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Neuronal cell adhesion molecule regulating neural systems underlying addiction

Hiroki Ishiguro[1] | Kunio Miyake[2] | Koichi Tabata[1] | Chiaki Mochizuki[1] | Takeshi Sakurai[3] | Emmanuel S. Onaivi[4]

[1]Department of Neuropsychiatry and Clinical Ethics, University of Yamanashi, Chuo, Japan

[2]Department of Health Sciences, University of Yamanashi, Chuo, Japan

[3]Medical Innovation Center, Kyoto University, Kyoto, Japan

[4]Department of Biology, William Paterson University, Wayne, New Jersey

Correspondence
Hiroki Ishiguro, Department of Neuropsychiatry and Clinical Ethics, University of Yamanashi, Chuo, Japan.
Email: hishiguro@yamanashi.ac.jp

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Abstract

Aims: The human *NRCAM* gene is associated with polysubstance use. *Nrcam* knockout mice do not acquire a preference for addictive substances. We aimed to elucidate the role of *Nrcam* in specific neural circuits underlying congenital preference for substances and the acquisition of addiction.

Methods: We analyzed gene expression patterns of neural molecules to find a common addiction pathway dependent on *Nrcam* function. We examined monoaminergic, glutamatergic, and GABAergic systems in the brains of *Nrcam* knockout mice following treatment with methamphetamine (METH) or saline (SAL) using microarray gene expression analysis, which was replicated using TaqMan gene expression analysis. To find a common addiction pathway, we examined similarities and differences between the expression patterns of molecules in METH-treated mice and in *Nrcam* knockout mice treated with cocaine (COC).

Results: Glutaminase expression in brain was reduced in *Nrcam* heterozygous mice after METH and COC treatment, consistent with our previous study. Metabotropic glutamate receptor 2 expression was reduced in *Nrcam* heterozygous mice that received either METH or COC treatment. Several other molecules could act in independent addiction pathways involving METH or COC. We also found that GABA receptor subunit g2 expression was reduced in *Nrcam* heterozygous mice that underwent SAL treatment, and that METH treatment attenuated this reduction.

Conclusion: Nrcam differentially regulates glutamatergic and GABAergic molecules in naive brains and in brains of animals with acquired addiction. Elucidating the complex neural mechanisms underlying polysubstance use will uncover biological features of addiction and may contribute to the development of effective pharmaceutical treatments.

KEYWORDS
alcohol- and substance-related disorders, genetics: animal, psychopharmacology, molecular neurobiology: animal, pharmacogenetics

1 | INTRODUCTION

The human neuronal cell adhesion molecule (NrCAM) is a protein encoded by the *NRCAM* gene. Our previous study revealed that human *NRCAM* gene polymorphisms and haplotype were associated with reduced gene expression in postmortem human brain tissue from patients with polysubstance use.[1] *Nrcam* knockout mice did not develop conditioned place preference (CPP) to either morphine, amphetamine, or cocaine (COC),[1] nor did they develop alcohol preference with free access to a 16%-32% ethanol solution.[2] These findings indicate that NrCAM may be involved in common addiction pathways, although these addictive substances could directly bind to the involved neurons and/or regulate different neural networks underlying the acquisition of addiction. NrCAM appears to work as an anchor of cell connections in neural networks in the adult brain under certain circumstances. These networks are associated with addiction-related behaviors, including reward and peripheral responses in social/personality behaviors. Indeed, the *NRCAM* gene is associated with methamphetamine (METH) addiction, as demonstrated by the duration of METH use and number of arrests that predispose individuals to addiction.[3] *Nrcam* knockout mice (both heterozygous and homozygous) showed reduced novelty-seeking, sociability, anxiety, and repetitive/perseverative responses in a marble burying test, which can be interpreted as obsessive behavior, as marble burying reflects a repetitive and perseverative behavior more than novelty-induced anxiety does.[4] Some molecules regulated by NrCAM in the brain may characterize addiction-related behaviors, including reward and other social/personality behaviors.[2]

