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Review article

The effects of proteasome on baseline and methamphetamine-dependent dopamine transmission

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ABSTRACT

The Ubiquitin Proteasome System (UPS) is a major multi-catalytic machinery, which guarantees cellular proteolysis and turnover. Beyond cytosolic and nuclear cell compartments, the UPS operates at the synapse to modulate neurotransmission and plasticity. In fact, dysregulations of the UPS are linked with early synaptic alterations occurring in a variety of dopamine (DA)-related brain disorders. This is the case of psychiatric conditions such as methamphetamine (METH) addiction. While being an extremely powerful DA releaser, METH impairs UPS activity, which is largely due to DA itself. In turn, pre- and post- synaptic neurons of the DA circuitry show a high vulnerability to UPS inhibition. Thus, alterations of DA transmission and UPS activity are intermingled within a chain of events underlying behavioral alterations produced by METH. These findings, which allow escaping the view of a mere implication of the UPS in protein toxicity-related mechanisms, indicate a more physiological role for the UPS in modulating DA-related behavior. This is seminal for those plasticity mechanisms which underlie overlapping psychiatric disorders such as METH addiction and schizophrenia.

1. Introduction

The ubiquitin-proteasome system (UPS) is a major multi-catalytic machinery that evolution has preserved to ensure cellular proteostasis from bacterial species up to eukaryotic cells (Darwin, 2009; Humbard and Maupin-Furlow, 2013). Protein degradation by the UPS begins with the ATP-dependent covalent attachment of ubiquitin chains to the target protein. This step is accomplished by a series of catalytic reactions which are carried out by three enzymes, namely ubiquitin-activating (E1), ubiquitin-conjugating (E2) and ubiquitin-ligase (E3). Once tagged, proteins are recognized by the proteasomal 26S (P26S) multimeric complex, which is formed by a catalytic core (P20S) and two regulatory subunits (P19S, also known as PA700) capping the ends of P20S (Livneh et al., 2016). P19S binds the poly-ubiquitin chain and cleaves it from the substrate. In this way, the unfolded substrate enters the P20S to be degraded by chymotrypsin-like, trypsin-like and caspase-like proteases. When UPS activity is impaired, early synaptic alterations occur as it was shown in dopamine (DA)-related neurodegenerative disorders (Fornai et al., 2003; Seo et al., 2004; Bennett et al., 2007; Wang et al., 2008; McNaught et al., 2010; Chen et al., 2011; Bentea et al., 2017). In addition to a well-established role in removing harmful misfolded/oxidized cytoplasmic proteins, a key function for the UPS in modulating neurotransmission has rapidly emerged in the last decade (Hegde, 2010). In fact, the UPS operates locally at both pre- and post-synaptic sites to degrade innumerous synaptic- and plasma membrane-associated proteins. In this way, the UPS guarantees the turnover of proteins encompassing those associated with synaptic vesicles (SV) and G-protein coupled neurotransmitter receptors (GPCR) (Speese et al., 2003; Alonso and Friedman, 2013). Thus, the UPS may act as a key modulator of synaptic plasticity by regulating the magnitude and duration of presynaptic neurotransmitter release. At the same time, it operates post-synaptically by tuning GPCR activation, de/sensitization, and subsequent intracellular signaling cascades. In turn, this translates into epigenetic and transcriptional events which provide the molecular basis for persistent behavioral changes. This rules out a mere implication of UPS in mechanisms underlying protein toxicity and neuronal degeneration while pinpointing a physiological role of UPS in regulating baseline synaptic transmission. In this way, the UPS is expected

