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Histone Glutamine Modification by Neurotransmitters: Paradigm Shift in the Epigenetics of Neuronal Gene Activation and Dopaminergic VTA Reward Pathway

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ABSTRACT

Normal brain function means fine-tuned neuronal circuitry with optimum neurotransmitter signaling. The classical views and experimental demonstrations established neurotransmitters release-uptake through synaptic vesicles. Current research highlighted that neurotransmitters not merely influence electrical impulses; however, contribute to gene expression, now we know, by posttranslational modifications of chromatinised histones. Epigenetic modifications of chromatin, like DNA methylation, histone methylation, acetylation, ubiquitilation etc., influence gene expression during neuronal development, differentiation and functions. Protein glutamine (Q) modification by tissue transglutaminase (TGM2) controls a wide array of metabolic and signaling activities, including neuronal functions. Dopamine neurons are central element in the brain reward system that controls the learning of numerous behaviours. The ventral tegmental area (VTA) consists of dopamine, GABA, or glutamate neurons. The VTA and adjacent substantia nigra are the two major dopaminergic areas in the brain. In view of this, and to focus insight into the neuronal functions caused by TGM2 mediated histone modifications at the Q residues, either serotonylation (for example, H3K4me3Q5 to H3K4me3Q5ser) in the context of cellular differentiation and signaling, or dopaminylation (for example, H3Q5 to H3Q5dop) in the dopaminergic VTA reward pathway and the precise role of cocaine withdrawal in this scenario are summarized and discussed in this contribution.

Keywords: Neurotransmission; Epigenetics; Glutamine modifications; Tissue transglutaminase 2; Ventral tegmental area; Reward system.

Introduction

The brain function largely depends on neuronal circuitry and neurotransmitter signaling (1-4). In the Brain, dopamine and related circuits are instrumental in decision-making, behavioural activation and exertion of efforts (3). Mesolimbic dopamine, also known as the ventral tegmental area (VTA) dopamine is one part of numbers of neurotransmitters signaling in several parts in the brain. Animal model studies related to decision making are highly relied upon characterizing human efforts and behaviour, since there are remarkable similarities among the brain areas of rodents and in humans (3, 4). Evidences implicate that

there is aberration in effort related decision making in several neurological disorders. VTA is the locus of mesolimbic dopamine cell bodies that stores and releases dopamine. As depicted in Scheme 1, the mesolimbic dopamine pathway projects from the VTA to the nucleus accumbens (NAcs) and plays an important role in reward processing (3, 5-7). Nigrostriatal dopaminergic pathway, responsible for regulation of locomotion, originates from the substantia nigra (6, 7) and dopamine release at the terminals is evoked by action potentials, and depends on dopamine stores (3, 7-9). Dopamine is transported back into the neuron by the dopamine transporter (10). Dopamine uptake is time dependent, whereas release and distributions in the circuitry depends on the frequency of action potentials (11-13). It is well established that basal ganglia control body movements. Basal ganglia also imparts in dopamine reward system (for a recent review, see Kim and Hikosaka, 2015; 14)

The housekeeping or specialized functions of cells requires metabolic activities; expression of the genes of respective enzymes involved in a metabolic process is controlled by transcription factor(s) and chromatin modifications. When gene expression is regulated by chromatin (DNA and histones) modifications it is known as epigenetic regulation of gene expression (15-20). Precisely epigenetics is mitotically and/or meiotically heritable changes in gene function that happen without changes in DNA sequence (16-20). Methylation of DNA at cytosine-5 carbon (DNA methylation; 18-20), methylation, acetylation and ubiquitilation modifications of specific lysine (K) and methylation of arginine (R) residues of histones are well studied examples (Table 1; refs. 15-17, 21-26). They play crucial roles in chromatin structure stabilization and dynamic gene expression. Phosphorylations of proteins, mainly, in the side chains of Ser (S), Thr (T) and Tyr (Y) are elsewhere in the cellular functions; including subcellular organelle functions, membrane signaling and chromatin templated processes (27-29).