To elucidate the precise molecular mechanisms that contribute to addiction-related cognitive and behavioral characteristics, transcriptomic analyses using *Nrcam* knockout mice could be useful. Using microarray, we evaluated the differences in gene expression in the brain that were related to polysubstance use, either in the naïve brain in which drug preference has not developed, or in the "acquired brain" after the development of drug addiction. Several molecules could act as shared factors in the acquisition of both METH and COC preference; there would also be some nonshared factors. Although many genes have been identified as candidate vulnerability genes by microarray analyses, we focused on monoaminergic, glutamatergic, and GABAergic molecules that have been investigated for associations with the substance use of METH and COC.[5–11]

2 | MATERIALS AND METHODS

2.1 | Subjects

Nrcam knockout mice, developed by Sakurai et al,[12] were used in this study. The mice were housed under a 12-hour light/12-hour dark cycle (lights off from 19:00 to 07:00) and given access to food and water ad libitum. Heterozygous sibling mating pairs were obtained from the same litter and used as breeding pairs to produce cohorts used in this study. None of the three genotypes was lethal; however, because no human has a complete deficit of the *NRCAM* gene, *Nrcam* heterozygous knockout (Het) and wild type (W) mice were analyzed as genetic models. The mice were injected intraperitoneally once a day for 4 days either with saline (SAL), METH (2 mg/kg), or COC (20 mg/kg). This protocol was sufficient to induce the acquisition of addiction to both substances, as shown by the CPP in our previous studies.[1,2] Each experiment was conducted in a separate group of animals. The experiments were performed in the test room from 16:00 to 20:00 under dim lighting conditions.

All animal procedures were performed according to protocols approved by the Institutional Animal Care and Use Committees at University of Yamanashi, in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 8023, revised 1978).

2.2 | Transcriptome analysis in brains from *Nrcam* knockout mice

Mice were sacrificed 1 hour after the last injection of SAL, METH, or COC. Brains were collected within 30 minutes after the sacrifice to avoid acute effects of drug treatment. The striatum and midbrain were dissected from the brains. Total RNA was extracted from the tissue, and the amount of RNA in each subject was measured. For the first screening, equal amounts (500 ng/μL) of RNA from three mice were pooled for microarray analysis. cDNA for each gene was synthesized from RNA using reverse transcription (ReverTra Ace, TOYOBO Co., Tokyo Japan). Three pooled RNA samples obtained from the tissue of nine mice were analyzed by the Affymetrix Array with GeneChip® Mouse Transcriptome Assay 1.0 to screen for differential gene expression among four groups of mice with different genotypes (W and Het *Nrcam* knockout) and treatment modalities (METH and SAL treatment). TaqMan gene-expression analysis was performed to confirm the differences indicated in the first screening with the microarray, using nonpooled cDNA samples, which included some of the samples used for the previous pooled analysis and some samples from additional mice. Replication analysis to confirm the similarities in gene regulation by COC was performed for the candidate genes identified in the METH study (total samples: SAL-treated mice, 21 W and 21 Het; METH-treated mice, 19 W and 21 Het; COC-treated mice, 15 W and 21 Het).

2.3 | Statistics

Differentially expressed genes (DEGs) were identified using Student's *t* test by using Subio Platform software (www.subioplatform.com, Subio Inc., Kagoshima, Japan). Differences in each gene-expression levels across groups of mice (genotype and treatment) were analyzed by two-way ANOVA, followed by post hoc analysis using the Tukey HSD test. The difference between COC-treated mice with different genotypes was analyzed by one-way ANOVA. ANOVA and Tukey HSD tests were carried out using JMP software version 13 (SAS Institute, Tokyo, Japan). Unless otherwise stated, $P < 0.05$ was considered statistically significant.

3 | RESULTS

Microarray analysis revealed that genes belonging to monoaminergic, glutamatergic, or GABAergic neural circuits showed nominal significant differences between W and Het mice, and between mice undergoing METH and SAL treatments (Tables S1–S12). Among these candidates, we failed to replicate the differential expression observed in the microarray analysis when we used TaqMan gene-expression analysis for the following genes: dopamine D5 receptor (*Drd5*), glutamine receptor and ionotropic kainite 3 (*Grik3*), and vesicular glutamate transporter (*Vglut1*, *Slc17a7*).