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to be involved in the physiological machinery producing natural behavior, while its impairment should result in long-lasting behavioral alterations which may be independent of neurodegeneration. In fact, *in vivo* studies report early psychomotor and cognitive changes following UPS inhibition (Romero-Granados et al., 2011; Bentea et al., 2015). Similarly, psychiatric and behavioral disorders such as methamphetamine (METH) addiction and schizophrenia are associated with various UPS dysfunctions (Fornai et al., 2004; Lazzeri et al., 2007; Moszczynska and Yamamoto, 2011; Lin et al., 2012; Breen et al., 2016; Bousman et al., 2010a, b; Rubio et al., 2013; Scott et al., 2016). METH addiction refers to the compulsive pattern of drug-taking behaviors, which are induced by reiterated intake/administration of METH in both human abusers and experimental models (Robinson and Berridge, 2000). These behavioral abnormalities underlie long-lasting neuronal adaptations which render reward and motivation brain systems hypersensitive to drug and drug-associated stimuli. In this way, repeated intake/administration of METH produces a phenomenon known as behavioral sensitization, which besides addiction includes behavioral abnormalities such as drug craving, relapse, and psychotic episodes (Homer et al., 2008). The biochemical basis underlying this phenomenon is largely due to altered synaptic transmission at the level of monoamine, mainly DA, systems. In fact, as measured by brain dialysis, reiterated METH administration produces peaks and drops of extracellular DA concentration, which surpass at large the slight oscillations produced by physiological DA release (Battaglia et al., 2002; Lazzeri et al., 2007). This, in turn, produces an abnormal pulsatile stimulation of post-synaptic DA receptors (DR) to trigger non-canonical transduction pathways, which alter the response of postsynaptic neurons (Calabresi et al., 2007; Surmeier et al., 2010; Limanaqi et al., 2018a). This occurs mostly within the striatum, where DA terminals are abundant, though specific limbic regions and isocortical areas are involved as well (Volkow and Morales, 2015). It is remarkable that METH, while being a powerful DA releaser also produces UPS inhibition (Fornai et al., 2003, 2004, 2006; Lazzeri et al., 2006, 2007; Moszczynska and Yamamoto, 2011; Lin et al., 2012). This indicates that DA transmission and UPS activity are interconnected to underlie behavioral control, which is altered when either DA release and/or UPS activity are altered. This is strengthened by growing evidence indicating various roles of UPS at synaptic level such as (i) intersecting with secretory pathways to modulate DA release; (ii) determining the fate of post-synaptic DRs; (iii) altering intracellular kinases and (iv) affecting transcription factors and epigenetic enzymes in post-synaptic neurons. In the present review, we analyze evidence about the involvement of UPS in modulating DA transmission in baseline conditions and following METH administration, at both pre- and post-synaptic levels. Understanding the molecular dynamics of UPS-mediated modulation of DA neurotransmission may provide novel insights into overlapping synaptic alterations, which occur in METH addiction and psychiatric disorders such as schizophrenia (Laruelle, 2000; Volkow, 2009).

2. Ubiquitin-proteasome system intersecting with secretory pathways at presynaptic sites

Neurotransmitter release entails coordinated molecular events underlying the SVs cycle, ranging from SV biogenesis, axonal trafficking and, once at the active zone, SV exocytosis, endocytosis as well as recycling and/or degradation (Südhof, 2004; Rizzoli, 2014). This cycle is finely tuned by interactions between secretory/trafficking pathways and degradative machineries, which are starting to shape as a single system operating locally at the synapse (Bingol and Sheng, 2011; Limanaqi et al., 2018b). In general, the UPS represents the first line quality control machinery by targeting and degrading misfolded or unfolded proteins, which are inappropriately processed within the endoplasmic reticulum (ER) and Golgi. This is key at synaptic level, since these organelles directly generate SVs by supplying them with membranes and proteins (Nirenberg et al., 1996; Hannah et al., 1999). In addition, ER and Golgi source endosomes, autophagosomes and lysosomes (Bento et al., 2016), which also take part in SV cycle and DA release (Hernandez et al., 2012; Limanaqi et al., 2018b). In fact, at the presynaptic terminal, a high and specialized turnover rate occurs for proteins underlying the SV cycle. This is provided by UPS, which directly contributes to generating the pools of SVs and the rate of neurotransmitter release (Speese et al., 2003; Willeumier et al., 2006; Wentzel et al., 2018). To accomplish such a task UPS interacts with the secretory machinery by mediating the sorting and degradation of those membrane proteins recruited by SVs. UPS continues to operate during further steps concerning endo-lysosome membrane fusion (Van Kerkhof et al., 2001; Kleijnen et al., 2007).

