline in both the conditioning and the CPP test phases (S-S), fluvoxamine only in the CPP test phase (S-Fv), fluvoxamine only in the conditioning phase (Fv-S), and fluvoxamine in both the conditioning and the CPP test phases (Fv-Fv). There was a significant CPP in all groups. Fluvoxamine pretreatment in the conditioning phase and/or the CPP test phase failed to inhibit METH CPP (pre- and post-conditioning preference test results were analyzed with paired t-tests, ***P < 0.001, **P < 0.01, *P < 0.05). (B) Decreases in transitions between the compartments by fluvoxamine pretreatment. There were significant decreases in transitions in the S-Fv, Fv-S, and Fv-Fv groups, but not in the S-S group [number of transitions in the pre- and post-conditioning phases was analyzed with paired t-tests, ***P < 0.001, **P < 0.01, ns: not significant (P

> 0.05)]. The transition score was defined as the number of transitions during the CPP test phase (Day 9) minus the number of transitions during the preconditioning phase (Day 2).

96x133mm (600 x 600 DPI)

Available online at www.sciencedirect.com
ScienceDirect
Drug and Alcohol Dependence 88 (2007) 174–181
DRUG and ALCOHOL DEPENDENCE
www.elsevier.com/locate/drugalcdep

Development and validation of the Stimulant Relapse Risk Scale for drug abusers in Japan☆

Yasukazu Ogai[a], Ayako Haraguchi[a], Ayumi Kondo[a,b], Yoko Ishibashi[a], Mitsuru Umeno[c], Hirotsugu Kikumoto[c], Toru Hori[d], Tokutaro Komiyama[d], Riki Kato[e], Katsuro Aso[f], Nozomu Asukai[b], Eiichi Senoo[b], Kazutaka Ikeda[a,*]

[a] *Division of Psychobiology, Tokyo Institute of Psychiatry, 2-1-8 Kamikitazawa, Setagaya-ku, Tokyo, Japan*
[b] *Division of Social Psychiatry, Tokyo Institute of Psychiatry, 2-1-8 Kamikitazawa, Setagaya-ku, Tokyo, Japan*
[c] *Tokyo Metropolitan Matsuzawa Hospital, 2-1-1 Kamikitazawa, Setagaya-ku, Tokyo, Japan*
[d] *National Center Hospital for Mental, Nervous and Muscular Disorders, National Center of Neurology and Psychiatry, 4-1-1 Ogawahigashi-cho, Kodaira, Japan*
[e] *Self Support Services, 3-61-22-202 Kameido, Koutou-ku, Tokyo, Japan*
[f] *Fukko-kai Tarumi Hospital, 566 Oshibedani-cho Nishimori, Nishi-ku, Kobe, Japan*

Received 16 March 2006; received in revised form 10 October 2006; accepted 17 October 2006

Abstract

Objective: To develop and validate a multidimensional measure of relapse risk for stimulants in Japanese drug abusers.
Methods: A Stimulant Relapse Risk Scale (SRRS) was developed based on the Marijuana Craving Questionnaire and a discussion among three psychiatrists. We created 48 items after confirming the items including a variety of relapse risk, such as craving (expectancy, compulsivity, etc.) and emotionality problems. One hundred inpatients and outpatients with a history of stimulant abuse (71 males and 29 females) were recruited with informed consent, and were administered the SRRS. The Visual Analogue Scale for drug craving (VAS), Addiction Severity Index for Japanese (ASI-J), and data on relapse within 3 and 6 months after the rating were used for the validation.
Results: Exploratory factor analysis highlighted five factors: anxiety and intention to use drug (AI), emotionality problems (EP), compulsivity for drug use (CD), positive expectancies and lack of control over drug (PL), and lack of negative expectancy for drug use (NE). These accounted for 48.3% of the total variance. Thirty of the 43 items were classified into the five subscales. Cronbach's alpha coefficient for each subscale ranged from .55 to .82, and was .86 for the total SRRS, indicating their adequate internal consistency. AI, CD, PL, and total SRRS were significantly correlated with the drug-use composite score of the ASI-J, supporting their concurrent validity. AI, PL, NE, and total SRRS were significantly correlated with relapse, implying their predictive validity.
Conclusions: The SRRS has multidimensional psychometric properties useful for assessing the various aspects of stimulant relapse risk.

Keywords: Stimulants; Relapse risk; Craving; Scale; Japanese

1. Introduction

Stimulants such as methamphetamine, methylphenidate, and methylenedioxymethamphetamine (MDMA) are the main drugs involved in cases of drug abuse in Japan (Wada et al., 2004). Stimulant dependence presents a serious problem not only for the patients but also for Japanese society (Ikeda et al., 2004). For example, about 25% of convicted prisoners have committed offences under the Stimulant Control Law (The Ministry of Justice Research and Training Institute, 2004). Medical treatment of stimulant abusers has mainly targeted their immediate psychotic symptoms such as hallucination and delusion, and the symptoms of relapse such as craving, which are significantly related to dependence and relapse has not been addressed sufficiently. Insufficient treatment of relapse risk is partly due to the lack of suitable instruments for measuring the severity of relapse risk. On the other hand, recent breakthroughs in genomic science and molecular pharmacology have made it possible to

☆ English and Japanese versions of the Stimulant Relapse Risk Scale (SRRS) can be found by accessing the online version of this paper at http://dx.doi.org by entering doi:10.1016/j.drugalcdep.2006.10.005.

* Corresponding author. Tel.: +81 3 3304 5701x508; fax: +81 3 3329 8035.
E-mail address: ikedak@prit.go.jp (K. Ikeda).

0376-8716/$ – see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.drugalcdep.2006.10.005

investigate the molecular mechanisms underlying the tendency of animals to prefer drugs, and to find candidate medicines that might inhibit this tendency (Sora et al., 2001; Takamatsu et al., 2006a,b). Some of these medicines may reduce craving, and ultimately the risk of relapse, in human drug abusers (Piasecki et al., 2002; Ciraulo et al., 2005). To further advance the development of medicines and programs for the prevention of relapse, scales for the appropriate assessment of relapse risk are necessary.

Craving, one of the main factor of relapse, is generally understood to be a subjective motivational state in which an individual experiences an intense desire to use a drug. However, craving and its generation process have been conceptualized in various ways (Drummond, 2001). For example, the 'expectancy theory' by Jones et al. (2001) has maintained that craving is a function of positive and negative expectancy for drug use. Anton and his colleagues (Anton, 2000; Anton et al., 1996), in his 'obsessive compulsive theory', have suggested that drug craving is closely related to obsessive compulsive feelings about a drug that cannot be controlled. Although each theory has some valid explanatory power, there is no theory that can explain craving integrally. Therefore, multidimensional scales have been frequently used to measure various aspects of craving.

Although it is considered that craving is closely related to relapse, the lack of consistency in the findings of studies on the relationship between craving and relapse may be due to the lack of consensus regarding the definition of craving (Drummond, 2001). Tiffany (1990) considered that craving, if simply conceptualized as a 'subjective desire for a drug', is not always related to relapse. Human's craving for drug is supposed to be expressed in various ways, such as desire, intention, expectancy, anticipation, and compulsivity. In addition, other factors such as negative emotional states (Cooney et al., 1997) and lack of insight into mental condition (denial) (Wallace, 1989) may also become the trigger of relapse. Thus, it is imperative to specify and measure a variety of factors related to relapse.

Some multidimensional scales for stimulants such as amphetamine have already been developed. Topp and Mattick (1997) have developed the Severity of Amphetamine Dependence Questionnaire (SAmDQ), which is a multidimensional scale for measuring the aspects of dependence syndrome such as withdrawal. James et al. (2004) have developed the Desires for Speed Questionnaire (DSQ) based on the Desires for Alcohol Questionnaire (DAQ) (Love et al., 1998) to measure craving for amphetamine, and this revealed four key factors: 'expectancy of positive and negative reinforcement', 'strong desires and intentions to use amphetamine', 'mild desires and intentions to use amphetamine', and 'control'. However, there is no scale that focuses on the multiple aspects of relapse risk including craving, emotional problems, and denial.