Glutaminase (*Gls*) was expressed at lower levels in brains from Het mice than in those from W naïve mice, as reported in our previous study[2] The expression in the striatum of the Het mice was lower than that in the striatum of the W mice after treatment with METH or SAL ($F(3,77) = 4.6$, $P = 0.005$; effect of genotype $F(1,1) = 12.9$, $P = 0.0006$; effect of treatment $F(1,1) = 0.3$, $P = 0.56$; effect of genotype × treatment $F(1,1) = 0.17$, $P = 0.69$; post hoc analysis: 20 W vs 21 Het, $P = 0.13$ in METH-treated mice, 21 W vs 21 Het, $P = 0.026$ in SAL-treated mice, Figure 1A). After treatment with COC, *Gls* expression in the striatum was lower in *Nrcam* Het mice than in W mice (14 W vs 20 Het, $F(1,32) = 5.4$, $P = 0.026$, Figure 1B).

Metabotropic glutamate receptor 2 (*Grm2*) expression was also differentially regulated ($F(3,73) = 1.7$, $P = 0.16$; effect of genotype $F(1,1) = 0.7$, $P = 0.40$; effect of treatment $F(1,1) = 0.003$, $P = 0.96$; effect of genotype × treatment $F(1,1) = 4.7$, $P = 0.033$, Figure 2A). However, post hoc analysis with the Tukey test did not show a significant difference among the groups, as the lowest P value was found for differences between mice with different *Nrcam* genotypes undergoing METH treatment ($P = 0.18$). Two-way ANOVA showed no significant difference in *Grm2* expression in the striatum between any of the *Nrcam* genotype–treatment pairs. One-way ANOVA indicated a significant reduction in *Grm2* expression after METH treatment (16 W vs 20 Het, $F(1,35) = 7.5$, $P = 0.010$, Figure 2B) and a trend for reduction after COC treatment (20 W vs 21 Het, $F(1,29) = 3.5$, $P = 0.072$ ($P = 0.036$, single sided), Figure 2B).

GABA receptor type g2 (*Gabrg2*) expression in the striatum seemed to be differentially regulated in *Nrcam* Het and W mice treated with METH ($F(3,77) = 4.0$, $P = 0.010$; effect of genotype $F(1,1) = 6.8$, $P = 0.011$; effect of treatment $F(1,1) = 4.1$, $P = 0.047$; effect of genotype × treatment $F(1,1) = 1.1$, $P = 0.30$, Figure 3A). The Tukey test indicated that *Gabrg2* expression was higher in *Nrcam* Het mice than in W mice when treated with SAL (20 W vs 21 Het, $P = 0.052$, Figure 3A), but METH treatment attenuated the difference between *Nrcam* genotypes (19 W vs 21 Het, $P = 0.70$, Figure 3A). *Gabrg2* expression was also significantly higher in *Nrcam* Het mice than in W mice when treated with SAL (21 Het vs 20 W, $P = 0.008$, Figure 3A). A differential regulation of *Gabrg2* expression after COC vs SAL treatment was observed, with lower expression in the striatum in *Nrcam* Het mice than in W mice (14 W vs 18 Het, $F(1,30) = 5.9$, $P = 0.022$, Figure 3B).

In the analysis of the midbrain, the first screening using microarrays indicated the upregulation of *Slc17a7* gene expression by METH in *Nrcam* Het mice. However, TaqMan analysis did not reveal any METH-associated difference in gene expression (Figure 4A). However, TaqMan analysis revealed that COC upregulated *Slc17a7* expression in *Nrcam* Het mice (14 W vs 19 Het, $F(1,31) = 8.4$, $P = 0.0068$, Figure 4B).

