Transcriptional and Epigenetic Substrates of Methamphetamine Addiction and Withdrawal: Evidence from a Long-Access Self-Administration Model in the Rat

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Abstract Methamphetamine use disorder is a chronic neuropsychiatric disorder characterized by recurrent binge episodes, intervals of abstinence, and relapses to drug use. Humans addicted to methamphetamine experience various degrees of cognitive deficits and other neurological abnormalities that complicate their activities of daily living and their participation in treatment programs. Importantly, models of methamphetamine addiction in rodents have shown that animals will readily learn to give themselves methamphetamine. Rats also accelerate their intake over time. Microarray studies have also shown that methamphetamine taking is associated with major transcriptional changes in the striatum measured within a short or longer time after cessation of drug taking. After a 2-h withdrawal time, there was increased expression of genes that participate in transcription regulation. These included cyclic AMP response element binding (CREB), ETS domain-containing protein (ELK1), and members of the FOS family of transcription factors. Other genes of interest include brain-derived neurotrophic factor (BDNF), tyrosine kinase receptor, type 2 (TrkB), and synaptophysin. Methamphetamine-induced transcription was found to be regulated via phosphorylated CREB-dependent events. After a 30-day withdrawal from methamphetamine self-administration, however, there was mostly decreased expression of transcription factors including junD. There was also downregulation of genes whose protein products are constituents of chromatin-remodeling complexes. Altogether, these genome-wide results show that methamphetamine abuse might be associated with altered regulation of a diversity of gene networks that impact cellular and synaptic functions. These transcriptional changes might serve as triggers for the neuropsychiatric presentations of humans who abuse this drug. Better understanding of the way that gene products interact to cause methamphetamine addiction will help to develop better pharmacological treatment of methamphetamine addicts.

Keywords Gene expression · Gene networks · Transcription factors · Epigenetics · HDAC · Repressor complexes · Cognition · Striatum

Abbreviations

| Abbreviation | Definition                                    |
|--------------|-----------------------------------------------|
| AD           | Alzheimer’s disease                           |
| AP1          | Activating protein 1                          |
| ARID         | AT-rich interactive domain                    |
| ATF          | Activating transcription factor               |
| BASP1        | Brain abundant signal protein/brain acid soluble protein 1 |
| BDNF         | Brain-derived neurotrophic factor             |
| CBP          | CREB-binding protein                          |
| CDK          | Cyclin-dependent kinase                       |
| CH           | Calponin homology                             |
| CNS          | Central nervous systems                       |
| CREB         | Cyclic AMP response element binding           |
| DA           | Dopamine                                      |
| DUSPs        | Dual-specificity phosphatases                 |
| Egr1         | Early growth factor 1                         |
| eIF          | Eukaryotic translation initiation factor      |
| ELK1         | ETS domain-containing protein                 |
| ER           | Endoplasmic reticulum                         |
| ERK          | Extracellular signal-regulated kinases        |
| ETS          | E-twenty-six domain transcription factor      |
| H3K4me3      | Trimethylated lysine 4 of histone 3           |
| HDAC         | Histone deacetylase                           |
| Helios/IKZF2 | Ikaros family zinc finger 2                   |
Introduction

Methamphetamine addiction is a major public health problem that is accompanied by recalcitrant neuropsychiatric and neuropathological complications [1–4]. The neuropsychiatric adverse consequences include subclinical cognitive deficits [5] that can, nevertheless, negatively impact activities of daily living [6, 7]. The clinical course of treatment for methamphetamine use disorders is also accompanied by variable outcomes and rates of recidivism [2, 8, 9] that are also thought to depend on neuroadaptative and/or neuropathological substrates consequent to repeated exposure to the drug [10, 11]. These adaptive changes appear to include, among others, alterations in gene and protein expression [11–14], some of which appear to influence physiological functions at striatal glutamatergic synapses [15]. It is also likely that the behavioral transition from occasional use of psychostimulants to drug addiction may involve a shift of control over drug intake from the ventral to dorsal striatum when the use of drugs becomes truly habitual and compulsive [16]. This transition to addictive behaviors appears to depend, in the case of some drugs, on transcriptional and epigenetic plastic changes in the brain [17, 18]. Similarly, several studies have reported that methamphetamine can significantly influence the expression of many genes in the nucleus accumbens and dorsal striatum after both acute and chronic administration of the drug [14, 19–23]. Although these studies have suggested that administration of methamphetamine might be associated with transcriptional neuroadaptations, much remains to be done in order to further dissect the molecular pathobiology of methamphetamine addiction. In our laboratory, we have envisioned methamphetamine use disorder as a progressive neuropsychiatric disorder that results from a diversity of altered gene expression in the dorsal striatum and other brain regions [10, 11, 15]. In addition, we and others have proposed that these transcriptional changes might be dependent on persistent, yet reversible, epigenetic modifications that drive or inhibit the expression of specific gene networks that regulate cellular and synaptic functions and behavioral responses to the drug [11, 12, 15]. Together, the epigenetically determined changes in gene expression and associated changes in protein levels might then lead to cognitive deficits observed in some methamphetamine-addicted individuals ([10], see Fig. 1). The present review was thus written to provide a summary of our more recent work in transcriptional effects of METH self-administration. The review will also serve to expand on our previous discussion of methamphetamine-induced transcriptional effects in the brain [11].

Towards that end, we will review recent genome-wide transcriptional data collected from the dorsal striatum of rats that had self-administered methamphetamine using a long-access paradigm [24]. We chose the striatum because it is an integral part of a circuit that regulates reward and habit forming [25, 26], both of which are core elements of addiction [10, 27]. We will also describe several gene networks that are affected during both early and late withdrawal times after cessation of methamphetamine self-administration. Moreover, we will touch on the evidence that methamphetamine intake is associated with some epigenetic changes in the dorsal striatum. These results will be discussed within the context of the need to generate novel hypotheses to elucidate the biological substrates of methamphetamine addiction.