With the progress of understanding the nature of DNA packaging into chromatin; "beads on a string" structure and folded complex in the nucleus (Kornberg RD 1974; 30); it was a puzzle, how DNA polymerase and RNA polymerase would progress forward to execute their respective function. It was the effort of a genius, Vincent Allfrey, who deciphered (in the year 1964!) that, histone undergoes methylation and acetylation modifications (31), thus put the founding stone of molecular basis of histone modifications in epigenetics arena (32). However, the progress took some time to identify the enzyme histone acetyltransferases and the cofactor, acetyl-coenzyme A (33-35). During those years almost parallelly histone deacetylase activity was discovered (36-40). During 1950s isolation of gamma-amino-butyric acid (GABA) from several plants and its role as neurotransmitter was established (41-44). Hence, scientists were curious to learn the effects of GABA on tissue cultures; however, lack of adequate supply of GABA perhaps coerced few labs to observe the effect of "butyric acids" on histone de/acetylation relating DNA/RNA synthesis (45-49).

This article attempts to provide an interdisciplinary lookout that integrates biochemistry, molecular biology and epigenetics research in the field of neuroscience and brain function.

Neurotransmission and the dopamine reward system

The ventral tegmental area (VTA) and adjacent substantia nigra (SN) are the two major dopaminergic areas in the brain. The VTA is considered as the integral part of a network of structures, together known as the reward system/pathway, which transports dopamine from the VTA to the nucleus accumbens, amygdala, and hippocampus (also known as mesolimbic pathway; and the amygdala and hippocampus are key components of the limbic system), that are involved in reinforcing behavior (Scheme 1; refs. 2-6). Several major efferents projects from the VTA; both the mesolimbic and mesocortical pathways are prominent (50). Combinatorial viral strategy to transsynaptically label afferents defined that, VTA consists of dopamine, GABA, or glutamate neurons. For a comprehensive knowledge of the input-output VTA

network for addiction and other maladaptive behavioral disorders see Faget et al. 2016 (51). In brief, VTA dopamine neurons receives major portion of input from striatal and globus pallidus. Glutamate neurons are enriched with cortical input and GABA neurons receive highest input from the lateral habenula and laterodorsal tegmental nucleus (51). Connectivity is best explored utilizing three known maker genes; enzyme tyrosine hydroxylase (TH) essential for dopamine synthesis, excitatory vesicular glutamate transporter 2 (vGluT2), and inhibitory glutamate decarboxylase 67 (Gad1) or Gad2 (52, 53).

Epigenetic modifications and function of the reward system

Epigenetic studies on neuronal circuitry are emerging (54, 55). Whether self-administration of cocaine could deliver any heritable phenotype in rats was explored recently. Increase of acetylated histone H3 in the Bdnf promoter was detected in the sperm of sires that self-administered cocaine (56). Earlier, Kumar et al. (57) demonstrated acute induction of hyperacetylation of H4 of cFos promoter within 30 min of a single cocaine injection, but not in chronic cocaine subjects in consistent with cocaine's inability to induce cFos chronically in striatum. However, histone H3 hyperacetylation of the gene promoters of Bdnf and Cdk5 were noted in chronic cocaine subjects only. Epigenetic mechanisms modulate physiology and functions associated with learning and memory, particularly the reward pathway and drug addiction. Various types of modifications on DNA and histones in postmitotic neurons in relation to brain functions, learning and memory are recently reviewed (58). Image-based informatics tools allowed global genome-scale structural analysis and cross-correlation, as well as identification of brain region specific enrichment of gene functions, facilitating better understanding of classical neuroanatomical atlases of brain organization and function (59-61).