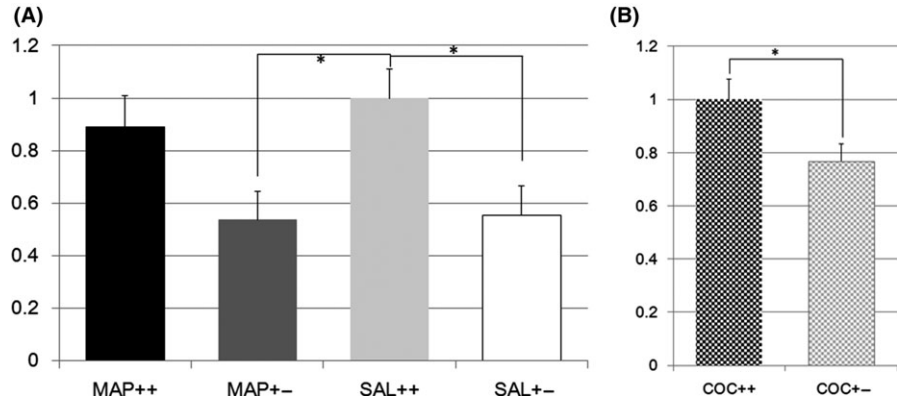

FIGURE 1 A, Glutaminase gene expression in methamphetamine or saline-treated *Nrcam* knockout mice. The vertical axis shows the *Gls* expression level in the striatum relative to that in *Nrcam* wild type (++) mice treated with saline (SAL) (light gray bar). The black bar indicates the relative *Gls* expression in methamphetamine (METH)-treated wild type (++) mice, the dark gray bar indicates that in METH-treated *Nrcam* heterozygous (+−) mice, and the white bar indicates that in SAL-treated *Nrcam* heterozygous mice. *A significant difference ($P = 0.026$) was found between SAL-treated mice with different *Nrcam* genotypes, while no difference was found between METH-treated mice with different *Nrcam* genotypes. A significant difference ($P = 0.018$) was also seen between SAL-treated wild type (++) mice and METH-treated *Nrcam* heterozygous (+−) mice; B, Glutaminase gene expression in cocaine-treated *Nrcam* knockout mice. The vertical axis shows the *Gls* expression level in the striatum relative to that in *Nrcam* wild type (++) mice (checkered black bar). The checkered gray bar indicates the relative *Gls* expression in heterozygous (+−) mice. *A significant differences ($P = 0.026$) were found for both comparison

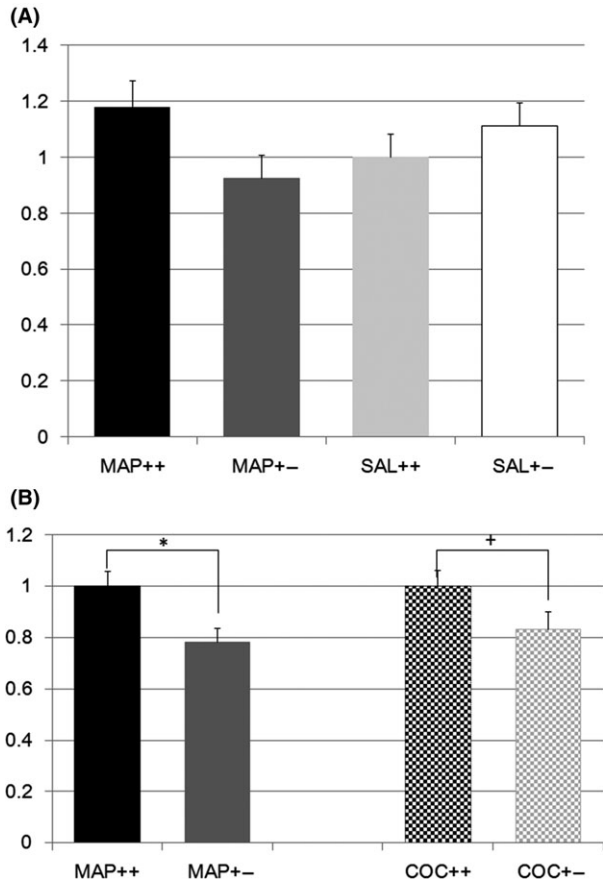

FIGURE 2 A, Metabotropic glutamate receptor 2 gene expression in methamphetamine or saline-treated *Nrcam* knockout mice. The vertical axis shows the *Grm2* expression level in the striatum relative to that in *Nrcam* wild type (++) mice treated with saline (SAL) (light gray bar). The black bar indicates the relative *Grm2* expression in methamphetamine (METH)-treated wild type (++) mice, the dark gray bar indicates that in METH-treated *Nrcam* heterozygous (+−) mice, and the white bar indicates that in SAL-treated *Nrcam* heterozygous mice; B, Metabotropic glutamate receptor 2 gene expression in methamphetamine and cocaine-treated *Nrcam* knockout mice. The vertical axis shows the *Grm2* expression level in the striatum relative to that in *Nrcam* wild type (++) mice treated with methamphetamine (METH) (plain black bar). The plain dark gray bar indicates the relative *Grm2* expression in the heterozygous (+−) mice treated with METH. The checkered black bar indicates this expression in *Nrcam* wild type (++) mice treated with cocaine (COC), and the checkered gray bar indicates the relative *Grm2* expression in the heterozygous (+−) mice treated with COC. *A significant difference ($P = 0.010$) and a $^{+}$trend of difference ($P = 0.072$) were found