In the present study, considering the clinical importance of relapse prediction, we developed a multidimensional scale to measure relapse risk for stimulants. The development of Stimulant Relapse Risk Scale (SRRS) was based on the Marijuana Craving Questionnaire (MCQ) (Heishman et al., 2001) and a discussion among three psychiatrists who are actively involved in the treatment of drug abuse. The discussion was focused on 'various cognitive and behavioral signs shown by drug abusers, which based on the clinical experience, have been found to precede relapse'. Forty-eight items were then developed that reflects a variety of relapse risk, such as craving (expectancy, compulsivity, etc.), emotionality problems, and denial. We administered the SRRS to 100 stimulant abusers in Japan and examined its inner structure, reliability and validity. The aim of the present study was to develop and validate the SRRS as a measure of relapse risk for stimulants.

2. Methods

2.1. Participants

A total of 100 inpatients (40), outpatients (52) and non-patients (8) with a history of stimulant abuse involving mainly methamphetamine (90), methylphenidate (8), and MDMA (7) participated in the study (Table 1). They were recruited for an ongoing research studies at Tokyo Metropolitan Matsuzawa Hospital, Tokyo (44), Self Support Services (a non-profit addiction recovery facility), Tokyo (20), National Center Hospital for Mental, Nervous and Muscular Disorders, National Center of Neurology and Psychiatry, Kodaira (18), GAIA (a non-profit addiction recovery facility), Naha (15), and Fukko-kai Tarumi Hospital, Kobe (3). The subjects comprised 71 males and 29 females, ranging in age from 19 to 60 years (mean = 32.6, S.D. = 8.7).

Recruitment criteria were as follows: at least 18-year-old, has a history of stimulant (methamphetamine, methylphenidate, or MDMA) abuse, diagnosed as a drug abuser (1) or as a drug dependent (99) on the basis of the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) criteria; be an inpatient or outpatient at a Japanese mental hospital or a recovery facility, or a non-patient recovering from stimulant abuse in a recovery facility; and has the ability to understand Japanese. The study was approved by the institutional review board of each facility. Each participant provided a written informed consent, and answered the SRRS, the Addiction Severity Index-Japanese version (ASI-J) (Senoo et al., 2006), the Visual Analogue Scale for drug craving (VAS), the Center for Epidemiological Studies Depression Scale, Japanese version (CES-D) (Shima et al., 1985), the 12-item General Health Questionnaire, Japanese version (GHQ-12) (Daibo and Nakagawa, 1985), and a number of questions related to demographics and experience with stimulants.

Table 1
Characteristics of the SRRS participants

Items	Values
Number of participants	100
Age ($M \pm$ S.D.)	32.6 ± 8.7
Gender (%female)	29
Treatment state (N)	
Inpatients	40
Outpatients	52
Non-patients	8
Relapse/no relapse within 3 months (N)	13/35
Relapse/no relapse within 6 months (N)	15/33
Primary substances abused[a] (N)	
Meth amphetamine	90
Methylphenidate	8
MDMA	7
ASI-J drug composite score (0–1; $M \pm$ S.D.)	.16 ± .17
VAS (current, 0–10; $M \pm$ S.D.)	2.74 ± 3.09
VAS (past 2 weeks, 0–10; $M \pm$ S.D.)	3.66 ± 3.69
CES-D (0–60; $M \pm$ S.D.)	20.48 ± 13.24
GHQ-12 (0–12; $M \pm$ S.D.)	4.45 ± 3.72

N: Number of participants; M: mean; S.D.: standard deviation.
[a] Some participants have more than one primary substance.

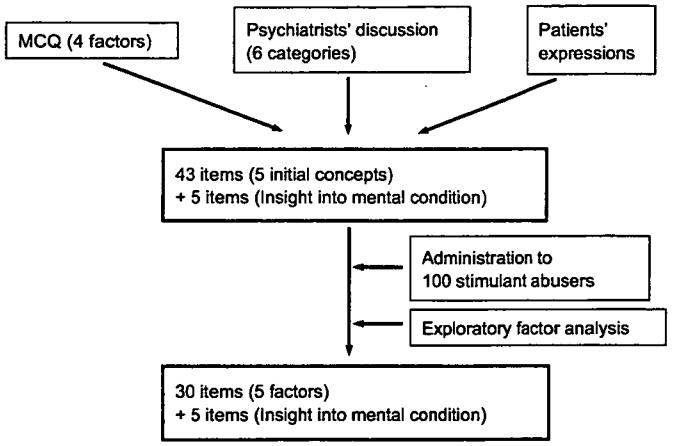


Fig. 1. A schematic flow of the development of SRRS. Four factors taken from the MCQ were compulsivity, emotionality, expectancy, and purposefulness. Six categories highlighted in the psychiatrists' discussion were patients' search for stimulants, common feelings and moods observed before relapse, recall of stimulant craving and negative moods, lack of resistance to inductive stimuli, lack of recognition of social support, and insight into mental condition. Five initial concepts of the 43 items were compulsivity (C), negative expectancy for drug (N), clear intention of drug use (I), positive expectancy for drug (P), and emotionality problems (E). These 43 items and 5 items to measure insight into mental condition were then administered to 100 subjects. The exploratory factor analysis resulted in 30 items with 5 factors that were anxiety and intention to use drug (AI), emotionality problems (EP), compulsivity for drug use (CD), positive expectancies and lack of control over drug (PL), and lack of negative expectancy for drug use (NE).

2.2. Development of the Stimulant Relapse Risk Scale[1]

The SRRS was developed based on a discussion among psychiatrists, and by referring to the MCQ (Fig. 1). Six items were adopted from the MCQ (e.g. 'smoke marijuana' was replaced with 'use the drug') and translated into Japanese. Seven items that seemed applicable to drug abusers were selected from the actual expressions used by patients during a preliminary consultation with us. The above 13 items were then classified into the four factors of the MCQ: compulsivity, emotionality, expectancy, and purposefulness. For instance, 'If I use a drug, I feel I have been saved from helpless loneliness' was classified under emotionality, and 'I am afraid of hallucinations with drug use' under expectancy (negative expectancy).

Next, 35 items were selected through a discussion among three psychiatrists who are currently involved in the treatment of drug abuse. The foci of the discussion were the following six categories of cognition and behavior that predicted relapse: (1) the action of seeking for stimulants, (2) common feelings and moods observed in patients before relapse, (3) recall of stimulant craving and negative moods, (4) lack of resistance to inductive stimuli, (5) lack of recognition of social support, (6) insight into mental condition. The fifth category included two reversal items (e.g. 'I need to make most of my friend's (and NA's) support'). The sixth category was added on the basis of the viewpoint that the lack of insight into one's mental condition (denial) may be related to relapse (e.g. I am sure that I will not use the drug in future).

After confirming the content of these items, including a variety of relapse risks such as craving (expectancy, compulsivity, etc.) and emotionality problems, the above 10 points were modified into a total of six initial concepts of the SRRS, which included a construct for insight into mental condition and five constructs as drug-reuse cues. The five constructs were: (1) compulsivity (C; inability to control stimulant-induced emotion), (2) negative expectancy for drug use (N; restraining relapse, anxiety due to negative outcome from drug use, and acknowledgment of social support), (3) clear intention of drug use (I; planning to use a drug, and intentional search for stimulants), (4) positive expectancy for drug use (P; anticipation of positive outcomes from reuse), (5) emotionality problems (E; not only feelings and moods before relapse but also a revival of memory).

Each of the 48 items was rated on a three-point Likert-type scale with a score ranging between 1 and 3 based on the subjects' strength of agreement with each statement. A three-point scale was employed to reflect patient feedbacks, which pointed out the difficulty answering a five-point scale. The written instruction, 'Please describe your state during the past week. For each statement below, please circle one answer that best describes you. For the word "drug" that appears in the statements, think about the drug you currently abuse.' was given before the 48 items.

2.3. Measurements for concurrent validity

In order to determine the severity of dependence, the Addiction Severity Index-Japanese version (ASI-J), a semi-structured interview lasting approximately 1 h, was administered to the participants. This instrument gathers information about seven areas of a patient's life: medical, employment/support, drug, alcohol, legal, family/social relationships, and psychiatric problems. Severity was rated as a composite score of between 0 and 1, calculated entirely on the basis of the patient's current status. In the present study, the composite score for the drug use was used as an index of the concurrent validity of the SRRS.