i The UPS plays a key role in mechanisms which sort endocytosed SV-cargoes for autophagy (ATG)-lysosomal degradation, namely the clathrin-dependent pathway and the endosomal sorting complex required for transport (ESCRT) (Ravikumar et al., 2010; Sheehan et al., 2016). In both mechanisms, site-specific ubiquitination of SV membrane proteins may serve as a signal for either UPS-mediated degradation or for SV-cargo endocytic internalization and subsequent recognition by clathrin- and ESCRT-sorting machineries (Piper and Lehner, 2011).

ii The UPS modulates the activity of Rab GTPases (GTP bound Ras proteins in brain), which are involved in all cell-trafficking mechanisms. In detail, the UPS regulates the GDP/GTP conversion and effector recruitment of Rab5, Rab7 and Rab35 (Mattera et al., 2006; Kleijnen et al., 2007; De Luca et al., 2014; Villarroel-Campos et al., 2016; Shin et al., 2017). These Rabs are crucial for SV endocytosis by promoting endo-lysosomal and ATG membrane fusion. In particular, Rab5 and Rab35 drive sorting of endocytosed SVs for ATG-lysosomal degradation (Sheehan et al., 2016). When focusing at the level of DA synapse, such an overlap between pathways which lead protein degradation and neurotransmission is magnified. For instance, dysfunctions in the endocytic presynaptic protein Endophilin-A disrupt both ATG, UPS and SV-cycle (Murdoch et al., 2016). Endophilin-A is downregulated by METH (Bosch et al., 2015), suggesting that such a cross-talk between secretory and degradative systems is crucial for DA neuronal activity.

iii The UPS degrades and recycles vesicle-associated transmembrane proteins already during axonal route towards the site of neurotransmitter release. In fact, in their route towards nerve endings, functional and assembled P26S particles associate with vacuolar organelles including precursor SVs, Golgi-derived vesicles, lysosomes and mitochondria (Otero et al., 2014). Such a coordinated moving of P26S along with vesicular organelles depends on the very same molecular machinery, namely the microtubule protein motor-kinesin-1. This is shown by ablation of KIF5B subunit of motor-kinesin-1, which occludes both P26S and SV axonal transport while producing local aggregation of active P26S co-localized with synaptosomal poli-ubiquitinated proteins such as synaptophysin and synaptotagmin (Otero et al., 2014). Nonetheless, other cell compartments are also involved in proteasome transport. This may be the case of ATG vacuoles, which also regulate DA release (Hernandez et al., 2012). In fact, it was recently demonstrated that P20S particles co-localize with LC3-positive ATG vacuoles within a novel organelle named “autophagoproteasome” (Lenzi et al., 2016). Such a merging is downregulated by METH while it can be rescued via inhibition of the mammalian Target Of Rapamycin (mTOR) (Lazzeri et al., 2018). This is in line with recent studies demonstrating that mTOR inhibition also potentiates UPS in addition to ATG (Zhao et al., 2015). Again, as for SVs and P26S, the axonal transport of ATG vacuoles in the presynaptic compart is coordinated by kinesin-1 (Stavoe et al., 2016). The activation of kinesin-1 requires the UNC51-like kinase (the *C.elegans* orthologue of the mammalian ULK1/Atg1 complex), which in turn, is negatively regulated by mTOR. Remarkably, mTOR inhibition also counteracts