4 | DISCUSSION

NrCAM is a cell adhesion molecule that modulates several neural processes including neurogenesis, neurite outgrowth, and synaptogenesis.[13] Although the exact role of NrCAM in cognition and behavior is still unknown, our previous study indicated that NrCAM was involved in addiction to morphine, amphetamine, COC, and alcohol, which could affect different neural systems. These findings imply that NrCAM regulates addiction-related neural systems, including glutamatergic, GABAergic, and monoaminergic systems, both during development and in the mature brain. Recent studies revealed that glutamate and GABA systems are affected by psychostimulants.[11,14,15] There may be a common molecular mechanism underlying the addiction to different substances; however, there may also be unique pathways, which may be regulated by NrCAM in the brain. NrCAM has a role in the development of addiction-related traits in both naive and "acquired brains," manifesting as behaviors that are associated with responses to novel stimuli, appetitive motivational states, anxiety, and possibly obsessive behavior, as indicated in our previous studies.[2]

The aversive role of NrCAM dysfunction in addiction may be explained by its regulation of certain neurochemical systems. Repeated exposure to either METH or COC leads to enduring changes in gene expression and subsequent functional CNS plasticity throughout multiple brain regions. The present study aimed to elucidate the neural targets both common and unique to METH and COC use. Changes in the expression of these molecules in the brain may occur following the development of addiction.

Glutamate is the principal excitatory neurotransmitter in the brain and has effects on drug-seeking behaviors for COC.[11,16] Further, glutamatergic and dopaminergic alterations in the brain are thought to contribute to the relatively long-lasting and recurrent nature of METH psychosis and depression.[17,18] In previous studies in our laboratory, we found that *Gls* expression was reduced in cultured cells, mice, and humans that have naturally low *Nrcam* expression in the brain and that the Gls inhibitor reduced the rewarding effects of substance use. After treatment with either SAL, METH, or COC, *Gls* expression was differentially regulated. SAL and COC treatment maintained the difference in expression between Het and W mice, similar to what is observed in the naïve condition, while METH treatment seemed to attenuate the difference. A recent study showed that acute COC treatment reduced *Gls* expression in the striatum but increased *Gls* expression in the prefrontal cortex,[11] while chronic exposure to COC did not change striatal gene expression, as shown in this study. Collectively, as the main glutamate-producing enzyme, Gls seems to be a common neural molecule involved in the effects of these substances. However, it is still unclear how Gls induces neural network remodeling for drug preference or during the acquisition of addiction.

The antagonism of mGlu2/3 receptors in the NAc reduced METH-seeking behavior in rats,[19] and a recent study indicated that acupuncture reduces METH-induced locomotion effects related to extracellular DA release in the NAc via the activation of mGluR2/3. *Grm2* mutant mice display altered emotionality, impulsivity, and risk-related behaviors, and show significantly higher levels of alcohol consumption and preference than do wild type control mice.[20,21] The levels of *Grm2* expression in both the striatum and hippocampus have been shown to be significantly lower in alcohol preferring (P) rats than in nonpreferring (NP) rats.[22] Therefore, we hypothesized that *Grm2* expression in the striatum would be lower in *Nrcam* Het mice than in W mice after METH or COC treatment. The results of