Early Transcriptional and Epigenetic Changes in the Methamphetamine Self-Administration Model

Studies of epigenetic and transcriptional changes associated with drug addiction have focused mostly on the effects of cocaine on gene expression and/or histone modifications in various brain regions [28, 29]. The epigenetic and transcriptional effects of cocaine have been reviewed at great length [17, 18]. However, very few studies have been conducted on
the transcriptional and/or epigenetic effects of methamphetamine self-administration. Authors focusing on methamphetamine self-administration have reported on the effects of these behavioral manipulations on dopaminergic [24, 30, 31] and glutamatergic systems as well as c-FOS [13] and brain-derived neurotrophic factor (BDNF) [33] protein expression. Others have reported that methamphetamine self-administration can negatively impact cognitive function [34–36] and cortical electrophysiology [37]. In addition, the effects of withdrawal from extended methamphetamine self-administration were found to be related to the survival of hippocampal progenitor cells [34]. Moreover, withdrawal from extended methamphetamine self-administration was also accompanied by a dysphoric-like state, the neurobiological basis of which is not known [38]. Taken together, the extended methamphetamine self-administration model appears to result in varied clinical and neurobiological outcomes. Nevertheless, there is very little information on the transcriptional effects of similar models of methamphetamine addiction. In an attempt to fill that gap, we have conducted and are continuing to conduct studies to investigate genome-wide transcriptional and epigenetic effects of methamphetamine in the hope of discovering specific substrates for methamphetamine-induced multifaceted behavioral and biochemical effects.

In the experiments being reviewed here, we have used an extended-access model of intravenous methamphetamine self-administration for eight consecutive daily sessions, with the control rats receiving yoked saline injection [11, 24]. The rats were given access to methamphetamine for 15 h per day and were euthanized 2 h after the last session. As described by others [39], rats exposed to extended daily sessions escalate their intake of methamphetamine. More details of the long-access self-administration paradigm can be found in our two recent papers on the subject [11, 24]. Global gene expression was measured in striatal tissues using Illumina 22K Rat microarrays. Detailed experimental protocols for tissue collection, RNA extraction, and performance of microarray analyses can also be found in our many publications on this subject [11, 14] and will not be described at length here. As reported by Krasnova et al. [11], we found that 543 transcripts were differentially expressed using a cutoff value of 1.7-fold \( p<0.05 \) (Fig. 2a). Using similar criteria, we have been able to replicate array expression data from nucleus accumbens, dorsal striatum, or midbrain by using quantitative PCR [14, 19, 40]. For the microarray data described here, Krasnova et al. [11] had also used quantitative PCR to confirm methamphetamine self-administration-induced changes in the expression of several immediate early genes (IEGs), neuropeptides, and plasticity-related genes. Of the methamphetamine-regulated genes, 356 showed increased expression whereas 187 showed decreased expression in the striatum. These genes were analyzed for networks and molecular functions by using Ingenuity Pathways Analysis (Ingenuity Systems). Figure 2b shows that methamphetamine can regulate many biological processes in the dorsal striatum. Specifically, methamphetamine caused upregulation of transcripts that are components of gene networks for neurological disease, cell-to-cell signaling and interaction, nervous system development and function, as well as cellular assembly and organization. Downregulated networks include genes that participate in drug metabolism, endocrine system development and function, cell-to-cell signaling and interaction, and control of gene expression (Fig. 2b). The observation that the drug alters the expression of a large number of transcripts is consistent with the varied clinical manifestations of methamphetamine-addicted patients [4, 5]. These clinical presentations include deficits in executive and memory functions, depression, and psychosis [4, 41]. Our gene expression data thus raise the intriguing possibility that there are subpopulations of methamphetamine addicts...
who might respond differentially to pharmacological therapeutic approaches.

Given the multifaceted effects of methamphetamine in the central nervous system (CNS) that include decreased dopamine (DA) and serotonin levels in the dorsal striatum, decreased striatal dopamine transporters, and abnormal glucose metabolism [42–44], it is of interest that several genes that participate in the regulation of transcription, including brain abundant signal protein/brain acid soluble protein 1 (BASP1) (Fig. 3a), ETS domain-containing protein (ELK1) (Fig. 3b), and Kruppel-like zinc finger 10 (KLF10) (Fig. 3a), are upregulated by the drug (Table 1). Interestingly, BASP1 was discovered in rat brain about two decades ago [45]. BASP1 attaches to plasma membrane in nerve terminals [46] and can modify adjoining membrane region through interactions with phosphatidylinositol 4,5-bisphosphate (PIP2) [47]. BASP1 has also been shown to regulate actin cytoskeleton dynamics [48] and to be involved in initiating neurite outgrowth [49]. In addition to its role at nerve terminals, BASP1 was found to be a co-repressor for the Wilms’ tumor suppressor protein (WT1) [50]. BASP1 is found in the nucleus where it is localized on the promoters of WT1 target genes [51, 52]. BASP1 acts by recruiting histone deacetylase 1 (HDAC1) to cause suppression of WT1 target genes [53]. Thus, the identification of these novel effects of methamphetamine suggests that BASP1 might participate in methamphetamine-mediated decreases in striatal gene expression (see Fig. 2b, Table 1). This potential epigenetic effect of methamphetamine is supported by our recent data that identified HDAC1 as an important regulator of methamphetamine-induced changes in the expression of striatal glutamate receptors [15].