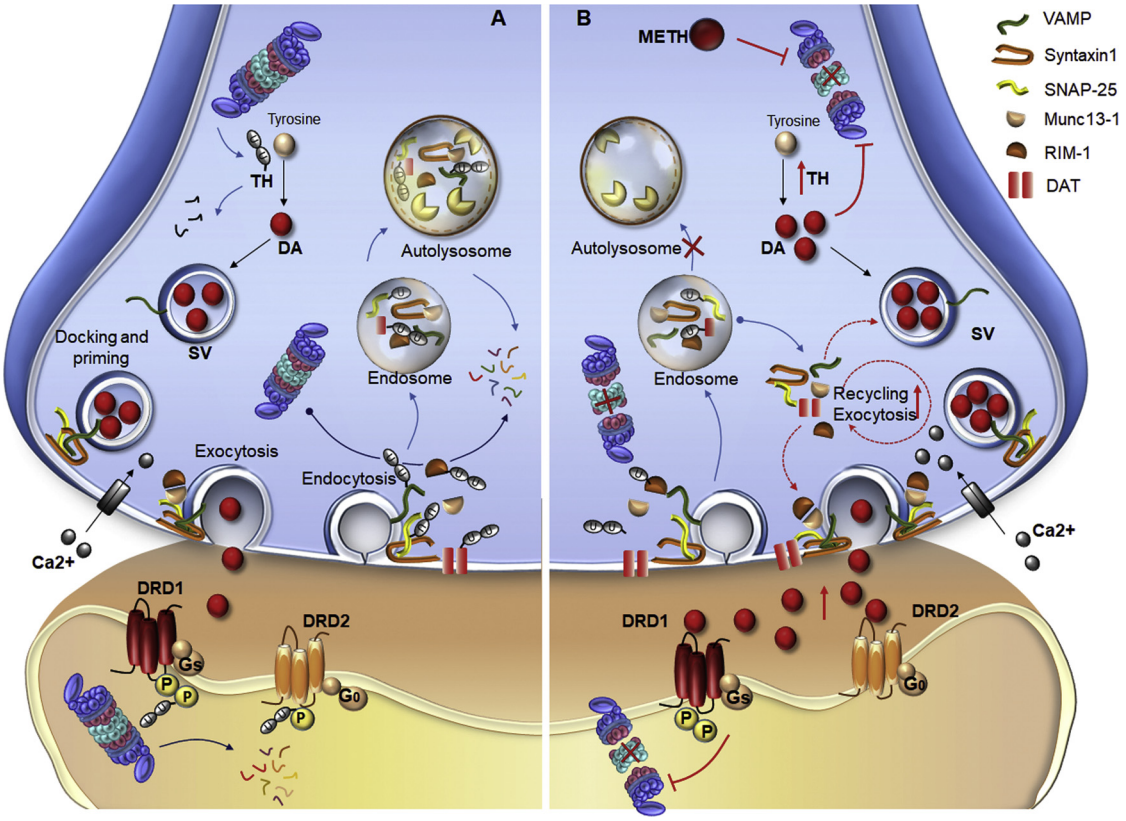

Fig. 1. Proteasome modulates DA release. The present figure roughly summarizes the roles of UPS in DA release during physiological conditions **(A)** and following METH **(B).**

In baseline conditions **(A)**, the UPS restrains DA synthesis by degrading TH enzyme. Once filled with DA, SVs dock and prime to the active zone where SNARE complex assembly together with Munc13-1 and RIM-1 foster DA release via Ca2+ driven-exocytosis. The UPS restrains DA release by ubiquitinating and targeting SNARE (VAMP, Syntaxin-1, SNAP-25) as well as Munc13-1 and RIM-1 for endosomal internalization and degradation. This occurs either via direct degradation by the UPS or by the ATG-lysosomal machinery after fusion with endosomes. Such a mechanism is seminal to limit the rapid endosomal recycling of these proteins back to the plasma membrane, which would otherwise favor subsequent rounds of DA release. In these conditions, post-synaptic DRs (DRD1-like and DRD2-like) are physiologically stimulated. At the post-synaptic side, the UPS is functionally operating to degrade these same DRs.