In order to evaluate the concurrent validity of the SRRS, the VAS was also administered to the participants, which measured their subjective desires for a drug. The VAS was composed of two questions: 'Please rate your current state of craving' and 'Please rate your strongest craving for the drug in the past 2 weeks'. Participants answered each question by placing a vertical mark on a 100-mm horizontal line, labeled 'not at all' at the left end and 'extremely' at the right end.

Participants also answered the CES-D and GHQ-12 that measured their emotional problems. These scales were used to examine the concurrent validity of the factor, 'emotionality problems' in the SRRS.

2.4. Measurements for predictive validity

To evaluate the risk of relapse, relapse within 3 months and 6 months after the SRRS rating were investigated. Relapse was operationally defined as "to use any stimulants-type drug including methylephedrine after the SRRS rating", and was judged from the patients' self-report and/or their psychiatrists in charge. Of 48 participants for whom the information was available, 13 and 15 participants relapsed within 3 and 6 months, respectively.

2.5. Questionnaire on drug experience and demographic factors

The participants were also asked to complete a short questionnaire in order to obtain information about their age, sex, the day the questionnaire was completed, and the main drug they were using (or had used). The question also included of the date when they had last used the drug, the period since they last used the drug, and the period for which they had used drugs.

2.6. Statistical analyses

Raw scores for the negatively worded items (item numbers 2, 6, 12, 14, 17, 18, 19, 20, 21, 23, 30, 37) were inverted to make these items positively correlate with other items. The inner structure of the 43-item SRRS without the items that assessed insight into the patient's mental condition, was examined by the exploratory factor analysis using a principal factor method with promax rotation to detect simple structure. Factors were extracted on the basis of their eigenvalues (>1) and the scree plot. Only those items loading higher than .4 were retained in the analyses, and all items cross-loading at higher than .4 were removed. The extracted factor scales were checked for their reliability by calculating the Cronbach's alpha value. Concurrent and predictive validity of the subscales, and inter-subscale correlations were analyzed by calculating the Pearson's product-moment correlation coefficient. For the analysis of relapse, 'relapse' was coded as '1', and 'no relapse' as '0'.

[1] English and Japanese versions of the Stimulant Relapse Risk Scale (SRRS) can be found by accessing the online version of this paper at http://dx.doi.org by entering doi:10.1016/j.drugalcdep.2006.10.005.

In addition, the function of the five items that assessed insight into mental condition was examined. The relationships among insight into mental condition, relapse within 6 months, and ASI-J drug composite score were analyzed by Fisher's exact test. Median split of average scores (average of the five items scores = 1.8; ASI-J composite score = .45) was used for dividing the variables into two groups. Thirty-eight participants' data on relapse within 6 months and ASI-J were used for the analysis.

All analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 12.0 for Windows.

3. Results

3.1. Factor analysis

The exploratory factor analysis of the SRRS scores of 100 patients with stimulant abuse revealed 5 factors with eigenvalues of 9.38, 4.60, 2.55, 2.33 and 1.96. These factors accounted for 48.41% of the overall variance (21.82%, 10.70%, 5.93%, 5.41% and 4.56%). Cronbach's alpha values for factors 1, 2, 3, 4, 5, and all items were .82, .80, .73, .79, .55 and .86, respectively. Subsequently, the factors were rotated using the promax method. Of the original 43 items, 30 items were retained and 13 items were discarded. The factor structure after the promax rotation is shown in Table 2. Cronbach's alpha values for each subscale and the total SRRS (all 30 extracted items) are shown in Table 3.

The first factor had significant loadings for eight items, and three of these items reflecting anxiety about relapse and recall of drug use (e.g. 'I am anxious about reusing the drug'; 'The feeling I had while using the drug sometimes comes back.') loaded exclusively on this factor. The remaining item reflected intention and desire to use drug (e.g. 'I will use the drug in the near future'). Thus, the first factor was labeled 'anxiety and intention to use drug' (AI).

Eight items loaded exclusively on the second factor. All of these items reflected emotional problems related to drug use (e.g. 'I cannot control my feeling.', 'I feel tired due to impatience', 'I am irritated'). This factor was therefore labeled 'emotionality problems' (EP).

The third factor had significant loadings for four items. All of these items reflected compulsivity for drug use (e.g. 'I want to obtain the drug even by working illegally'; 'I would do anything to get money for the drug.'). Consequently, this factor was labeled 'compulsivity for drug use' (CD).

The fourth factor comprised six items. Three of these items reflected positive expectancy about drug use (e.g. 'If I used the drug, I would feel invigorated'; 'If I used the drug, I would be less nervous'), and the remaining three items reflected lack of resistance to an inductive stimulus (e.g. 'If the drug is placed in front of me, I would use it'; 'I would use the drug if I am alone'). Therefore, the fourth factor was labeled 'positive expectancies and lack of control over drug' (PL).

The fifth factor comprised four reverse-scored items. Three items had originally been classified as negative expectancy for drug use (e.g. 'I would not be able to control myself if I use the drug', 'If I use the drug, it would badly influence my job'), and the remaining one item as emotionality problems (i.e. 'I feel easier than before'). This factor was therefore labeled 'lack of negative expectancy for drug use' (NE).

In addition, we analyzed the function of the five items for assessing insight into mental condition. In the group with high ASI-J drug composite scores, the association between insight into mental condition and relapse within 6 months was nearly significant (Fisher's exact test: $p = .088$). On the other hand, the association was not significant in the group with low ASI-J drug composite scores. These results suggest that poor insight into mental condition may be related to relapse in the high-severity group, whereas insight is not related to relapse in the low-severity group.

3.2. Basic statistics of the SRRS and inter-subscale correlations

Table 4 presents mean, standard deviation, and inter-correlations of the five SRRS factor scales (subscales). There were no significant correlations between 'lack of negative expectancy for drug use (Factor 5)' and other subscales. The other factors exhibited low to moderate, positive inter-correlations. In addition, one-way ANOVA showed that the SRRS total and subscale scores were not significantly different across methamphetamine, methylphenidate, and MDMA, although there are often considerable differences in the use patterns and subjective effects of these drugs.

3.3. Concurrent validity of the SRRS

Correlation coefficients between the SRRS scores (total score for the 30 items, and subscale scores) and the variables measured to examine concurrent validity were calculated (Table 3). The ASI-J drug composite score was significantly and positively correlated with the scores of total SRRS, anxiety and intention to use drug, compulsivity for drugs, and positive expectancies and lack of control over drug score. The two VAS scores for drug craving, 'current craving' and 'craving in the past 2 weeks', were also significantly and positively correlated with the total SRRS, anxiety and intention to use drug, compulsivity for drugs, and positive expectancies and lack of control over drug scores. In addition, the scores of emotionality problems, anxiety and intention to use drug, and total SRRS were significantly and positively correlated with the CES-D and GHQ-12 scores.

3.4. Predictive validity of the SRRS

Table 3 also presents correlations between the SRRS score and relapse within 3 and 6 months after the scoring. Relapse within 3 months was significantly and positively correlated with the anxiety and intention to use drug, positive expectancies and lack of control over drug, lack of negative expectancy, and total SRRS. Similarly, relapse within 6 months was significantly and positively correlated with the positive expectancies and lack of control over drug and lack of negative expectancy. No significant relation was seen between the SRRS scores and participants' compliances with follow-up (48 participants approved, 19 participants refused, and 33 participants were not asked).