Epigenetic mechanisms which might be responsible for addiction primarily focus on behavioral responses by a systemic measure of drug treatment and reward. Most uncertain issues in interpretation of data lies with the fact that there couldn't be any noise free model that would benefit the interpretation of epigenetic studies; however, assessment of drug-induced molecular changes, like DNA methylation and histone marks must be relied upon those factors. Cocaine addiction and alteration of histone acetylation and methylation are known in the NAc. Experiments on correlating the acetylation mediated potentiation of cocaine sensitivity and reward were performed by inhibition of HDAC function. It was intriguing to observe that while HDAC1 deletion in the NAc attenuated behavioral responses to cocaine, deletion of HDAC2 or HDAC3 does not; Kennedy et al., 2013 (62). HDAC3 is the most highly expressed HDAC in the brain (63), enhances extinction and prevents reinstatement of cocaine seeking in a conditioned place preference paradigm (63-65). Long term application of cocaine reduces the deposition of H3K9me2 chromatin was correlated with inactivation of the methyltransferase G9a in the NAc. Inhibition of G9a activity by genetic disruption or using inhibitors typically enhances locomotive responses to cocaine, and ectopic expression of G9a reverses it (66, 67).

A recent study from Maze lab (Lepack et al, 2020; 68) forwarded the science of the reward system finding dopamine in the heart of nucleosome; they deciphered that nucleosomes of the VTA region neurones are enriched with chromatin having histone 3 glutamine 5 (H3Q5) dopaminylated (H3Q5dop). They hypothesized that susceptibility to cocaine relapse during periods of attempted abstinence from cocaine use is due to result from the rewiring of brain reward circuitries. The VTA dopamine neurons (Scheme 1) may achieve H3Q5dop enrichment in the midbrain. Rats undergoing withdrawal from cocaine showed an accumulation of H3Q5dop in the VTA. Reduction of H3Q5dop precipitation by epigenetic engineering reversed cocaine-mediated gene expression changes, attenuated dopamine release in the nucleus accumbens (NAc), and reduced cocaine-seeking behavior. To define their findings clinically relevant they traced the deposition of H3Q5dop in the VTA brain of cocaine-dependent postmortem individuals and relevant controls. It is very interesting that reduced deposition of H3Q5dopin the VTAs of cocaine patients;

H3K4me3Q5dop, H3K4me3, total H3, and TGM2 were unchanged in their relative levels of expression. This is something novel among the findings in this field of neurobiology that establish a neurotransmission-independent role for nuclear dopamine in relapse-related transcriptional plasticity in the reward system. As depicted in Figure 1, the enzyme tissue transglutaminase 2 (TGM2) is identified as the responsible enzyme for the reaction H3Q5 to H3Q5dop by transamidation

Diverse function of transglutaminase 2: new role as epigenetic writer during neuronal development and in the reward pathway

Transglutaminases (EC 2.3.2.13) family contains factor XIII (plasma transglutaminase), keratinocyte transglutaminase (TGM1), hair follicle transglutaminase, prostate transglutaminase (TGM4), and tissue transglutaminase (TGM2). The amino acid sequences of these enzymes differ, but share the unique active site sequence –YGQCW- and calcium dependence. Notable TGM2 functions are: incorporation of amines into proteins, crosslinking of proteins, site-specific deamidation, isopeptidase activity, promotion of cell–matrix interactions by conjointly binding integrin and fibronectin (69-71). Gentile et al. (72) deciphered cDNA encoding TGM2 from mouse and human. Amino acid sequence of human TGM2 protein is 84% and 81% identical to mouse and guinea pig TGM2 respectively. Human TGM2 in vitro translation and SDS-PAGE analyses predicted an apparent molecular mass of 85 kD. Chen et al. (73) found that mutation of the active site cysteine (cys277) in TGM2 compromised enzyme activity in transfected COS-1 cells.

The structure of TGM2 dimer in complex with GDP deciphered four functional domains: N-terminal β-sandwich for fibronectin and integrin binding; catalytic core containing the catalytic triad for the acyl-transfer reaction and a conserved Trp essential for this catalytic activity; and two C-terminal β-barrel domains. The second β-barrel contains a phospholipase C binding sequence and the guanidine nucleotide-binding site is unique to TGM2 (74). Antonyak et al. described a splice variant of TGM2 consisting of 548-amino acids in which phospholipase C binding domain is truncated. Ectopic expression of this isoform is cytotoxic/apoptotic due to inappropriate oligomer formation retaining its transamidation activity (75). In the central nervous system (CNS) TGM2 plays a pivotal role; however, mode of action of TGM2 in response to a challenge differs in astrocytes and neurons. In primary neurons, TGM2 expression protects cells from oxygen and glucose deprivation (OGD)-induced cell death and knockdown of TGM2 in primary neurons results in a loss of viability. However, deletion of TGM2 from astrocytes results in increased survival following OGD and improved ability to protect neurons from injury (76-80). TGM2 constitutively activates G-proteins Gαq, Gαo1 and Cdc42 by histaminylation of glutamine residues in their catalytic core (81).