Administration of METH disassembles UPS and inhibits its activity **(B)**. This contributes to raising the level of newly synthesized DA. In turn, increased levels of intracellular DA fuel UPS dysfunction. Thus, the UPS cannot provide degradation of SNAREs, Munc13-1 and RIM1, which recycle back to the plasma membrane to prevent de-priming of SVs and boost DA release. This is further amplified by the increased Ca2+ influx, which occurs when UPS is inhibited. Again, under the effects of METH and UPS inhibition, the direction of the DAT is reversed and its degradation is occluded. In turn, increased levels of Syntaxin-1, which binds to the DAT at the plasma membrane, contribute to strengthening DA release via both exocytosis and efflux. These effects translate into peaks of extracellular DA concentration, which over-stimulate postsynaptic DRs. At this level, abnormal stimulation of DRD1 impairs UPS, which leads to occlude degradation of DRs.

METH-induced behavioral sensitization (Huang et al., 2018).

These pieces of evidence underlining the effective involvement of the UPS in several steps of the secretory pathway, make it mandatory to dissect those molecular events occurring at the synapse which may link UPS dysfunctions with altered DA release and altered behavior.

3. Ubiquitin-proteasome system and dopamine release

Defects in UPS machinery are reported in both human METH abusers and experimental models (Lazzeri et al., 2006, 2007; Moszczynska and Yamamoto, 2011; Lin et al., 2012; Breen et al., 2016). The mechanisms of action through which METH impairs UPS activity are largely dependent on DA itself. In fact, similarly to METH, in vitro perfusion of striatal slices with DA or in vivo administration of DA agonists, disassembles P26S and produces a dose- and time-dependent decrease in UPS activity (Keller et al., 2000; Zhou and Lim, 2009; Berthet et al., 2012; Barroso-Chinea et al., 2015). Dysfunctional UPS following DA over-exposure is likely to be due to the joined contribution of oxidative DA-derived by-products and non-canonical biochemical cascades triggered by abnormal stimulation of post-synaptic DRs (Keller et al., 2000; Zhou et al., 2009; Berthet et al., 2012; Barroso-Chinea et al., 2015), which will be dealt with in paragraph 4. In baseline conditions, the UPS is essential to restrain DA synthesis and release. In fact, acute inhibition of UPS mimics the mechanisms of action of METH by producing an early increase in tyrosine hydroxylase (TH) levels, the rate-limiting enzyme for DA synthesis (Congo Carbajosa et al., 2015) and an early potentiation of DA release, which occurs along with behavioral alterations (Subramaniam et al., 2014; Konieczny et al., 2016). Prolonged UP inhibition leads to a progressive loss of DA synaptic efficacy and striatal DA depletion while producing psychomotor alterations (Fornai et al., 2003; Bentea et al., 2015; Lillethorup et al., 2018). Thus, a feedback loop between progressive DA hyperactivity and impaired UPS is likely to fuel the accumulation of specific synaptic proteins which in turn, boost DA release and UPS dysfunction. This is confirmed by several studies demonstrating a rapid strengthening of neurotransmission following UPS inhibition. This is bound to an increased SV pool and impaired degradation of a variety of SV-associated proteins involved in docking, priming and exocytosis (Aravamudan and Broadie, 2003; Speese et al., 2003; Willeumier et al., 2006; Yao et al., 2007; Wentzel et al., 2018). Consistently, *in vivo* METH administration persistently alters gene expression and protein levels of SV-associated components, which are substrates of UPS degradation (Isao and Akiyama, 2004; Bosch et al., 2015; Krasnova et al., 2016). This is the case of Soluble N-

ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex proteins, as well as SNARE accessory proteins such as Munc18, Munc13-1 and Rab3 interacting molecule (RIM-1), which modulate synaptic plasticity by fostering SNARE complex assembly and SV exocytosis (Kaeser and Südhof, 2005; Südhof, 2013; He et al., 2017). Intriguingly, alterations of these proteins have been also linked to schizophrenia (Katrancha and Koleske, 2015), providing a further overlap between synaptic alterations occurring in METH addiction and schizophrenia.