Table 2
Promax rotated factor pattern for the 43-item SRRS

	Factor				
	1	2	3	4	5
Factor 1: Anxiety and intention to use drug (AI)					
E 8) I am anxious about reusing the drug	**.806**	.251	−.046	−.014	−.284
E 3) The feeling I used to have while using the drug sometimes comes back	**.797**	.056	−.002	−.261	−.192
N 18) Thinking about my family, I can no longer use the drug (inverse)	**.648**	.123	−.126	−.237	−.009
I 46) I will use the drug in near future	**.580**	.027	.058	−.084	.232
I 4) There are times I want to use the drug	**.556**	−.048	.122	.136	.120
C 32) If my friend gives me the drug, I would use it even in the hospital	**.502**	−.029	−.036	.101	.148
C 48) Even though I know I will be arrested, I would use the drug	**.479**	−.067	.094	.086	−.256
I 38) If I have a large sum of money, I want to buy the drug	**.475**	.117	.082	.094	.081
Factor 2: Emotionality problems (EP)					
E 33) I cannot control my feeling	.158	**.685**	.005	−.058	−.124
E 36) I feel tired due to impatience	.110	**.662**	.067	−.092	−.014
E 10) I am irritated	−.167	**.601**	.050	.107	.186
E 22) I feel lonely	.095	**.574**	−.092	.206	.039
E 15) I am not motivated to do anything	.093	**.525**	.103	−.062	−.116
E 28) I am anxious about my future	.329	**.490**	−.204	.206	−.110
E 7) I am annoyed by words from others	.010	**.478**	.104	−.109	.176
E 5) I feel a constant need to put something in my mouth	.007	**.407**	.238	−.008	.068
Factor 3: Compulsivity for drug (CD)					
C 47) I want to obtain the drug even by working illegally	.062	.063	**.817**	−.220	.101
C 40) I would do anything to get money for the drug	.051	.024	**.659**	.008	−.124
C 13) I would do almost anything in order to use the drug	−.037	−.064	**.627**	.233	−.260
C 44) I want the drug even if I have to steal	.104	.152	**.586**	.057	.041
Factor 4: Positive expectancies and lack of control over drug (PL)					
P 45) If I use the drug, I would feel invigorated	−.093	.010	.046	**.820**	−.211
P 41) If I use the drug, I would be less nervous	−.079	.320	−.134	**.688**	−.122
P 43) If I use the drug, I would feel everything is going well	−.208	.294	.250	**.455**	−.080
C 35) If the drug is placed in front of me, I would use it	.253	−.139	.186	**.427**	.328
C 29) I would use the drug if I am alone	.139	.359	.168	**.421**	−.047
C 24) If someone holds the drug under my nose, I would not be able to refuse it	.212	−.237	−.038	**.418**	.291
Factor 5: Lack of negative expectancy for the drug (NE)					
N 23) I would not be able to control myself if I use the drug (inverse)	−.034	.079	−.081	−.098	**.661**
N 30) If I use the drug, it would badly influence my job (inverse)	.141	−.113	−.331	−.126	**.552**
E 14) I feel easier than before (inverse)	−.166	.272	.097	−.085	**.538**
N 20) I am afraid of hallucinations due to drug use (inverse)	−.130	−.188	.151	−.242	**.449**
Ambiguous items					
I 27) I would use the drug if my friends offer it to me on a street	**.530**	−.169	−.029	**.414**	.063
E 34) I have significant job-related problems	−.095	**.622**	.004	−.012	**.441**
E 31) I occasionally have nightmares	−.020	**.503**	**−.410**	.303	.026
P 26) The drug would save me from feeling lonely	−.154	.035	**.490**	**.424**	.038
N 12) If I use a small amount of the drug, I would not be able to stop using it (inverse)	**−.448**	.104	−.326	−.011	**.520**
Other items					
I 9) It would be difficult for me to refuse if someone offers me the drug before my eyes	.372	−.279	.068	.271	.264
I 11) I am dying to use the drug	.364	.018	.288	.066	.191
I 42) I might use the drug at a party or a gathering	.257	.195	.199	−.228	.289
E 1) I want to find a job or need to improve my work environment	−.293	.375	.156	.230	−.157
E 25) I feel bored	.277	.256	.010	−.084	.281
P 16) I recall the relief from feeling blue from the time I was using the drug	.256	.284	−.053	−.007	.315
N 39) I would feel restless if I use the drug (inverse)	−.015	−.053	−.032	.109	.383
N 2) I need to make most of my friend's (and NA's) support (inverse)	−.101	−.130	.026	−.041	.140

E: emotionality problems; C: compulsivity; I: clear intention of drug use; P: positive expectancy for drug; N: negative expectancy for drug in terms of the initial 5 concepts. Numbers followed by single parentheses indicate the order in the SRRS values higher than .4 are in bold.

4. Discussion

In the present study, we developed the SRRS to assess relapse risk for stimulant in Japanese drug abusers, and statistically examined its inner structure, reliability, and validity. As a result, five factors were found, and the internal consistency, concurrent validity, and predictive validity of these factors were revealed. It was especially meaningful that part of the SRRS was related to relapse, implying its possibility of predicting relapse. Our findings demonstrated that the SRRS has multidimensional psy-

Table 3
Cronbach's alpha of each subscale of the SRRSand correlation of the SRRS against VAS ASI, CES-D, GHQ-12, and relapse

	Cronbach's α	Correlation						
		VAS (current craving)	VAS (craving in the past 2 weeks)	ASI-drug	CES-D	GHQ-12	Relapse (3 months)	Relapse (6 months)
SRRS subscale								
Anxiety and intention to use drug (AI)	.819	.645**	.706**	.483**	.228*	.287**	.418**	.309†
Emotionality problems (EP)	.800	.138	.218*	.177	.686**	.667**	−.011	−.168
Compulsivity for drug (CD)	.730	.255*	.390**	.348**	.220*	.160	−.017	−.013
Positive expectancies and lack of control over drug (PL)	.785	.413**	.516**	.430**	.210	.265*	.414**	.353*
Lack of negative expectancy (NE)	.545	.182	.170	.170	−.014	−.026	.320*	.328*
Total SRRS	.864	.504**	.617**	.505**	.415**	.440**	.381*	.274

Note: Reliability was calculated according to Cronbach's alpha. Concurrent validity was calculated according to correlation of SRRS against VAS, ASI, CES-D, and GHQ-12. Predictive validity was calculated according to correlation of SRRS against relapse.
* $p<.05$.
** $p<.01$.
† $p<.10$.

chometric properties and thus useful for assessing the various aspects of relapse risk.

One aspect of the multidimensional structure of the SRRS was a variety of craving. In cases of 'positive expectancies and lack of control over drug' (Factor 4) and 'lack of negative expectancy' (Factor 5), the items corresponding to 'expectancy' and 'emotionality' in the MCQ were mainly extracted. These subscales were considered to reflect craving based on the 'expectancy theory' (Jones et al., 2001) and also similar to 'expectancy of positive and negative reinforcement' of the DSQ (James et al., 2004). Moreover, in 'compulsivity for drug use' (Factor 3), the items asking about a strong desire for a drug were mainly extracted from the items that were previously assumed to represent 'compulsivity' in the MCQ. This subscale was considered to reflect craving based on the 'obsessive compulsive theory' (Anton, 2000) and also similar to 'strong desires and intentions to use amphetamine' of the DSQ. The items included in 'anxiety and intention to use drug' (Factor 1) reflected anxiety about relapse, anticipation of relapse, revival of memory about drug use, and clear intention to use drugs. Therefore, we propose that not only expectancy and compulsivity, but also anxiety about relapse and intention to use drug are important components of craving.

Another aspect of the multidimensional structure of the SRRS revealed negative emotional states. In the case of 'emotionality problems' (Factor 2), the items that were considered to reflect 'common feelings and moods observed in patients before relapse' in the discussion among the psychiatrists were mainly extracted.

With regard to concurrent validity, the scores for anxiety and intention to use drug, positive expectancies and lack of control over drug, and compulsivity for drug use were moderately correlated with the ASI-J drug composite score and the VAS score. On the other hand, there was no correlation among the scores for emotionality problems, lack of negative expectancy, ASI-J, and VAS. These results indicated that anxiety and intention to use drug, positive expectancies and lack of control over drug, and compulsivity for drug use are important factors of craving related to the subjective desire for a drug and severity of drug dependence, although it should be noted that the timeframe of the SRRS (past 1 week) and the VAS (current and past 2 weeks) was not the same.

Concerning about predictive validity, the scores for 'anxiety and intention to use drug', 'positive expectancies and lack of control over drug', 'lack of negative expectancy for drug use', and 'total SRRS' were correlated with relapse within 3 months.