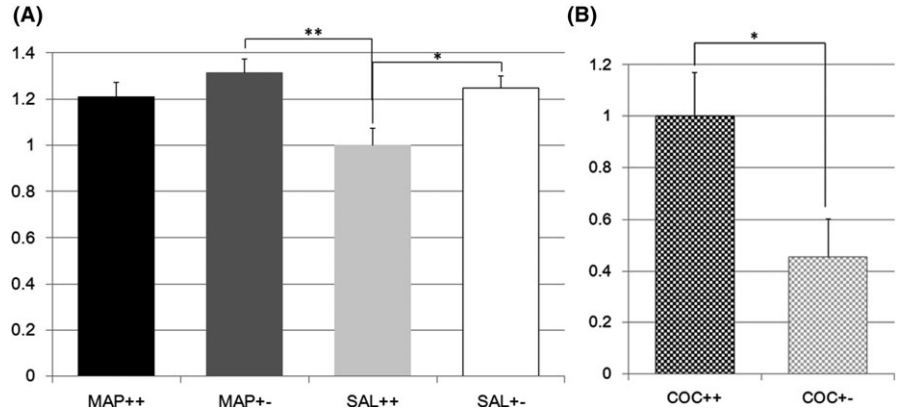

FIGURE 3 A, GABA receptor type g2 gene expression in methamphetamine or saline-treated *Nrcam* knockout mice. The vertical axis shows the *Gabrg2* expression level in the striatum relative to that in *Nrcam* wild type (++) mice treated with saline (SAL) (light gray bar). The black bar indicates the relative *Gabrg2* expression in methamphetamine (METH)-treated wild type (++) mice, the dark gray bar indicates that in METH-treated *Nrcam* heterozygous (+−) mice, and the white bar indicates that in SAL-treated *Nrcam* heterozygous mice. A non-significant tendency ($P = 0.052$) was found between SAL-treated mice with different *Nrcam* genotypes. **A significant difference ($P = 0.008$) was seen between SAL-treated wild type (++) mice and METH-treated *Nrcam* heterozygous (+−) mice; B, GABA receptor type g2 gene expression in cocaine-treated *Nrcam* knockout mice. The vertical axis shows the *Gabrg2* expression level in the striatum relative to that in *Nrcam* wild type (++) mice (checkered black bar). The checkered gray bar indicates the relative *Gabrg2* expression in heterozygous (+−) mice. *A significant difference ($P = 0.022$) was found

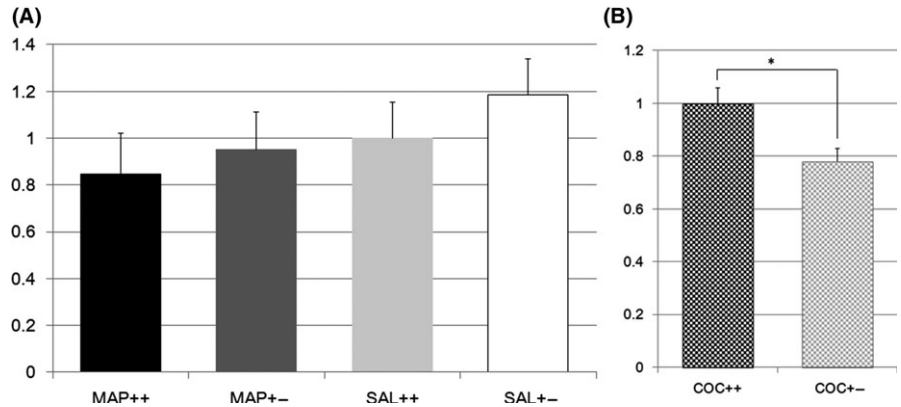

FIGURE 4 A, Vesicular glutamate transporter gene expression in methamphetamine or saline-treated *Nrcam* knockout mice. The vertical axis shows the *Slc17a7* expression level in the striatum relative to that in *Nrcam* wild type (++) mice treated with saline (SAL) (light gray bar). The black bar indicates the relative *Slc17a7* expression in methamphetamine (METH)-treated wild type (++) mice, the dark gray bar indicates that in METH-treated *Nrcam* heterozygous (+−) mice, and the white bar indicates that in SAL-treated *Nrcam* heterozygous mice; B, Vesicular glutamate transporter gene expression in cocaine-treated *Nrcam* knockout mice. The vertical axis shows the *Slc17a7* expression level in the striatum relative to that in *Nrcam* wild type (++) mice (checkered black bar). The checkered gray bar indicates the relative *Slc17a7* expression in heterozygous (+−) mice. *A significant difference ($P = 0.0068$) was found

the study could support the hypothesis by single-sided statistical analysis for METH and COC treatment ($P < 0.01$ and $P = 0.03$, Figure 2). Thus, the reduction in *Grm2* expression appears to be acquired after the development of addiction.