Another gene of interest whose expression is upregulated in this model is Elk1 (Fig. 3b, Table 1) which is a member of a ternary complex factor (TCF) subgroup of the family of the E-twenty-six (ETS)-domain transcription factors [54]. Elk1 is an important target of the canonical extracellular signal-regulated kinases 1 (ERK1) and 2 (ERK2) pathways [55, 56]. In the general context of addiction, various pharmacological agents have been shown to activate ERK1 and ERK2 in a DA and glutamate-dependent manner [57–60]. ERK1 and ERK2 are two very closely related kinases whose activation is dependent on their phosphorylation by mitogen-activated protein kinases [61, 62]. ERKs, in turn, phosphorylate ELK1 [55, 56]. ELK1 is widely distributed in the adult rat brain [63] and is involved in the regulation of functionally distinct networks of genes [64], including c-fos [65, 66] and early growth factor 1 (Egr1) in the striatum [63, 67]. Thus, the methamphetamine-induced expression of ELK1 suggests that the drug might have altered the expression of some genes, in part, by activating the MAP-ERK-ELK1 pathway. This suggestion is
Fig. 3  Methamphetamine self-administration causes differential expression of genes involved in several networks. A network of genes involved in neurological disease, behavior, and cell-to-cell signaling and interaction. This list includes BASP1, BDNF, and some phosphatases. B A network of genes that participate in cell-to-cell signaling and small molecule metabolism. These genes include CCK, ELK1, and neurotensin. C A network of upregulated genes involved in nervous system development and function as well as cellular assembly and organization. Among these genes are neuromedin U and syntaxin 1A. These gene networks emphasize the complex molecular effects of methamphetamine in the brain.
Table 1 Partial list of 2-h METH-upregulated genes in comparison to 1-month group

| Symbol | Entrez gene name | Fold change |
|--------|-----------------|-------------|
|        |                 | 2 h         | 1 month     |
| **Calcium ion binding** | | | |
| CADPS2 | Ca++-dependent secretion activator 2 | 2.56 | −1.35 |
| NECAB3 | N-terminal EF-hand calcium-binding protein 3 | 8.53 | −1.94 |
| **Cell adhesion** | | | |
| CNTNAP4 | Contactin-associated protein-like 4 | 3.71 | −1.03 |
| DSCAM | Down syndrome cell adhesion molecule | 1.78 | −1.49 |
| **Cell growth** | | | |
| DCBLD2 | Discoidin, CUB and LCCL domain containing 2 | 4.63 | −1.47 |
| INHBE | Inhibin, beta E | 3.44 | 1.25 |
| **Cell migration** | | | |
| SNX13 | Sorting nexin 13 | 2.12 | 1.34 |
| **Development** | | | |
| PLAC1 | Placenta-specific 1 | 5.11 | −1.70 |
| **DNA binding** | | | |
| ETV2 | Ets variant 2 | 4.73 | 1.00 |
| KLF10 | Kruppel-like factor 10 | 1.97 | 1.25 |
| TP53I11 | Tumor protein p53 inducible protein 11 | 6.34 | −1.26 |
| **Ion transport** | | | |
| CACNA1G | Calcium channel, voltage-dependent, T type, alpha 1G subunit | 4.41 | −1.36 |
| HCN1 | Hyperpolarization-activated cyclic nucleotide-gated K+ channel 1 | 2.92 | −1.99 |
| KCNC2 | Potassium voltage-gated channel, Shaw-related subfamily, member 2 | 1.90 | −2.56 |
| KCNH2 | Potassium voltage-gated channel, subfamily H, member 2 | 9.90 | −1.77 |
| SLC17A7 | Solute carrier family 17, member 7 | 3.95 | −1.06 |
| SLC35B2 | Solute carrier family 35, member B2 | 1.92 | −1.39 |
| SLC8A1 | Solute carrier family 8 (sodium/calcium exchanger), member 1 | 7.56 | 1.04 |
| **Metabolism** | | | |
| AGL | Amylo-alpha-1, 6-glucosidase, 4-alpha-glucanotransferase | 6.39 | −2.02 |
| CDO1 | Cysteine dioxygenase type 1 | 1.76 | −1.56 |
| HSD3B2 | Hydroxy-δ-5-steroid dehydrogenase, 3 β- and steroid δ-isomerase 2 | 4.52 | −1.23 |
| **Neuropeptide/hormone activity** | | | |
| CCK | Cholecystokinin | 7.93 | −1.47 |
| CORT | Cortistatin | 3.53 | 1.30 |
| FST | Follistatin | 2.20 | 1.00 |
| NMU | Neuromedin U | 3.84 | −1.00 |
| NTS | Neurotensin | 3.08 | −1.86 |
| PNOC | Prepronociceptin | 3.42 | −2.35 |
| VIP | Vasoactive intestinal peptide | 8.89 | −5.03 |
| **Neurotransmitter transporter** | | | |
| CPLX3 | Complexin 3 | 3.51 | 1.93 |
| **Neurotransmitter release** | | | |
| STX1A | Syntaxin 1A (brain) | 2.30 | −1.10 |
| SYN2 | Synapsin II | 2.12 | 1.03 |
| SYP | Synaptophysin | 1.74 | −1.53 |
| **Protein binding** | | | |
| INCENP | Inner centromere protein antigens 135/155 kDa | 2.33 | 1.16 |
| MED31 | Mediator complex subunit 31 | 4.78 | 1.19 |
| **Protein transport** | | | |
consistent with previous demonstration that some amphetamine analogs can increase ERK phosphorylation [68–70] and with the report that ELK1 activation is involved in cocaine-induced behavioral and molecular alterations [71]. This notion is also supported by the fact that the ERK mitogen-activated protein (MAP) kinase pathway is involved in cognitive processes [72] that are involved in the development of addiction [10].

Further evidence for the involvement of phosphorylation/dephosphorylation cascades in methamphetamine addiction is also provided by the observation of methamphetamine-induced increased phosphorylation of cyclic AMP response element binding (CREB) protein in the rat striatum [11]. CREB is a member of the CREB/activating transcription factor (ATF) family of transcription factors and is phosphorylated by cAMP-dependent protein kinase A (PKA) and other kinases [73]. Interestingly, the MAPK/ERK cascade has been shown to phosphorylate both ELK1 and CREB to increase c-fos and Egr1 expression in the striatum [67] and to control long-term potentiation-dependent transcription in the hippocampus [74]. CREB phosphorylation is indeed involved in the propagation of signals from various neurotransmitters [75–77]. CREB phosphorylation also promotes the recruitment of co-activators, such as CREB-binding protein (CBP)/

| Symbol | Entrez gene name | Fold change 2 h | Fold change 1 month |
|--------|-----------------|-----------------|--------------------|
| CYTH2  | Cytohesin 2     | 1.75            | −1.40              |
| PRSS12 | Protease, serine, 12 (neurotrypsin, motopsin) | 36.14 | 1.40 |