Modifications of glutamine residues in histones and discovery of new epigenetic mark in brain function

With the advances of diverse activity of TGM2 several groups were curious about monoaminylation of proteins by transamidation (reviewed in 70, 71, 76, 80). The in vitro assays of TGM2 activity upon proteins, including nuclear histones were of particular interests (82-88). The accessibility of a glutamine to TGM2 depends on the exposed tails of H2B and H3 from the nucleosome core was deciphered by monodansylcadaverine labelling studies of residues, Q104 and Q112 of H2A (82, 83). The studies of Ballestar et al. thus implicated that unwinding of DNA and the dissociation of the H2A−H2B dimers is essential. The Q76 of H3 was labelled in the H3−H4 tetramer only when the H2A−H2B dimers are dissociated. Q95 of H2B was labelled only after unwinding of DNA (82).

Posttranslational modifications (PTMs) of nuclear histones are additional layers of information necessary to preserve and/or decode the "program of eukaryotic lives" stored in the DNA sequences of respective genome. Thus PTMs of histones means gene expression for myriads of cellular functions according to the

information despatched by signal transduction pathways and metabolic requirements (89-96). Table 1 shows a brief about the major amino acids side chain modifications by different chemical groups and respective enzymes involved with the specific reaction process, including the enzyme(s) for the reverse reaction.

Discovery from Maze lab, an year ego depicted that histone serotonylation independent of neurotransmitter function of serotonin with the functional consequences is the quantum jump in our understanding of epigenetic regulation of gene expression and cellular functions (97). It is well established that serotonin form covalent bonds with cytosolic/organelle proteins by the enzyme TGM2; the transamidation modification modulates the signalling properties of the modified proteins to facilitate their functions in the organelle (98, 99). Serotonylation of histone H3 at glutamine 5 (H3Q5) position in the context of pre-existing H3K4me3 nucleosomes has recently been documented (97). H3K4me3 is an expressive mark contributed by MLL and SET1 family proteins (100, 101). The combinatorial H3K4me3Q5ser modification is ubiquitous in mammalian tissues and enriched in the euchromatin territory. Notably, in brain and gut tissues majority of serotonin is produce, and interestingly, the H3K4me3Q5ser deposition is very high. To provide an insight of the functional implications of H3K4me3Q5ser deposition the authors performed genome wide analyses in human embryonic stem cells, serotonergic neurons, developing mouse brain and cultured serotonergic cells. It is deciphered that H3K4me3Q5ser modifications facilitate TFIID4 binding and enhance gene expression require for cellular differentiation (97, see also 102, 103).

As already discussed in the section of 'epigenetic modifications and the reward system'; the recent report from Maze lab (68) implicated that neurotransmission by dopamine and chromatin modification, H3Q5 dopaminylation (H3Q5dop) achieve simultaneously for rewiring of brain reward circuitries during periods of attempted abstinence from cocaine. They executed that rats undergoing withdrawal from cocaine showed an accumulation of H3Q5dop in the VTA. Reduction of H3Q5dop by inhibition of TGM2 in the VTA within the processing of withdrawal, cocaine-mediated gene expression changes were reversed, along with attenuated dopamine release in the NAcs, and reduced cocaine-seeking behavior. This is very exciting discovery in epigenetics, molecular biology and neurobiology that establish neurotransmission dependent and independent roles for nuclear in the reward system (68, see also 104).