Table 4
Mean and S.D. of the SRRS and inter-subscale correlations

	Mean (S.D.)	AI	EP	CD	PL	NE
SRRS subscale (range: 1–3)						
Anxiety and intention to use drug (AI)	1.70 (.52)	–	.330*	.468**	.575**	.171
Emotionality problems (EP)	2.00 (.54)		–	.227*	.326**	−.098
Compulsivity for drug (CD)	1.30 (.48)			–	.505**	.160
Positive expectancies and lack of control over drug (PL)	1.82 (.60)				–	.143
Lack of negative expectancy (NE)	1.53 (.49)					–
Total SRRS (range: 1–3)	1.67 (.35)					

S.D.: standard deviation.
* $p<.05$.
** $p<.01$.

Moreover, the scores for 'positive expectancies and lack of control over drug' and 'lack of negative expectancy for drug use' were correlated with relapse within 6 months. These results indicated that the higher these scores, higher the risk of relapse. This is consistent with the idea that relapse triggered by the expectation or anxiety for the risk situation related to drug use rather than the subjective desire for the drug (Drummond, 2001; Jones et al., 2001).

The emotionality problems score was not related to the VAS or ASI-J composite score, nor to relapse. However, the moderate correlation of the emotionality problems score with the CES-D and GHQ-12 scores, and the significant correlations of this score with other subscale scores of the SRRS suggest that this factor may have an indirect effect that increases the subjective desire for a drug and thus the risk of relapse. Also, the correlation between the lack of negative expectancy score and relapse within 6 months was nearly significant, although this score had no correlation with the VAS and ASI-J drug composite scores, and internal consistence of this subscale was insufficient. Further examination with more samples may reveal the correlation between the score for lack of negative expectancy and relapse.

One possible limitation to the present study was the sampling procedure. The participants were not recruited randomly but were limited only to inpatients or outpatients who gave informed consent and whose doctors in charge recognized their ability to answer a 2 h interview. Therefore, the results of this study were not obtained from drug abusers as a whole such as dropout patients and non-patients, but from cooperative patients with a relatively low severity of drug dependence. In addition, the relatively low rate of availability of relapse data (48/100) may have influenced assessment of the SRRS's predictive validity. In order to gain a better understanding of relapse risk in stimulant abusers as a whole, it would be necessary to conduct follow-up surveys for dropout cases and to recruit participants from other facilities, including prisons. Another limitation was the relatively low sample size. A sample of one hundred participants was small to sufficiently support the factor analysis, and the further study of the SRRS to examine the stability of the factor structure by confirmatory factor analysis is required.

While the result of the items assessing insight into mental condition was not significant, it may have potential value for recognizing 'denial' patients; patients who have low scores for these items and high ASI-J drug composite scores tended to show a high risk of relapse. Since it is very important for self-rating scales to distinguish dishonest responses from honest ones, these items should be retained in the scale. It would be necessary to examine whether 'denial' patients are recognized by combination with other dependence severity ratings, such as the ASI drug composite score.

The SRRS was developed in Japanese language, thus the items shown in Table 2 were translated into English. While there was no word or phrase that could not be translated, the items were more directly expressed in English. It is possible that Japanese people use more indirect form of expression, which may explain the result that the subjective desire for drug was not significantly related to relapse. Additionally, some items of the SRRS such as the one that indicates peer pressure (e.g. If someone holds the drug under my nose, I would not be able to refuse it), may be interpreted and answered differently between a collectivistic culture (e.g. Japan) and an individualistic culture.

The present results suggest that the SRRS would be an effective tool with which psychiatrists, psychologists, social workers, and patients themselves can assess the level of craving and recognize the risk of relapse. Also, the SRRS may contribute to the assessment of craving-inhibitory effects of medicines and treatment programs. To improve the usefulness of the SRRS, further studies of at least the following will be necessary: (1) applicability of the SRRS to other substances of abuse such as alcohol, cannabis (marijuana, hashish), and solvents (e.g. toluene, benzene), (2) cross-validity using other stimulant abusers with confirmatory factor analysis, and (3) modification of the SRRS for a better prediction of relapse.

Conflict of interest

None.

Acknowledgements

We are grateful to the subjects for their participation in this study. We are also grateful to Drs. Sachiko Suetsugu, Michiko Ohara, Yoshihisa Aketa, Hideko Yamamoto, Yukio Takamatsu and Ms. Fumiyuki Chin for fruitful discussion. This work was supported by grants from the Ministry of Education, Culture, Sports, Science and Technology of Japan (17025054), Ministry of Health, Labor and Welfare of Japan (H17-Pharmaco-001, H16-Iyaku-029, H15-KOU-3-03, H14-Toxico-011), and the Japan Society for the Promotion of Science (quasi-governmental organization) (17730421, 17591238).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.drugalcdep.2006.10.005.

References

Anton, R.F., 2000. Obsessive-compulsive aspects of craving: development of the Obsessive Compulsive Drinking Scale. Addiction 95 (Suppl. (2)), 211–217.

Anton, R.F., Moak, D.H., Latham, P.K., 1996. The obsessive-compulsive drinking scale: a new method of assessing outcome in alcoholism treatment studies. Arch. Gen. Psychiatry 53, 225–231.

Ciraulo, D.A., Sarid-Segal, O., Knapp, C.M., Ciraulo, A.M., Locastro, J., Bloch, D.A., Montgomery, M.A., Leiderman, D.B., Elkashef, A., 2005. Efficacy screening trials of paroxetine, pentoxifylline, riluzole, pramipexole and venlafaxine in cocaine dependence. Addiction 100 (Suppl. (1)), 12–22.

Cooney, N.L., Litt, M.D., Morce, P.A., Bauer, L.O., Gaupp, L., 1997. Alcohol cue reactivity, negative-mood reactivity, and relapse in treated alcoholic men. J. Abnorm. Psychol. 106 (2), 243–250.

Daibo, I., Nakagawa, Y., 1985. Japanese Version of GHQ (General Health Questionnaire) by Goldberg. Nihon Bunka Kagakusha, Tokyo.

Drummond, D.C., 2001. Theories of drug craving, ancient and modern. Addiction 96, 33–46.

Heishman, S.J., Singleton, E.G., Liguori, A., 2001. Marijuana Craving Questionnaire: development and initial validation of a self-report instrument. Addiction 96, 1023–1034.

Ikeda, K., Yamamoto, H., Takamatsu, Y., Haraguchi, A., Umeno, M., Senoo, E., 2004. New approaches toward treatment of methamphetamine dependence. Seishin Igaku 46 (8), 57–72.

James, D., Davies, G., Willner, P., 2004. The development and initial validation of a questionnaire to measure craving for amphetamine. Addiction 99, 1181–1188.

Jones, B.T., Corbin, W., Fromme, K., 2001. A review of expectancy theory and alcohol consumption. Addiction 96, 57–72.

Love, A., James, D., Willner, P., 1998. A comparison of two alcohol craving questionnaire. Addiction 93, 1091–1102.

Piasecki, M.P., Steinagel, G.M., Thienhaus, O.J., Kohlenberg, B.S., 2002. An exploratory study: the use of paroxetine for methamphetamine craving. J. Psychoactive Drugs 34 (3), 301–304.

Senoo, E., Ogai, Y., Haraguchi, A., Kondo, A., Ishibashi, Y., Umeno, M., Kikumoto, H., Hori, T., Komiyama, T., Kato, R., Aso, K., Asukai, N., Wada, K., Saitoh, S., Ikeda, K., 2006. Reliability and validity of the Japanese version of the Addiction Severity Index (ASI-J). Nihon Arukoru Yakubutsu Igakkai Zasshi 41 (4), 368–379.

Shima, S., Shikano, T., Kitamura, T., Asai, M., 1985. New self-rating scales for depression. Seishin Igaku 27, 717–723.

Sora, I., Hall, F.S., Andrews, A.M., Itokawa, M., Li, X.F., Wei, H.B., Wichems, C., Lesch, K.P., Murphy, D.L., Uhl, G.R., 2001. Molecular mechanisms of cocaine reward: combined dopamine and serotonin transporter knockouts eliminate cocaine place preference. Proc. Natl. Acad. Sci. U.S.A. 98 (9), 5300–5305.