3.1. Proteasome, SNARE proteins, D2 dopamine auto-receptors, and dopamine release

SV exocytosis is preceded by docking and priming of SVs to the active zone, which requires the assembly of the SNARE complex. This, in turn, consists of the vesicular synaptobrevin/VAMP-2 protein, which binds the target membrane proteins SNAP-25 and Syntaxin-1 to mediate membranes fusion. Once assembled, the SNARE complex interacts with calcium (Ca2+) channels, which is key to trigger exocytosis and neurotransmitter release. Synaptobrevin and SNAP-25 are targeted by ubiquitination, suggesting that UPS mediates either direct degradation or ATG-lysosomal sorting of these proteins (Ma et al., 2005; Wang et al., 2008; Uytterhoeven et al., 2011; Sharma et al., 2011; Sheehan et al., 2016). Contrariwise, Syntaxin-1 is selectively degraded by the UPS in DA neurons (Chin et al., 2002). Compelling evidence indicates that application of DA to striatal slices produces *per se* a 4-fold increase in SNARE complex assembly, which can be reversed by the DA-antagonist haloperidol (Fisher and Braun, 2000). Enhanced SNARE-complex assembly produces a dramatic increase in neurotransmitter release (Acuna et al., 2014), which suggests that potentiated SNARE assembly and enhanced DA release may, in turn, be coupled with impaired UPS activity as it does occur following METH (Fig. 1). In fact, increased SNAP-25 and Syntaxin-1 levels have been detected following METH administration (Isao and Akiyama, 2004; Bosch et al., 2015; Krasnova et al., 2016). The degradation and fine turnover of SV proteins involved in exocytosis are key for those DA-dependent behavioral alterations induced by METH. In fact, these are due to a combined mechanism consisting of enhanced exocytosis and decreased uptake via inhibition of the plasma membrane DA transporter (DAT) (Daberkow et al., 2013). METH also reverts the DAT to enhance DA efflux from nerve terminals (Fleckenstein et al., 2007; Sulzer, 2011). Remarkably, Syntaxin-1 also regulates synaptic DA release via binding to the DAT, which besides retaking up extracellular DA, also generates voltage-gated currents that regulate neuronal excitability and DA release (Carvelli et al., 2008). Noteworthy, METH increases the binding of Syntaxin-1 to the DAT, and in turn, Syntaxin-1 overexpression dramatically enhances METH-induced DA release via DAT reversal (Binda et al., 2008). This is in line with studies showing that, as a rapid response to both METH and DA administration, a SNARE-dependent increase in DAT recycling to the plasma membrane occurs (Furman et al., 2009). Apart from degrading SNARE proteins, the UPS also tunes the endocytic internalization of DAT, which can be either addressed to degradation or recycled back to the plasma membrane. Amphetamines down-regulate DAT, which, independently by ubiquitin is sequestered and stored into recycling endosomes (Saunders et al., 2000; Hong and Amara, 2013). While further studies are needed to elucidate in-depth molecular mechanisms, these pieces of evidence suggest that an impairment of UPS by METH or DA *per se* may affect DA transmission even via mechanisms which regulate the density of DAT on nerve terminals.