Histone glutamine modification other than H3Q5

Few years back a study on H2AQ104 methylation from Tony Kouzarides lab published in Nature. The modification is specific to rDNA transcription and operates in nucleolus and the responsible enzyme is human fibrillarin as the H2AQ104-specific methyltransferase in addition to its well characterized function of methylating 2´ribose sites of nascent rRNA (105). Prior to their report, glutamine methylation was observed on translation termination factors and ribosomal proteins at the universally conserved –GGQ- sequence site for the release of nascent peptide (106-108).

Facilitator of chromatin transcription (FACT) is a histone chaperone with nucleosome destabilizing activities required for the efficient passage of RANPII and transcription (101). FACT interacts with H2A over a consensus sequence spanning H2AQ104. Methylation of H2AQ104 or mutation of H2AQ104A reduced FACT binding and enhance transcription potential of RNAPI by a mechanism that differs from the RNAPII. It was suggested that most of H2A from rDNA chromatin is thrown out by FACT, resulting in low nucleosome occupancy of H2A during the transcription and reloading of glutamine methylated H2A by the chaperone NAP1 (109, 110). Till date the mechanism is not clear! The functional relationship between FACT and H2AQme in rDNA transcription requires more data.

Fibrillarin as histone H2AQ104 methyltransferase is further characterized (109). Fibrillarin is reversibly acetyl-modified at several lysine residues by the acetyltransferase CBP and deacetylated by SIRT7.

Interestingly, acetylation of fibrillarin do not impair pre-rRNA methylation; however, hyperacetylated fibrillarin loss its interaction with chromatin histone H2A and eventually cannot methylate H2AQ104 halting rDNA transcription. Deacetylation of fibrillarin activates its H2AQ104 methylation potential and RNAPI mediated rRNA synthesis (111).

Discussion

A comprehensive neurochemical, epigenomic anatomical map is essential for understanding gene expression and brain function. The classical experiments established roles of neurotransmitters in varied aspects neurophysiology. Studies with dyes and tracers have been made to map the neuronal circuitry. Among the tracers; the retrograde tracers horseradish peroxidase, wheat germ agglutinin etc., and anterograde tracers, including biotinylated dextran amine are important. There were technical inabilities to precisely judge input-output efficacies of cells differing in gene expression patterns (3, 4, 52 and references therein). Current research implicated the roles of neurotransmitters beyond electrical impulses (68, 97). Chemical modifications of histones, including methylation, acetylation, and ubiquitilation etc. modulate tissue functions, neuronal development and differentiation. The dopaminergic VTA neurons contribute to gene expression by posttranslational modifications of nucleosomal histones (68). Modifications of glutamine, Q side chains of proteins by TGM2 serve numerous functions; to name a few are, tissue integrity, cellular metabolism and G-protein signaling activities (71-83).

Dopaminylation and serotonylation (hereafter, neurotransmitylation, NTM) of histone at H3Q5 are new findings both from Maze lab (68, 97); while dopaminylation is involved in regulation of aberrant neuronal gene expression patterns in the VTA in response to cocaine consumption (68), serotonylation of H3Q5 is context dependent. Pre-existing trimethylated histone H3 at K4 followed by unmodified Q5 (H3K4me3Q5) is the ideal substrate for TGM2 to serotonylate (Figure 1) which in vivo might activate chromatin for gene expression in eukaryotic cells. These findings reveal that neurotransmitters may be the right compounds for chemical modifications of histones, and glutamine (Q) joined the elite club of amino acids K, R, S to be counted. This invites Herculean task ahead to figure out whether NTM of histone is specific to neuronal genes or else contribute in other tissues. Few important questions remain; (i) the accessibility of the Q at different sites of the histones, (ii) reversibility of the neurotransmitylation (NTM) of histone, and (iii) where the –NH3 goes?

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Competing Interests

I declare that there is no conflict of interest.

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Table –I: Prominent amino acids of nuclear histones those undergo posttranslational modifications and modulate gene expression.