Takamatsu, Y., Yamanishi, Y., Hagino, Y., Yamamoto, H., Ikeda, K., 2006a. Differential effects of donepezil on methamphetamine and cocaine dependence. Ann. N. Y. Acad. Sci. 1074, 418–426.

Takamatsu, Y., Yamamoto, H., Ogai, Y., Hagino, Y., Markou, A., Ikeda, K., 2006b. Fluoxetine as a potential pharmacotherapy for methamphetamine dependence: studies in mice. Ann. N. Y. Acad. Sci. 1074, 295–302.

The Ministry of Justice Research and Training Institute, 2004. White paper on crime in Japan 2003. Ministry of Finance Printing Bureau, Tokyo, pp. 305–314.

Tiffany, S.T., 1990. A cognitive model of drug urge and craving research: role of automatic and non-automatic process. Psychol. Rev. 97, 147–168.

Topp, L., Mattick, R.P., 1997. Validation of the amphetamine dependence syndrome and the SAmDQ. Addiction 92 (2), 151–162.

Wada, K., Kikuchi, A., Nakano, R., Ozaki, S., 2004. Current situation on drug abuse in Japan: using a general population survey and a junior high school student's survey. Nihon Arukoru Yakubutsu Igakkai Zasshi 39 (1), 28–34.

Wallace, B.C., 1989. Psychological and environmental determinants of relapse in crack cocaine smokers. J. Subst. Abuse Treat. 6 (2), 95–106.

日薬理誌（*Folia Pharmacol. Jpn.*）**130**，450～454（2007）

特集

トランスポーター研究の新しい展開2

依存性薬物の分子標的としてのモノアミントランスポーター

曽良　一郎[1)]，猪狩　もえ[1)]，山本　秀子[2)]，池田　和隆[2)]

要約：モノアミントランスポーターはコカイン，メチルフェニデート，メタンフェタミン（MAP）などの覚せい剤の標的分子であることから，覚せい剤依存の病態における役割を明らかにするための詳細な精神薬理学的研究が行われてきた．モノアミントランスポーターには，各モノアミンの前シナプス終末に主に発現する細胞膜モノアミントランスポーターと，すべてのモノアミンを基質とするシナプス小胞モノアミントランスポーター（VMAT）の2種類がある．覚せい剤は，モノアミン輸送を阻害し，神経細胞内外の分画モノアミン濃度を変化させ薬理効果を示す．コカインは細胞膜モノアミントランスポーター阻害作用を有し，その報酬効果はドパミントランスポーター（DAT）を介しているとする「DAT仮説」が提唱された．しかし，DATとセロトニントランスポーター（SERT）が共に関与していることが示された．ただし，SERTよりもDATがより大きな役割を果たしていると考えられる．「DAT仮説」は当初提唱された以上に複雑であると思われる．また，メチルフェニデートを健常人に投与すると投与が興奮や過活動を引き起こすが，注意欠陥多動性障害（ADHD）患者へは鎮静作用がある．DAT欠損マウスはメチルフェニデートを投与されると移所運動量が低下することから，ADHDの動物モデルの一つと考えられる．MAPはコカインとは異なる薬理作用を有する．コカインがDATを阻害し，細胞外ドパミン（DA）を増加させるのに対して，MAPはDATに作用して交換拡散によりDAを細胞外へ放出させることで細胞外DA濃度を増加させる．さらに，MAPはVMATに作用して小胞内のDAを細胞質へ放出させる．MAPの反復使用は，逆耐性現象（行動感作）や認知機能に障害を引き起こすことから，覚せい剤精神病や統合失調症などの動物モデルの一つと考えられている．依存性薬物のモノアミントランスポーターへの複雑な作用機序を明らかにすることにより，薬物依存の病態の新たな知見が得られてくると期待される．

はじめに

カテコラミンを含むモノアミンは運動調節や情動など高次神経機能に幅広く関与することから，薬物依存を含むさまざまな神経精神疾患の病態に深く関わっていると考えられている(1-3)．モノアミンは合成後に神経終末内のシナプス小胞に蓄えられて神経終末から放出され，後シナプス受容体に情報を伝達する(4)．細胞間隙に放出されたモノアミンは速やかに神経終末に回収される．このモノアミンの放出，および再取り込みに関与するモノアミントランスポーターは，細胞膜トランスポーターとシナプス小胞トランスポーターの2種類が知られている．モノアミントランスポーターはメタンフェタミンなどの覚せい剤の標的分子であることから，覚せい剤依存の病態における役割を明らかにするための詳細な精神薬理学的研究が行なわれてきた(5,6)．

1．2種類のモノアミントランスポーター

モノアミン受容体は多数のサブタイプが存在するのに対し，細胞膜モノアミントランスポーターは各モノアミンに対し1種類ずつしかなく，さらにシナプス小胞モノアミントランスポーター（VMAT）はすべてのモノアミンを基質としている．このことから，モノアミントランスポーターはモノアミン神経伝達の制御に極めて重要な役割を果たすと考えられる．

キーワード：コカイン，メチルフェニデート，メタンフェタミン，ノックアウトマウス
[1)] 東北大学大学院医学系研究科 神経・感覚器病態学講座 精神神経生物学分野（〒980-8574 仙台市青葉区星陵町1-1）
e-mail: isora@mail.tains.tohoku.ac.jp
原稿受領日：2007年9月18日，依頼原稿
[2)] 財団法人東京都医学研究機構 東京都精神医学総合研究所 精神生物学研究分野（〒156-8585 東京都世田谷区上北沢2-1-8）
Title: Monoamine transporter as a target molecule for psychostimulants.
Author: Ichiro Sora, Moe Igari, Hideko Yamamoto, Kazutaka Ikeda

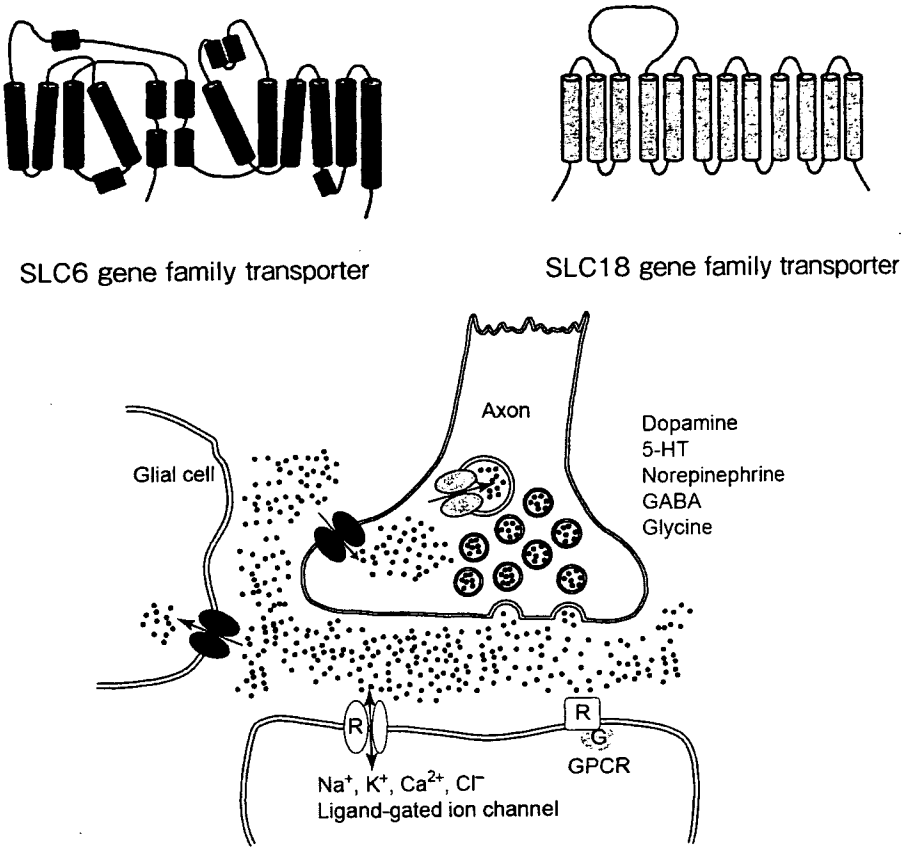


図1 モノアミントランスポーターファミリー
細胞膜モノアミントランスポーターはSLC6遺伝子ファミリーに，シナプス小胞モノアミントランスポーターはSLC18遺伝子ファミリーに属している．(文献7. Gether u, et al. Trends Pharmacol Sci. 2006;27:375-383より改変)