The experimental model and microarray analyses were performed as described in the text. This partial list of genes was generated from the 2 h microarray data. The expression data were then compared to the fold changes in expression obtained for these genes after 1 month of withdrawal. To be included, the genes had to meet the inclusion criteria: + 1.7-fold at p<0.05 at the 2 h time point.
p300, to the basal transcriptional machinery, a process that is followed by increased expression of CREB target genes [78]. These genes include immediate early genes (IEGs) such as arc, c-fos, egf1, several dual-specificity phosphatases (DUSPs), as well as BDNF [79, 80]. Consistent with these observations, we found that methamphetamine self-administration was accompanied by increased c-fos and BDNF at the early time point of withdrawal from drug taking by the rats [11]. These results are consistent with the report of Cornish et al.[13] who had reported significant increases in c-Fos protein expression in the dorsal striatum and cortex after a 3-week period of METH self-administration of 2-h daily sessions. Their paradigm is different from the one used in our study because the rats had 15-h access to drug for 8 days [11]. In both models, nevertheless, the METH effects might have occurred via stimulation of striatal DA receptors, followed by activation of various kinases, phosphorylation of CREB, and consequent CREB-mediated transcription [81–84]. This idea is supported by our findings that METH self-administration was accompanied by increased recruitment of phosphorylated CREB on the promoters of c-fos, fosB, and Bdnf [11]. In addition, these observations indicate that c-fos, fosB, and Bdnf genes might be co-regulated in some brain regions at both epigenetic and transcriptional levels and may work together to maintain some of the plasticity changes that might generate the regional substrates of methamphetamine addiction. This conclusion is supported by the demonstration of the important roles that activation of CREB and IEGs, including c-fos and egf1, plays in processes related to learning and memory formation [85–87]. The methamphetamine-induced increases in Bdnf messenger (m)RNA expression are accompanied by increased BDNF protein expression at the early time point. Our observations of METH self-administration-induced BDNF expression is consistent with those of McFadden et al. [33] who also reported that METH self-administration was accompanied by increased BDNF expression in the rat hippocampus. Taken together, it appears that METH self-administration might influence the expression of certain genes in various brain regions including the cortex, striatum, and hippocampus [11, 13, 33]. These results are also consistent with clinical studies that had reported increases in BDNF levels in the plasma of chronic METH users [88]. Moreover, this notion is supported by the possibility that BDNF signaling may play an integral part in producing plastic changes that lead to addiction [89] through processes that involved changes in the expression of proteins such as synapsin and synaptophysin that are involved in synaptic functions [90, 91]. Our findings that methamphetamine does increase the expression of synaptophysin (Fig. 3a), syntaxin 1A (Fig. 3c), and synapsins [11] provide further evidence that altered synaptic plasticity is at the core of methamphetamine self-administration. Synapsins are a family of phosphoproteins that are located in presynaptic terminals [92, 93]. They promote synaptogenesis and regulate vesicle dynamics and neurotransmitter release [94–96], functions that are dependent on phosphorylation/dephosphorylation events [97, 98]. Thus, our observations of methamphetamine-induced changes in the expression of these synaptic proteins might be relevant to the report that repeated methamphetamine exposure causes changes in the density of dendritic spines on medium spiny neurons [99], changes that are dependent on activation of the BDNF-tyrosine kinase receptor, type 2 (TrkB) signaling pathway [100].

Related to the discussion of the role of a potential convergence of the MAP/ERK/ELK1 and CREB phosphorylation pathways in methamphetamine addiction (Fig. 4), it is of interest that the microarray analysis also identified several phosphatases, including dual-specificity phosphatase 12 (DUSP12), protein tyrosine phosphatase receptor, type E (PTPRE), and protein tyrosine phosphatase receptor, type U (PTPRU) that were also upregulated by methamphetamine self-administration (Fig. 3a, Table 1). Protein phosphorylation/dephosphorylation processes are major mechanisms that regulate signal transduction pathways [101]. These processes are tightly regulated by protein tyrosine kinases (PTKs) and phosphatases (PTPs) that are highly expressed in the brain [101]. Other members of the general PTP family can also remove phosphate groups from phosphoserine, phosphothreonine, and phosphotyrosine residues and constitute a family of versatile enzymes called DUSPs [102]. PTPs are also divided into receptor-like or membrane-bound PTP (RPTP) and non-receptor or cytosolic, soluble PTPs [103]. DUSPs serve to provide negative feedback to MAPK and cyclin-dependent kinase (CDK) pathways by deactivating these enzymes via dephosphorylation events [102]. Because of their ubiquity, the DUSPs are involved in the regulation of many cellular functions [104]. However, in contrast to other DUSPs such as DUSP1-DUSP10, the role of DUSP12, an atypical DUSP [105], in the central nervous system has not been investigated actively. Nevertheless, DUSP12 has been shown to interact with Hsp70, and its overexpression protects against heat shock- and hydrogen peroxide-induced cell death, a function that requires its phosphatase activity [106]. Its antioxidative properties might be due to the fact that DUSP12 can sense oxidative stress by its thiol-rich zinc-coordinating domain [107]. Although the role of DUSP12 in methamphetamine addiction remains to be clarified, its increased expression in the present model is consistent with the fact that acute injections of the drug can cause oxidative stress in various brain regions [3, 108]. Increased markers of striatal toxicity have also been found in rats that self-administered methamphetamine [24] in a pattern similar to the one used in the present report. Together, these observations suggest that methamphetamine self-administration may result in oxidative stress in the rat striatum.
In addition to DUSP12, PTPRE and PTPRU were also upregulated in the methamphetamine self-administration model. PTPRE and PTPRU are members of the receptor-like PTPs [109] that are expressed in the brain [110–113]. PTPRE has been shown to regulate voltage-gated potassium channels in Schwann cells [114]. Of interest, we observed significant increases in the expression of KCNC2 and KCNH2 in the methamphetamine-treated rats (Fig. 3c, Table 1). Related to this discussion is the fact that PTPRE can inhibit ERK1 and ERK2 kinase activities and block ELK1-induced transcriptional activity [115] in a fashion similar to the DUSPs [102]. PTPRU (also called RPTP lambda or psi) is co-localized with cell adhesion molecules including catenin and E-cadherin [116]. The phosphatase contains a large region that is homologous to the intracellular cellular domain of cadherins and interacts directly with and dephosphorylates beta-catenin [117], an important component of Wnt signaling [118]. This action of PTPRU leads to inhibition of beta-catenin signaling [119, 120]. PTPRU also participates in Delta/Notch signaling [121]. This phosphatase is highly expressed in the midbrain/hindbrain boundary [122] and plays important role in the development of the midbrain [120]. Interestingly, PTPRU mRNA expression is regulated by the combined action of Nr4a2 and Pitx3 [111], both of which are upregulated by methamphetamine administration [14, 21]. These observations support the view that methamphetamine self-administration can activate gene networks that participate in various brain regulatory functions. Our results also suggest that the drug might cause activation of phosphorylation/dephosphorylation cascades to regulate and balance the activity of multiple signaling pathways during the transition to escalating methamphetamine intake in this model (see Fig. 4 for a scheme). Our results also support the thesis that drug addiction is related to changes in synaptic plasticity that may be mediated by the activation of a combination of molecular networks that impact neurotransmission in the dorsal striatum. Finally, the idea that protein phosphatases might be involved in addiction is supported by the observation that striatal PTP alpha promotes alcohol addiction in rodents [123].