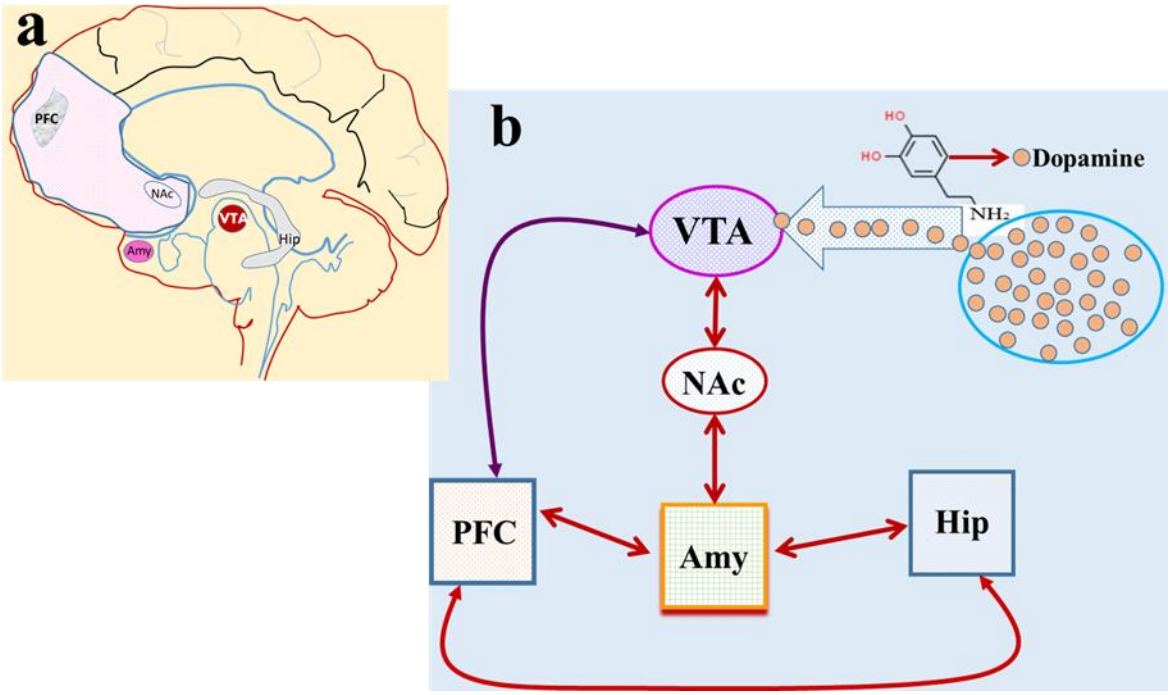
Amino acid	Type(s) of modification(s) of the respective side chain	Enzyme of the forward reactions (writers)	Enzymes of the reverse reactions (erasers)
K	Acetylation	Acetyltransferases (HATs)	Histone deacetylases (HDACs)
	Methylation	Histone lysine Methyltransferases (HKMT)	Histone Lys demethylases (KDMs)
	Ubiquitilation	Rad6	Ubiquitin proteases (UBPs)
	Sumoylation	UBC9	ULP-related proteases
S T Y	Phosphorylation	Kinases	Phosphatases
R	Methylation	Protein arginine methyltransferases (PRMT)	Protein arginine demethylases (PADs), also some KDMs
Q	Methylation	Fibrillarin as methyltransferase	KDMs?
	Serotonylation	Transglutaminase 2 (TGM2)	?
	Dopaminylation	Transglutaminase 2 (TGM2)	?

Schematic and Figures with legends

Scheme 1: Schematic view of the VTA Dopamine reward pathway. The ventral tegmental area (VTA) comprises heterogeneous cell types with diverse projections consisting of dopamine, GABA, or glutamate neurons. VTA is one of the two major dopaminergic areas in the brain (adjacent, substantia nigra is the other). a. apparent locations of the organs of the reward system. b. The VTA neurones transport dopamine from the VTA to the prefrontal cortex (PFC), the nucleus accumbens (NAc), the amygdala (Amy), and the hippocampus (Hip), those are involved in reinforcing behavior. Several major efferents projects from the VTA in both the mesolimbic and mesocortical pathways. VTA dopamine neurons receives major portion of input from striatal and globus pallidus. See the text for further details (see also refs. 2-6, 50-53, 61 and 68). Note that, the distribution of dopamine and non-dopamine axons within a given VTA projection differs target to target. For example, and as depicted here, dopaminergic VTA projections are 85% to the NAc; ~12-15% to the PFC; and only 1–3% to Hip.