1) 細胞膜モノアミントランスポーター

細胞膜モノアミントランスポーターは，神経終末の細胞膜に存在しNa^+/Cl^-依存性にモノアミンを神経終末内に取り込む膜タンパク質であり，アミノ酸トランスポーターなどとともにSLC6 (solute carrier 6) と呼ばれる遺伝子ファミリーを形成している(7)(図1)．SLC6ファミリーに属するモノアミントランスポーターは，細胞膜を12回貫通し，N，C末端はともに細胞内に存在する構造をとっている．神経終末から放出されたドパミン (DA)，ノルエピネフリン (NE)，セロトニン(5-HT) は細胞膜モノアミントランスポーターにより素早く神経終末に再取り込みされ，神経伝達が終了する．細胞膜モノアミントランスポーターは，主にそれぞれのモノアミン作動性ニューロンの前シナプス神経終末の細胞膜に位置し，各基質ごとに，ドパミントランスポーター (DAT) はDA作動性ニューロンの，NE，5-HTも，それぞれの対応する基質の作動性ニューロンの主に前シナプス神経終末の細胞膜に発現している(4)．

DA，NE，5-HTのトランスポーターは抗うつ剤や覚醒剤の標的分子である(5)．特に，DATはコカイン，アンフェタミン，メチルフェニデート等の覚醒剤の標的分子，あるいはMPP^+，6-OHDA等の神経毒の侵入経路としても長らく研究されてきた．アミノ酸トランスポーターは神経細胞にもグリアにも見出されるが，DATはDA神経にのみ存在するため，DA神経活動の最も良い指標となる．ノルエピネフリントランスポーター (NET)，セロトニントランスポーター (SERT) は抗うつ剤の標的分子であり，躁うつ病，不安などの病態に関与していると考えられている．

2) VMAT

一方，VMATは，DA，NE，5-HT，ヒスタミンすべてを基質とする単一のタンパク質であり，神経終末内のシナプス小胞膜に存在し，シナプス小胞アセチルコリントランスポーター (VAChT) とともにSLC18 (solute carrier 18) と呼ばれる遺伝子ファミリーを形成している(7) (図1)．このシナプス小胞モノアミントランスポーターは細胞質で合成されたモノアミンをH^+依存的にシナプス小胞に貯蔵し，シナプス間隙へのモノアミン放出に備える．VMAT1は副腎に，VMAT2は

中枢神経系に主に発現している．アンフェタミンはVMATを介してシナプス小胞に貯蔵されているアミンを細胞質に排出させ，そのアミンを細胞膜のDATを通じてシナプス間隙に放出させる．レセルピンはVMATに結合しシナプス小胞のアミン輸送を阻害する(6)．

3）VMAT2発現によるDAT機能制御

神経終末からのDA放出は，合成されたDAがシナプス小胞内にVMAT2によって取り込まれる過程に続いて起こる．このDAの放出過程における神経終末あるいはシナプス小胞内外の分画中のDAは，DATおよびVMAT2によって制御されていると考えられる(6)．その制御機序はVMAT2完全欠損マウスモデルを用いることにより明らかにされることが期待されるが，VMAT2完全欠損マウスは生後数日以内に死亡するため，筆者らはVMAT2完全欠損マウス由来の初代培養DA細胞を用いて解析を行った(8)．その結果，VMAT2が完全欠損した初代培養DA細胞において，DATの活性の低下が見られた．また，生後1日目のVMAT2完全欠損マウス線条体の粗シナプス画分を用いても同様のDAT活性の低下が見られたこと，レセルピンを用いて，野性型マウス由来の初代培養DA細胞のVMAT2活性を抑制するとDAT活性も抑制されることから，VMAT2完全欠損によってDA神経細胞質でDAが増加したときにDAT活性を調節する機構が存在することが推測される(9)．

2. コカインの標的分子としてのモノアミントランスポーター

依存性薬物の共通作用部位として腹側被蓋野のドパミン神経細胞から，辺縁系ことに側坐核や扁桃体に投射する神経回路が注目されている．コカインは抗うつ剤と同様に細胞膜モノアミントランスポーター阻害作用を有する．コカインは3種類のモノアミントランスポーターに親和性を持つが，報酬効果はDATを介していると考えられ，「DAT仮説」が提唱されている(10)．

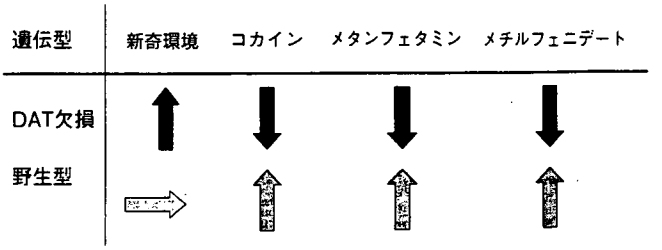
上で述べたように，コカインはDAT，SERT，NETの何れにも作用するが，その主たる作用部位を明らかにするために，我々はモノアミントランスポーター欠損マウスを作製し，コカインの作用機序を検討した(11)．DAT欠損マウスは，組織形態学的異常は認められないものの，発育は遅延している．興味深いことに，野生型にくらべて3～6倍の極めて活発な運動量を示し，DA再取り込み機能の欠如は，DA合成酵素，DA受容体のダウンレギュレーションにおいても代償できなかったことを示している．また，SERT，NETの発現に代償性の変化は見られなかった．しかし，コカイン，アンフェタミンの投与により野生型マウスで見られる運動量の増加作用は，DAT欠損マウスにおいては消失していることから，覚せい剤の運動量増加作用にはDATが不可欠であることが示唆される(11)（表1）．前述のとおり，コカインの報酬は3種類のモノアミントランスポーターの中でもDATを介しているというDAT仮説が想定されてきたが，DAT欠損マウスにおいてコカインの報酬が保たれていたことから，DAT仮説の見直しが行われている(11,12)．

他のモノアミントランスポーター欠損におけるコカインの報酬効果については，SERT，NETが欠損するとコカインの報酬効果はかえって増加する結果が得られた(11,13)．これらのことから，コカインの報酬効果は，DAT，SERT，NETがそれぞれ単独に欠損しても，他が代償することで保持されると考えられる．そこで，ダブルノックアウトマウスを作製して検討した．コカインの報酬はDATが完全欠損し，SERTが完全欠損あるいは部分欠損している遺伝型マウスでは消失した．しかし，SERTが完全欠損していても，DATが部分欠損の場合では保持された(14)．これらの結果により，コカインの報酬効果にはDATとSERTが共に関与し，SERTよりもDATが，より大きな役割を果たしていると考えられた．これらのことからも，「DAT仮説」は最初に提唱された以上に複雑であると思われる(5)．In vitroの結合実験において，モノアミンのトランスポーターへの結合親和性は，基質特異性が知られているものの，この点も含めてモノアミン同士の補完作用の可能性を今後検討していくことが重要である．

3. メチルフェニデートの標的分子としてのモノアミントランスポーター

マウスを新しい環境に置き，移所運動量を測定すると，野生型マウスは探索行動を行うので運動量が増加する．この活動量は馴化により徐々に低下していくが，DAT欠損マウスの場合，活動量は低下しない(11)（表1）．また，野生型マウスにメチルフェニデートを投与

表1 野生型，DAT欠損マウスにおける依存性薬物投与時の移所運動量



すると，活動量が顕著に増加するのに対して，DAT欠損マウスに投与すると活動量は劇的に低下する．これは，健常人への覚せい剤の投与が興奮や過活動を引き起こすにもかかわらず，注意欠陥多動性障害（ADHD，Attention Deficit/Hyperactivity Disorder）患者へは鎮静作用があることと一致している．これらのことからDAT欠損マウスはADHDの動物モデルの一つと考えられている(15,16)．