RNA-Seq analysis revealed that *GABRG2* was downregulated in alcoholics and COC addicts,[23] while stem cells obtained from alcoholics showed an increase in *GABRG2* expression after chronic treatment with alcohol.[24] Similar to a previous study indicating that *Gabrg2* expression was upregulated in P rats,[23] *Gabrg2* expression was downregulated by COC in the *Nrcam* Het mice that showed less preference to addictive substances in this study. When these findings are taken together, Gabrg2 reduction appears to not be a congenital factor, but may instead be an acquired factor during the development of COC and alcoholism. The involvement of Nrcam in METH addiction is still controversial; however, METH treatment eliminates the congenital reduction in *Gabrg2* expression in the *Nrcam* W mice. Because *GABRG2* is involved in the suicidal behavior of schizophrenia patients with alcohol use disorder,[25] GABRG2 could also have a role in behavioral characteristics related to addiction in addition to its role in reward itself. Future pharmaco-behavioral

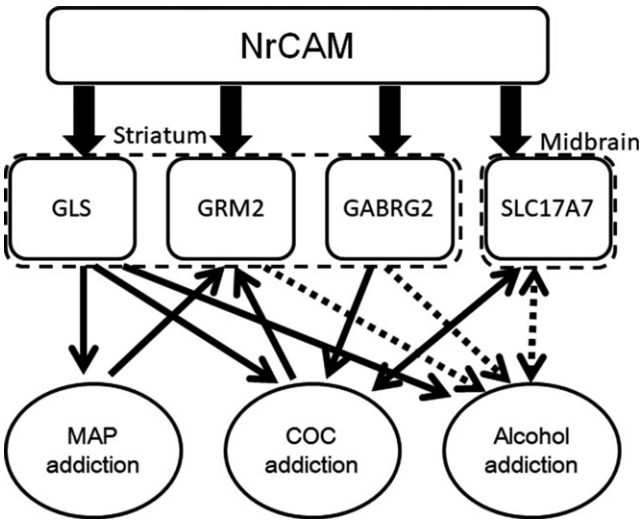

FIGURE 5 Schema describing the Nrcam-related molecules and their roles in polysubstance use indicated in this study. Nrcam regulates the gene expression of the glutamatergic and GABAergic molecules *Gls*, *Grm2*, and *Gabrg2* in the striatum and *Slc17a7* in the midbrain. The down arrow indicates an effect for each addiction. The up arrow indicates the regulation of gene expression in the brain of a substance user. Solid lines indicate the findings in the study, while dotted lines show the results from previous studies

experiments may demonstrate the exact role of GABRG2 in the overall biology of addiction.

In addition, the analysis also indicated an involvement of *Slc17a7* in COC addiction. A gene-expression network underlying alcoholism that involves recognized substrates for addiction, including *SLC17A7*, is known to be present in the hippocampus. However, analyses showed that this network was not conserved in COC users.[26] Further studies are needed to identify the exact role of the vesicular glutamate transporter in this type of addiction.

5 | CONCLUSION

This study supports the proposed involvement of several glutamatergic and GABAergic molecules, as well as that of NrCAM, in addiction vulnerability. However, this study has several limitations: (a) We used only nine subjects in three pooled samples for the microarray analysis and analyzed only METH and COC addiction models. (b) We focus on monoaminergic, glutamatergic, and GABAergic molecules evaluated from the microarray analysis, although other molecules could have important roles in addiction. (c) While we can observe the development of preference to either METH or COC by series of four daily injections in CPP test, more treatment might be needed to develop addiction-related behavioral changes including cognitive dysfunction. Further studies are necessary to confirm these findings using larger sample sizes and model mice treated longer with METH, COC, and other addictive substances. As demonstrated by Figure 5, some molecules act as congenital factors, whereas others act as factors acquired either during or after the development of addiction. The results of the present study may be consistent with the possible roles of some neural molecules in addiction, which have been indicated by previous studies using different methods such as genetics and transcriptome analyses. Compounds targeting these molecules may be potential therapeutics for polysubstance users. Further analysis may help to develop and identify pharmaceutical molecules targeting these systems for the treatment of addiction.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

DATA REPOSITORY

I agree to deposit the data and publish part of it as Supporting Information.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD AND ANIMAL STUDIES

All animal procedures were performed according to protocols approved by the Institutional Animal Care and Use Committees at University of Yamanashi, in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 8023, revised 1978).

INFORMED CONSENT

N/A.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

N/A.

ORCID

Hiroki Ishiguro http://orcid.org/0000-0002-1620-7204

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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