Methamphetamine self-administration is also accompanied with increases in KLF10 expression (Fig. 3a). KLF10 is a member of the family of Sp1/Kruppel-like zinc finger transcription factors [124, 125]. KLF10 contains three repression (R1–R3) domains at the N-terminal [126], with the R1 domain being important for its interaction with the co-repressor, Sin3A, which suppresses gene expression by recruiting HDACs [127]. KLF10 can also suppress transcription via its interaction with Jumonji AT-rich interactive domain 1B/lysine-specific demethylase 5B (JARID1B/KDM5B) [128], an enzyme that removes methyl residues from trimethylated...
lysine 4 of histone 3 (H3K4me3) [129], a marker that is associated with active gene transcription [130]. The increased KLF10 expression might therefore be an attempt to correct methamphetamine-induced increased H3K4me3 abundance in the striatum [11]. The potential increased expression of repressor proteins during methamphetamine self-administration is consistent with the observations of decreased expression of several gene networks (Fig. 2b) in this model of methamphetamine addiction. This discussion suggests the possibility that KLF10 might be an important regulator of methamphetamine-induced epigenetic events. The potential role for these epigenetic marks in the long-term effects of the drug can also be inferred from the observed downregulation of several gene networks at a later time point of withdrawal from methamphetamine self-administration (see discussion below). In any case, more studies are needed to dissect the role of methylation processes in methamphetamine addiction [12], given the important of this histone mark in various biological functions [131].

Delayed Transcriptional Changes After Methamphetamine Self-Administration

Methamphetamine-addicted individuals show differential outcomes during the course of various therapeutic modalities [2, 8]. Interviews at 2–3 years after treatment showed that 50 % had returned to using drugs, with 36 % doing so within the first 6 months after the treatment period [8]. Methamphetamine addicts appear to relapse for a multitude of reasons that include pleasure seeking, impulsivity, habits, and pain avoidance [132]. In animal models of methamphetamine addiction, the number of lever pressing for an absent methamphetamine award is higher at later withdrawal times than that observed during early withdrawal [133], a phenomenon that has been referred to as incubation of drug craving [134]. Recently, it was reported that animals that were rendered abstinent from methamphetamine self-administration by response-contingent foot-shocks also demonstrated incubation of methamphetamine craving [135]. These clinical and preclinical results suggest that different molecular changes that occur during early and/or late withdrawal states might differentially influence striatal functions and cause different motoric behavioral outcomes that might manifest as larger number of lever presses at longer withdrawal times [133, 135]. The notion that striatal gene expression changes might play a role in behaviors observed after several weeks of withdrawal is consistent with data from microarray analyses that we describe below.

In the set of experiments examining the delayed effects of methamphetamine withdrawal, rats underwent the same self-administration procedure described elsewhere [11, 24] and were euthanized at 1 month after the last session. Global striatal gene expression was again measured using Illumina 22K Rat microarrays. We found that 673 transcripts were differentially expressed at that time point (Fig. 5a). Of these methamphetamine-regulated genes, only 82 were upregulated whereas 591 were downregulated. These results are different from those obtained at the early withdrawal time point when the majority of genes were upregulated (see Fig. 2a). The observation of large number of downregulated genes after methamphetamine withdrawal is consistent with previous results showing that methamphetamine can cause increased expression of histone deacetylases (HDACs) in the nucleus accumbens [14] and the dorsal striatum [15]. HDACs are enzymes that can cause histone deacetylation and repression of gene expression [136, 137]. HDACs are important regulators of synaptic formation, synaptic plasticity, and long-term memory formation [138–141]. Several HDACs also appear to play significant roles in various models of drug abuse and addiction [142–147].

The differentially expressed genes were analyzed for networks and molecular functions by using Ingenuity Pathways Analysis (Ingenuity Systems). Figure 5b shows that methamphetamine can regulate many biological processes in the dorsal striatum. Specifically, withdrawal from methamphetamine self-administration is accompanied with upregulation of transcripts that are components of gene networks involved in embryonic and organ development, amino acid metabolism, cellular growth and proliferation, and cellular assembly and organization, among others (Table 2). Downregulated networks include genes that participate in developmental disorders, neurological diseases, cell-to-cell signaling, and cardiovascular development and function (Fig. 5b, Table 2).