Figure 1. Tissue transglutaminase 2 (TGM2) mediated transamidation reactions in dopaminergic and serotonergic neurone, (1) release of ammonia. Histone 3 lysine 4 (H3K4) trimethylation (1a) triggers incorporation of serotonin at H3Q5 forming H3K4me3Q5ser (2a). TGM2 incorporates dopamine at H3Q5 depositing H3Q5dop (2b). Enzyme(s) for reversal of both H3K4me3Q5ser and H3Q5dop to H3K4me3Q5 and H3Q5 respectively are yet to be deciphered

Figure 2. METABOLIC: Monoaminylation of proteins at glutamine (Q) residues are well established (reaction shown in figure 1.) and play crucial roles in signal transduction pathways regulating cellular metabolism and homeostasis. Monoamine chemicals like, histamine, serotonin and dopamine are important neurotransmitters. G-protein signaling is modulated by: histaminylation, Vowinckel et al., 2012 (81), and serotonylation, Walther et al., 2003 (99). TGM2 catalyzes inactivation of glyceraldehyde 3-phosphate dehydrogenase and alpha-ketoglutarate dehydrogenase in CAG-repeat diseases, Cooper et al., 1997 (85, 86). TGM2 mediated transglutamination inactivates mitochondrial aconitase in the Huntington patients brain, Kim et al. 2005 (88).
EPIGENETIC: Modification of Q residues in histone tails influencing gene expression in vivo is emerging. Histone 3 glutamine 5 (H3Q5) dopaminylation (H3Q5dop) by TGM2 in the VTA region regulates gene expression in VTA neurons, Lepack et al., 2020 (68). This is very exciting discovery in epigenetics, molecular biology and neurobiology that establish neurotransmission dependent and independent roles for nuclear in the reward system (68, see also 104). Serotonylation of histone H3 at glutamine 5 (H3Q5ser) augments RNAPII catalyzed gene expression, facilitating binding of TFIID4 with the combinatorial H3K4me3Q5ser sites, Farrelly et al., 2019 (97). The processing of H3K4me3 is executed by MLL and SET1 family proteins (100, 101). The functional insights of H3K4me3Q5ser deposition in human embryonic stem cells, serotonergic neurons, developing mouse brain and cultured serotonergic cell is enhanced expression diverse array of genes require for cellular differentiation and signaling (97, see also 102, 103). Fibrillarin catalyse methylation of human histone H2A at Q 104 (H2AQ104me) enhances the transcription of rDNA by RNAPI. S-Adenosylmethionine (SAM) is the cofactor which donates the –CH3 group and converted to SAH (S-Adenosylhomocysteine).



Scheme 1.