Among the various mechanisms through which UPS modulates baseline and METH-induced DA release, an interaction with presynaptic DA auto-receptors may be involved as well. Presynaptic D2-like DRs placed on midbrain DA neurons modulate DA neuron firing, DA synthesis, DA vesicular storage, and DA release through a negative feedback (Mercuri et al., 1992; Ford, 2014). While both D2DRs and D3DRs are present on midbrain DA neurons, the vast majority of auto-feedback inhibition is thought to be mediated by D2DRs. METH administration reduces the ability of D2DRs to inhibit DA release, which contributes to augment DA release induced by METH (Kamata and Rebec, 1984; Seutin et al., 1991; White and Wang, 1984; Schmitz et al., 2001; Nimitvilai and Brodie, 2010; Calipari et al., 2014). This occurs through several mechanisms where UPS is implicated. For instance, it was recently shown that D2 auto-receptors physically interact with DAT to recruit it to the plasma membrane and potentiate its activity in taking-up extracellular DA (Lee et al., 2007; Su and Liu, 2017). Such a D2DR-DAT coupling appears to be necessary for the molecular mechanisms of METH in downregulating D2DRs monomers while inducing the overexpression of D2DRs dimers, similarly to what occurs in schizophrenia (Wang et al., 2010). Disrupting the D2DR-DAT coupling prevents the effects of both METH (Wang et al., 2010) and DA overload (Su and Liu, 2017). Thus, under the effects of METH, an abnormal D2DRs activity may add on the abnormal DA release and DAT internalization which cannot be properly regulated by UPS through SNARE-dependent mechanisms. Again, the D2DR-DAT complex is regulated and stabilized by protein kinase C (PKC), which in baseline conditions enhances D2DR desensitization to decrease presynaptic D2DR activity and promote neurotransmitter release (Luderman et al., 2015). PKC is remarkably increased by METH, and is it implicated in METH-induced potentiation of synaptic DA release via DAT phosphorylation and D2DR downregulation, and also in METH-induced oxidative stress and UPS inhibition (Luderman et al., 2015; Shin et al., 2019; Lin et al., 2012). Recent studies suggest that METH downregulates D2DR activity by abolishing the interaction between D2DR and Gαi/o-proteins (Calipari et al., 2014). In fact, METH increases the amount and activity of the regulator of G-protein signaling (RGS), which in turn downregulates the activity of D2DRs (Calipari et al., 2014). Remarkably, RGS transcription, protein levels and function are tightly coupled by UPS degradation (Xie et al., 2009; Kanai et al., 2017). These findings further support the hypothesis that METH-induced downregulation of both D2DRs and UPS may be part of the same chain of events leading to abnormal DA release which underlies both addictive behavior and schizophrenia.

3.2. Proteasome and accessory proteins involved in synaptic vesicle exocytosis

To complete SVs fusion, SNARE proteins require the specialized proteins complexin and synaptotagmin along with accessory factors such as Munc18-1, Munc13-1 and RIM-1. Complexin binds to partially assembled SNARE complex during priming and enables synaptotagmin to sense intracellular Ca2+ increase. At the active zone Munc13 forms a ternary complex with Rab3 and RIM-1 in order to prime SVs in close proximity to Ca^{2+} channels and ready them for release (Südhof, 2013). Munc13-1 also co-chaperones SNARE complex assembly to facilitate exocytosis by opening the “closed” conformation of Syntaxin-1, which is maintained by Munc18-1 (Ma et al., 2013). The UPS is key to degrade Munc13-1 and RIM-1, thus facilitating de-priming of SVs, which otherwise is impeded by these proteins. This leads to tuning down neurotransmitter release, which would otherwise occur persistently (Aravamudan and Broadie, 2003; Speese et al., 2003; Yao et al., 2007; Jiang et al., 2010; Fig. 1). The role of RIM1 and Munc13-1 in synaptic transmission is underscored by several experimental models and clinical cases featuring genetic ablation and “gain of function” mutations (Lipstein et al., 2017; Haws et al., 2012). Intriguingly, both these opposite conditions lead to severe synaptic dysfunctions producing movement-, neurodevelopmental- and psychiatric- disorders, which underlines the key role of Munc13-1 and RIM-1 in neurotransmission. The mechanisms of action of Munc13-1 specifically within DA neurons have not been investigated yet. However, there is some indirect evidence based on diacylglycerol (DAG) levels. DAG levels increase following DA exposure (Liu et al., 2003) while enhancing Munc13-1 activity (Betz et al., 1998), which suggests a possible mechanism linking DA activity with an impaired turnover of Munc13-1 by the UPS. This is