One of the upregulated genes of interest is the eukaryotic initiation factor alpha (eIF2alpha) (Fig. 6a, Table 2) because of its potential involvement in memory formation [148]. Methamphetamine-addicted individuals are known to suffer from memory deficits that may remain obvious even after long periods of drug withdrawal [44]. The clinical observations suggest that methamphetamine addiction might be associated with abnormalities in protein synthesis since long-term memory is dependent on de novo protein synthesis that is regulated by eIF2alpha [148, 149]. Newly translated proteins are thought to indeed contribute to the formation of new synapses that are involved in long-term storage of memory traces [150, 151]. In eukaryotes, translation initiation is stimulated by the delivery of initiator methionyl-tRNA in the form of an eIF2*GTP*Met-tRNA ternary complex [152]. This complex also includes eIF1A and eIF3 and binds near the 5’ end of mRNAs to initiate translation [153]. Thus, the methamphetamine-induced increased eIF2alpha mRNA suggests the possibility that there might be increased expression of certain proteins at this delayed time point after withdrawal from the drug. However, the possibility also exists that these changes might constitute compensatory increases due to
decreased expression of a large number of proteins, given our observations that many transcripts are downregulated in the methamphetamine-treated rats (Table 2). This idea is also consistent with our demonstration that rats that had undergone the methamphetamine self-administration paradigm showed decreased BDNF, TrkB, and delta fosB protein levels at the 1-month withdrawal time point ([11]; see discussion above). A recent study has also reported that there is a fine regulation of transcription and translation to modulate gene expression under different stressful conditions including oxidative stress and heat shock [154]. It may be therefore possible to conclude that these biochemical events might trigger compensatory responses that included increased eIF2alpha transcription because exposure to methamphetamine causes oxidative stress, heat shock, and endoplasmic reticulum (ER) stress [108, 155, 156].

It is also of interest to discuss the changes in eIF2alpha in relationship to the cognitive deficits observed in some methamphetamine abusers [44]. For example, another neuropsychiatric disorder in which patients show cognitive deficits is Alzheimer’s disease (AD) [157]. The brains of these patients show accumulation of beta-amyloid [158]. AD brains also show increased levels of activated and phosphorylated double-stranded RNA-dependent kinase (PKR) [159]. Animal models of AD also show activated PKR [159, 160]. PKR is a serine-threonine protein kinase that is involved in cellular responses to oxidative stress, ER stress, and decreased expression of trophic factors [161]. Importantly, PKR phosphorylates eIFalpha and leads to decreased protein synthesis [152, 162]. Another eIF2alpha kinase, the ER-responsive PKR-like ER-resident kinase (PERK) [163], is also activated in animal models of AD [164]. Together, these observations had suggested that these stress-responsive kinases might play an important role in the cognitive manifestations of AD. This idea was tested by Ma et al. [165] who reported that PERK deletion prevented deficits in protein synthesis and in spatial memory in mice models of AD. These findings are relevant to our discussion of methamphetamine addiction because methamphetamine also activates the ER PERK-dependent pathway [156]. Therefore, the possibility exists that cognitive deficits observed in methamphetamine-addicted individuals might also be due to ER stress-dependent PERK-mediated eIF2alpha phosphorylation, followed by decreased expression of plasticity-related proteins as demonstrated for BDNF and TrkB protein expression in this methamphetamine self-administration model [11]. The idea that there might be a
| Symbol   | Entrez gene name                              | Fold change | 2 h | 1 month |
|----------|-----------------------------------------------|-------------|-----|---------|
| **Autophagy** |                                               |             |     |         |
| TBC1D14  | TBC1 domain family, member 14                | 1.41        |     | −3.67   |
| **Cell cycle** |                                           |             |     |         |
| CCNA1    | Cyclin A1                                    | 1.57        |     | −1.81   |
| CD82     | CD82 molecule                                 | 1.05        |     | −1.71   |
| CDC25A   | Cell division cycle 25A                      | 1.27        |     | −4.25   |
| CDK4     | Cyclin-dependent kinase 4                    | 1.17        |     | −1.7    |
| CHEK2    | Checkpoint kinase 2                          | 1.12        |     | −3.59   |
| GADD45G  | Growth arrest and DNA-damage-inducible, gamma | 1.21        |     | −1.73   |
| **Cell differentiation** |                                             |             |     |         |
| BAMBI    | BMP and activin membrane-bound inhibitor      | 1.42        |     | −1.96   |
| DHH      | Desert hedgehog                              | −1.85       | 3.06|         |
| DLX1     | Distal-less homeobox 1                       | 1.16        |     | −1.71   |
| LIMD1    | LIM domains containing 1                     | 1.72        |     | −2.19   |
| NNAT     | Neuronatin                                   | −1.03       |     | −2.11   |
| VPS52    | Vacuolar protein sorting 52 homolog          | 1.26        |     | −2.70   |
| **Chromatin remodeling** |                                             |             |     |         |
| ARID2    | AT-rich interactive domain 2                 | 1.46        |     | −2.84   |
| ARID4A   | AT-rich interactive domain 4A                | −1.20       |     | −1.73   |
| CTR9     | CTR9, Paf1/RNA polymerase II complex component | 1.32        |     | −1.74   |
| EPC1     | Enhancer of polycomb homolog 1               | 1.44        |     | 4.78    |
| RNF187   | Ring finger protein 187                      | 1.10        |     | −3.91   |
| RNF113A  | Ring finger protein 113A                     | 1.22        |     | −1.71   |
| Sp2      | Sp2 transcription factor                     | −1.22       |     | 3.14    |
| **Coagulation** |                                             |             |     |         |
| PLG      | Plasminogen                                  | 1.48        |     | −1.94   |
| **Cytoskeleton** |                                         |             |     |         |
| KIF4A    | Kinesin family member 4A                     | 1.42        |     | −1.95   |
| MFAP1    | Microfibrillar-associated protein 1          | 2.34        |     | −2.17   |
| **DNA repair** |                                         |             |     |         |
| MPG      | N-methylpurine-DNA glycosylase               | 2.00        |     | −1.88   |
| RAD51    | RAD51 recombinase                            | 1.82        |     | −2.03   |
| **DNA replication** |                                         |             |     |         |
| POLD1    | Polymerase (DNA directed), delta 1, catalytic subunit | −1.02     |     | −1.71   |
| POLH     | Polymerase (DNA directed), eta               | 1.22        |     | −5.38   |
| **Growth factor** |                                       |             |     |         |
| HGF      | Hepatocyte growth factor                     | −1.98       |     | −1.87   |
| OSM      | oncostatin M                                 | −1.00       |     | −3.9    |
| **Homeostasis** |                                         |             |     |         |
| OCM      | Oncomodulin                                  | −2.05       |     | 2.63    |
| **Immune system** |                                     |             |     |         |
| Klr4     | Killer cell lectin-like receptor, subfamily A, member 4 | −1.93     |     | −3.10   |
| **Ion transport** |                                       |             |     |         |
| SLC22A7  | Solute carrier family 22, member 7           | 1.08        |     | −1.85   |
| **Metabolism** |                                             |             |     |         |
| PLD4     | Phospholipase D family, member 4             | 1.50        |     | −1.76   |
| PROCA1   | Protein interacting with cyclin A1          | 1.37        |     | −3.54   |
general reduction of protein synthesis in the methamphetamine self-administration model is supported by the observation of decreased expression of another translation initiation factor, eIF2D [166] (Fig. 6b).