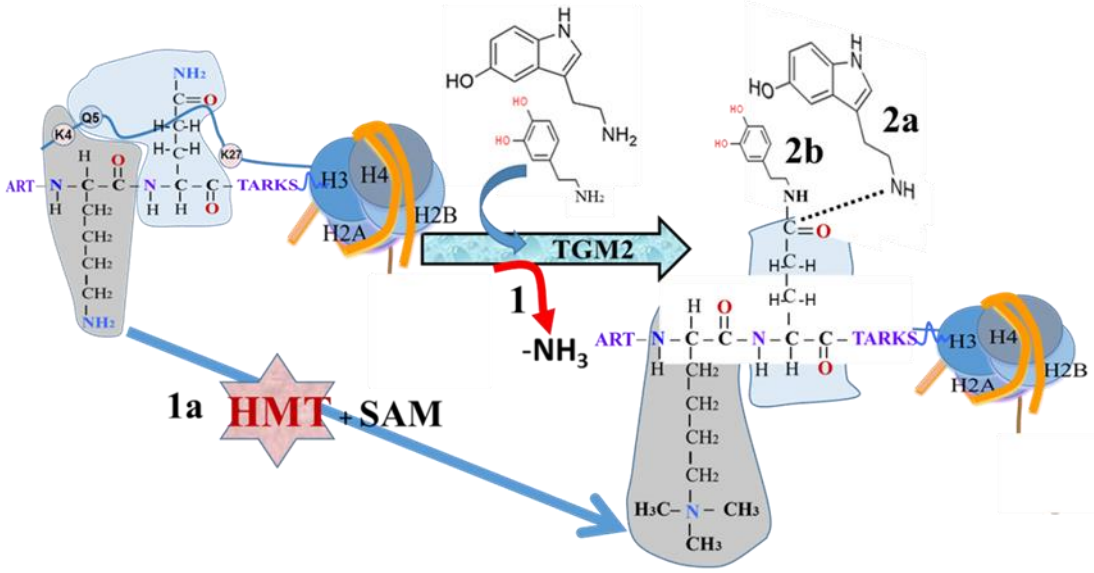


Figure 1.

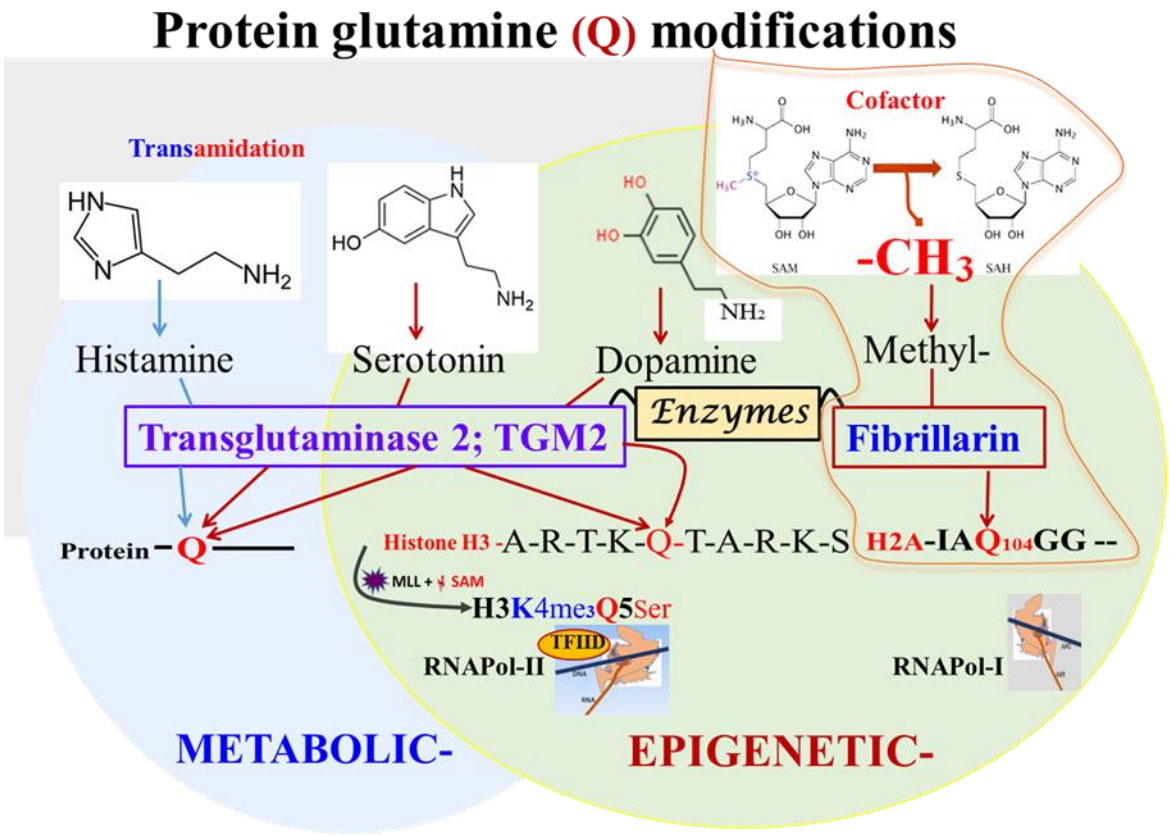


Figure 2.

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