脳内微少透析法によってDAT欠損マウスの細胞外DA量を測定すると，大脳基底核における細胞外DA量は野生型の約10倍に増加しているが，前頭前野皮質では野生型と同程度のDA濃度を示した(17)．また，野生型マウスでは，メチルフェニデート投与後に線条体で細胞外DA量が顕著に増加したが，DAT欠損マウスでは変化がなかった．これに対して，前頭前野皮質では，野生型マウス，DAT欠損マウスともにメチルフェニデートによる細胞外DA量の顕著な上昇が起こった．この違いは，大脳基底核と前頭前野皮質のDA神経の制御機構が異なることに起因すると考えられる．黒質から線条体を含む大脳基底核に投射するDA神経線維にはDATが多数存在するので，線条体でのDAの再取り込みはDATによってのみ行われているが，前頭前野皮質ではDA神経終末上にDATが少ないために(18)，DAの再取り込みの役割を，NETが代わりにしていると考えられている(19,20)．メチルフェニデートは非特異的なモノアミントランスポーターの阻害薬である．DAT欠損マウスには，SERTとNETが残存しているが，メチルフェニデートのSERTに対する親和性が低いことから(21)，メチルフェニデートが，前頭前野皮質のNETに作用し，NETによる再取り込みを阻害するため，NEとともにDAが上昇すると考えられる．筆者らは，この前頭前野皮質におけるDA濃度の上昇が，メチルフェニデートによるDAT欠損マウスの運動量低下作用に関与しているのではないかと考えている．

4. メタンフェタミン(MAP)の標的分子としてのモノアミントランスポーター

MAPはコカインとは異なる薬理作用を有する．コカインがDATを阻害し，細胞外DAを増加させるのに対して(22)，MAPは，DATに作用して交換拡散によりDAを細胞外へ放出させることで，細胞外DA濃度を増加させ，また，MAPは，VMAT2に作用して小胞内のDAを細胞質へ放出させる(23, 24)．しかし，MAPがDATに作用し，DAを細胞質内から細胞外へ放出させるメカニズムは十分に明らかにされていない．

MAPなどの中枢刺激薬の反復使用は，逆耐性現象（行動感作）や認知機能に障害を引き起こすことから，統合失調症などの動物モデルの一つと考えられている(25)．逆耐性現象の形成には，中脳皮質辺縁系DA神経伝達の変化が関与していると考えられているが，形成に至る機序は，まだ十分に解明されていない．MAPの標的部位であるDATおよびもう一つの標的部位であるVMAT2の遺伝子の発現は，前頭前野皮質や大脳基底核において，DA神経細胞内外のDA分画に影響を与え，中枢刺激薬の運動刺激効果や逆耐性現象に変化を生じさせる．

我々が，DAT，あるいはVMAT2欠損マウスにおけるMAP逆耐性現象について検討したところ，DATヘテロ欠損マウスでは，MAP急性投与後の運動増加が，野生型マウスより少なかったことから，DATの半減が，MAPの急性運動増強効果を減弱させる可能性が示唆された(26)．VMAT2ヘテロ欠損マウスでは，MAP急性投与による反応は野生型マウスに比して有意に高かった．しかしながら，DAT，VMAT2両者の発現が同時に低下したマウスでは，MAP急性投与による運動量増加はDATヘテロ欠損マウスとほぼ等しかったことから，MAP投与による急性運動量増加効果には，VMAT2よりもDATの発現変化が大きな影響を及ぼすことが示唆された．

DATヘテロ欠損マウスでは，逆耐性現象の発展が抑制され，形成も遅延した．この持続的な運動量の低値は，MAP初回投与時の低反応が持続したものと思われるが，このような急性投与では有意な運動量の増加を示さない量のMAPでも，反復投与により逆耐性現象が形成されたのは興味深い．DATヘテロ欠損マウスにおけるMAPの反復投与では逆耐性現象の発展が促進された．これらの結果から，MAP逆耐性現象の発展は，DATの発現が低下している場合も，野生型マウスと同様に促進されることが示された．MAP反復投与により，VMAT2ヘテロ欠損マウスでは逆耐性現象形成の遅延を認めたが，逆耐性現象の発展は野生型と同等であった．DAT，VMAT2がともに半減したマウスにおけるMAP反復投与では，運動量，逆耐性現象の発展・形成はDATヘテロ欠損マウスと等しく，MAP逆耐性現象の形成には，VMAT2の発現低下よりもDATの発現低下がより大きな影響をもたらすことが示唆された(26)．これらの結果は，モノアミントランスポーターが制御するモノアミン神経伝達が，統合失調症などの動物モデルの一つと考えられている逆耐性現象に，重要な役割を果たしていることを示している．

5. まとめ

覚せい剤であるコカイン，メチルフェニデート，MAPはモノアミントランスポーターを標的分子とする．コカイン，メチルフェニデートが細胞膜モノアミントランスポーターの阻害により薬理効果を生じる一方，MAPは細胞膜に加えてVMATにも作用する．さらに，MAPは，細胞膜モノアミントランスポーターの基質として輸送の対象となるなど複雑な作用機序を有する．これらの複雑な作用機序を明らかにすることにより，薬物依存の病態の新たな知見が得られてくると期待される．

文　献

1) 曽良一郎，他．実験医学．2005;23:1159-1163.
2) 曽良一郎，他．実験医学．2006;24:84-89.
3) 曽良一郎．実験医学．2007;25:179-184.
4) 曽良一郎，他．自律神経．2003;40:238-243.
5) Uhl GR, et al. Mol Psychiatry. 2002;7:21-26.
6) Uhl GR, et al. Faseb J. 2000;14:2459-2465.
7) Gether U, et al. Trends Pharmacol Sci. 2006;27:375-383.
8) Takahashi N, et al. Proc Natl Acad Sci U S A. 1997;94:9938-9943.
9) Yamamoto H, et al. Neurochem Int. 2007;51:237-244.
10) Kuhar MJ, et al. Trends Neurosci. 1991;14:299-302.
11) Sora I, et al. Proc Natl Acad Sci U S A. 1998;95:7699-7704.
12) Rocha BA, et al. Nat Neurosci. 1998;1:132-137.
13) Xu F, et al. Nat Neurosci. 2000;3:465-471.
14) Sora I, et al. Proc Natl Acad Sci U S A. 2001;98:5300-5305.
15) 曽良一郎，他．日薬理誌．2006;128:8-12.
16) van der Kooij MA, et al. Neurosci Biobehav Rev. 2007;31:597-618.
17) Shen HW, et al. Neuropsychopharmacology. 2004;29:1790-1799.
18) Sesack SR, et al. Adv Pharmacol. 1998;42:171-174.
19) Carboni E, et al. Crit Rev Neurobiol. 2004;16:121-128.
20) Carboni E, et al. J Neurochem. 2006;96:473-481.
21) Gatley SJ, et al. Life Sci. 1996;58:231-239.
22) Amara SG, et al. Annu Rev Neurosci. 1993;16:73-93.
23) Seiden LS, et al. Annu Rev Pharmacol Toxicol. 1993;33:639-677.
24) Sulzer D, et al. Prog Neurobiol. 2005;75:406-433.
25) Kalivas PW, et al. Behav Pharmacol. 1993;4:315-334.
26) Fukushima S, et al. Psychopharmacology (Berl). 2007;193:55-62.

著者プロフィール

曽良　一郎（そら　いちろう）

東北大学大学院医学系研究科 精神・神経生物学分野，教授，医学博士．
◇1986年 岡山大学大学院医学研究科（神経精神医学専攻）博士課程修了，'96年 米国立衛生研究所（NIH）付属薬物依存研究所 分子遺伝学研究室長，'02年 東北大学大学院医学系研究科 神経・感覚器病態学講座 精神神経生物学分野教授．◇研究テーマ：薬物依存などの機能的精神疾患の分子神経生物的研究．isora@mail.tains.tohoku.ac.jp

猪狩　もえ（いがり　もえ）

東北大学大学院医学系研究科 精神神経生物学分野，博士課程．
◇2002年ロンドン大学ゴールドスミスカレッジ心理学部卒業，国立情報学研究所勤務を経て'07年3月京都大学大学院人間・環境学研究科修士課程を修了．◇研究テーマ：薬物依存．moet-igari@mail.tains.tohoku.ac.jp