In addition to the possible involvement of changes in protein synthesis in the manifestation of methamphetamine addiction, our study has documented substantial decreases in the levels of transcripts that are transcription regulators (Fig. 6b–c, Table 2). These include AT-rich interactive domain 2 (ARID2) (Fig. 6a), ARID4A (Fig. 6b), junD (Fig. 6c), and leucine-rich repeats and calponin homology (CH) domain containing 4 (LRCH4) (Fig. 6b), among others (Table 2). JunD is an intronless gene [167] that is regulated at the translational level [168]. JunD is a member of the activating protein 1 (AP1) family of transcription regulators [169, 170]. The AP1 complexes contain members of the FOS (c-fos, fosB, Fra1, Fra2), JUN (c-jun, junB, and junD), and ATF/CREB (multiple ATFs) families [171, 172]. The Jun family members can homodimerize or heterodimerize with FOS family members to regulate gene expression. AP1 complexes also differ in their binding and transactivating efficiencies based on their compositions and they can either activate or repress the transcription of genes that mediate multiple cellular functions [171, 173, 174]. JunD binds to the TPA-responsive element when it is in the form of homodimers or heterodimers with FOS and JUN family members [175]. In contrast, it binds CRE when it

### Table 2 (continued)

| Symbol | Entrez gene name                                                                 | 2 h    | 1 month |
|--------|----------------------------------------------------------------------------------|--------|---------|
| ALDOB  | Aldolase B, fructose-bisphosphate                                                 | −1.00  | −1.93   |
| Hddc3  | HD domain containing 3                                                           | 1.51   | −1.87   |
| Photoreceptor |                                             |        |         |
| RHO    | Rhodopsin                                                                        | −1.22  | −3.70   |
| Protein binding |                                      |        |         |
| ANKRD50 | Ankyrin repeat domain 50                                                        | 3.69   | 4.48    |
| LRRRC59 | Leucine-rich repeat containing 59                                                | 1.15   | −1.76   |
| Proteolysis |                                            |        |         |
| MMP13  | Matrix metallopeptidase 13 (collagenase 3)                                      | −1.00  | −4.18   |
| Signal transduction |                                  |        |         |
| DUSP10 | Dual-specificity phosphatase 10                                                  | 1.43   | −3.00   |
| DUSP19 | Dual-specificity phosphatase 19                                                  | −1.45  | −3.41   |
| HIPK3  | Homeodomain-interacting protein kinase 3                                         | 1.04   | 1.82    |
| Structural |                                            |        |         |
| LAMB3  | Laminin, beta 3                                                                 | 1.12   | −2.14   |
| Transcription |                                          |        |         |
| IKZF2  | IKAROS family zinc finger 2 (Helios)                                             | 1.11   | −2.32   |
| JUND   | jun D proto-oncogene                                                             | −1.14  | −1.72   |
| KLF12  | Kruppel-like factor 12                                                           | 2.17   | −3.15   |
| LEO1   | Leol, Paf1/RNA polymerase II complex component                                   | 1.00   | −1.78   |
| LMO1   | LIM domain only 1 (rhombotin 1)                                                  | −1.34  | −1.80   |
| LRCH4  | Leucine-rich repeats and calponin homology domain containing 4                  | −1.52  | −2.50   |
| NFYB   | Nuclear transcription factor Y, beta                                             | 1.38   | −2.37   |
| NKX2-4 | NK2 homeobox 4                                                                   | 1.29   | 3.55    |
| RCOR2  | REST corepressor 2                                                               | 1.19   | −4.88   |
| TAL2   | T-cell acute lymphocytic leukemia 2                                              | −1.54  | −2.08   |
| YY1    | YY1 transcription factor                                                         | 1.35   | −2.52   |
| Translation |                                         |        |         |
| EIF2A  | Eukaryotic translation initiation factor 2A, 65 kDa                             | −2.68  | 3.86    |
| EIF2D  | Eukaryotic translation initiation factor 2D                                       | 1.37   | −1.81   |

The experimental model and microarray analyses were performed as described in the text. This partial list of genes was generated from the 1 month withdrawal dataset. The gene expression data were then compared to the fold changes obtained for these genes at the 2h time point. To be included, the genes had to meet the inclusion criteria: + 1.7-fold at $p < 0.05$ at the 1 month withdrawal time point.
Fig. 6 Withdrawal form methamphetamine self-administration causes differential changes in the expression of genes involved in several networks. a A network of upregulated genes involved in tissue morphology and cellular assembly. b A network of downregulated genes that participate in cell cycle, DNA replication, and repair, as well as cell death and survival. c A network of downregulated genes involved in cellular and tissue development. This network includes several transcription regulators including JunD, KLF12, and RCOR2.
is in the form of heterodimers with ATF family members [176, 177]. The JUN family members also display different patterns of expression during cell cycle progression, with JunD showing no significant changes [178]. JunD protects against p53-induced cell death [179] and regulates the expression of genes involved in cellular antioxidant responses [180, 181] and inflammatory responses [182, 183]. JunD is also involved in nerve growth factor (NGF)-induced upregulation of Nr4a1 in PC12 cells [184]. JunD also dimerizes with Fra2 to mediate NGF-mediated changes in gene expression in PC12 cells [185]. The protein also dimerizes with FosB to regulate okadaic acid-induced transcriptional changes [186] and glutamate-mediated death [187]. JunD also regulates the expression of proenkephalin expression in vitro models [188]. Altogether, these studies had identified a larger number of JunD target genes in various organ systems (see [183] for an extensive list of JunD-regulated genes). JunD is also highly expressed in the nervous system [189–191] where its expression is responsive to methamphetamine administration [22]. The observations of decreased JunD expression after 1 month of withdrawal from methamphetamine self-administration are consistent with our previous observations that repeated methamphetamine injections for 2 weeks caused decreases in striatal JunD expression [22]. The decreased JunD expression suggests that alterations in JunD expression might play an important role in regulating the expression of the large number of genes that are downregulated at the 30-day withdrawal time point. Because one of JunD binding partners, deltaFosB, is also downregulated at that time [11] and because deltaFosB is also a key regulator in gene expression in other models of drug addiction [17], our findings suggest that, together, the downregulation of both JunD and deltaFosB model might serve to generate the increased motoric behaviors (e.g., increased lever presses) observed after lengthy withdrawals from methamphetamine self-administration [135]. Together, these observations implicate AP1 transcription factors as important players in addiction processes.

Another transcription regulator of interest is AT-rich interactive domain 2 (ARID2) (Fig 6b). ARID2 [192, 193] is a subunit of the polybromo- and BRG1-associated factor (PBAF) chromatin-remodeling complex that regulates gene expression [194, 195]. The protein contains an N-terminal AT-rich DNA binding domain and two C-terminal motifs that serve to bind DNA [196]. The ARID gene family consists of 15 members that are conserved from yeast to humans [197]. The ARID2-containing complex uses energy generated by ATP hydrolysis to remodel chromatin and facilitate binding of transcription factors, with resulting increased in gene expression [198, 199]. The ARID proteins have also been implicated in the control of cell growth and differentiation [200, 201]. Thus, decreased ARID2 expression is consistent with the results of methamphetamine withdrawal-induced decreased levels of many transcripts at the delayed time point (see Table 2). In addition to ARID2, another member of the ARID chromatin-remodeling genes, ARID4A, also showed decreased expression at that time point (Fig. 6b). ARID4A possesses an ARID domain, a chromodomain, a Tudor domain, and two repression domains [197, 202]. Chromodomains and Tudor domains regulate binding to methylated lysines in the tails of histones H3 and H4 [203, 204]. ARID4A binds the retinoblastoma protein (pRB) [205, 206], an important regulator of cell proliferation and differentiation [207]. Binding of ARID4A to pRB has been reported to suppress E2F target genes by both HDAC-dependent and HDAC-independent mechanisms [202]. The downregulation of these two ARID transcripts whose protein products are involved in transcription regulation further implicates epigenetic mechanisms in the long-term effects of methamphetamine withdrawal.

Thus, it is of interest that the transcription regulator, LRCH4 (also called LRRN1 or SAP25), a component of the mSin3 co-repressor complex [208, 209] that is used by several classes of transcriptional repressors including MeCP2 [210] and Ikaros [211], is also downregulated after a lengthy withdrawal from methamphetamine. Interestingly, the Ikaros family zinc finger 2 (Helios, IKZF2) is also downregulated at the same time point (see Fig. 6b). Helios is involved in the silencing of IL2 gene in regulatory T cells [212], and its presence in striatal cells [213] suggests that Helios might play a comparable role in the brain immune responses to methamphetamine [43, 214]. In any case, the fact that the levels of several transcripts of proteins that participate in co-repressor complexes are decreased at 1 month after methamphetamine withdrawal suggests that there might be a general depressing effect on transcription at that time, with only a few genes being upregulated after that time interval. It remains to be determined whether the upregulated genes are targets of these co-repressor complexes since the downregulation of transcriptional suppressors would result in their increased transcription.

Concluding Remarks

In summary, methamphetamine use disorder is a chronic neuropsychiatric disorder that is characterized by a complex clinical course with periods of active drug-taking behaviors filled with bingeing episodes interspersed between drug-free intervals and repeated relapses. Although various neuroimaging studies have identified potential loci for the functional neuroanatomy of its varied clinical presentations, much remains to be done to identify the pathobiological substrates of methamphetamine addiction. It is important to note that human methamphetamine addicts use the drug according to different scheduling patterns and the amount of drug ingested. They also present with a diversity of clinical findings including depression, suicidal ideations, and psychotic symptoms. These clinical observations suggest that the drug might cause differential molecular and neurobiological alterations that
produced complex clinical pictures. These statements suggest the need for the development of a diversity of models in which investigators could study the molecular impact of different drug doses that are self-administered by rats. Importantly, similar to the case of other complex neuropsychiatric disorders such as the major affective disorders or schizophrenia, it is very likely that single-gene approaches will fail to provide a comprehensive understanding of the basic neurobiology of drug addiction. Approaches that include genome-wide studies in conjunctions with models that are more representative of the human condition will create better opportunity to clarify the molecular neuropathology of methamphetamine addiction. These approaches promise to help to generate testable hypotheses and ideas that might be translatable to therapeutic approaches. The veracity of this notion is presently being tested in our laboratory by using behavioral models in conjunction with modern molecular techniques.

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Conflict of Interest The authors declare that they have no conflict of interest.

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