further supported by findings showing that Munc13 is activated by DAG via protein kinase A (PKA) - and phospholipase C (PLC) - dependent signal transduction pathways (Aravamudan and Broadie, 2003), which are all coupled to DRs. In addition to Munc13-1 degradation, the UPS is key for the removal of the SV-related dystrobrevin-binding protein 1 (Dysbindin-1), which is implicated in METH-addiction, and also in schizophrenia (Kishimoto et al., 2008; Hikita et al., 2009; Wentzel et al., 2018). Dysbindin-1 fosters SV fusion and neurotransmitter release by interacting with several SNARE-associated proteins. Recent findings demonstrated that UPS inhibition increases presynaptic Ca^{2+} influx as well as Dysbindin-1 and RIM-1 expression while potentiating neurotransmitter release (Wentzel et al., 2018).

3.3. Proteasome and cytomatrix active zone proteins

Beyond regulating SV exocytosis, RIM-1 is a component of the cytomatrix at the active zone, the primary site of DA release (Daniel et al., 2009). The organization of the active zone is carried out by RIM-1 together with the scaffolding proteins Bassoon and Piccolo. An increase in Bassoon and Piccolo levels has been detected in striatal synaptosomes from METH-treated animals, suggesting that they are implicated in increased SV production and excessive DA transmission induced by METH (Cen et al., 2008; Bosch et al., 2015). Interestingly, Bassoon and Piccolo inhibit UPS at the level of an E3 ligase and slow down SV protein degradation (Waites et al., 2013). This is in line with previous findings demonstrating that even early steps of protein ubiquitination are crucial to restrain neurotransmission in the same way as UPS-dependent degradation (Rinetti and Schweizer, 2010). In summary, these pieces of evidence converge in that UPS-mediated targeting and degradation of synaptic proteins is essential to tune neurotransmitter release and guarantee presynaptic homeostatic plasticity.

4. Ubiquitin-proteasome system at post-synaptic neurons of the dopamine circuitry

At post-synaptic sites, the UPS modulates synaptic plasticity (Ehlers, 2003; Dong et al., 2014; Hegde, 2017). In particular, the UPS targets both D1- and D2-like DRs as well as glutamate N-Methyl-D-aspartate (NMDA) and Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors for endocytic internalization and degradation (Kim, 2008; Rondou et al., 2008; Alonso and Friedman, 2013; Peeler et al., 2017). This occurs via ubiquitin targeting of either phosphorylated G-proteins coupled to DRs or beta-arrestin 1 and 2 (β-arr1 and β-arr2) proteins, which work as adaptors for the internalization and degradation of GPCRs by the UPS (Shenoy and Lefkowitz, 2003). In the case of METH, due to the massive release of DA, receptor degradation which follows-up receptor internalization contributes to desensitization and prevents the transduction of non-canonical downstream cascades, which otherwise may lead to plasticity and addiction (Fig. 2). Thus, it is expected that following UPS inhibition or massive DA release (i.e. following METH), non-canonical pathways are recruited in post-synaptic neurons. In fact, UPS tones down key messengers of DRs-dependent non-canonical cascades. This is seminal since these DA-dependent transduction pathways translate into long-lasting behavioral alterations. As we shall see in the present paragraph, while triggering these non-canonical cascades *per se,* METH also alters UPS activity, which in turn may potentiate the switch in DRs signaling towards maladaptive plasticity.

4.1. Proteasome and D1-like dopamine receptor transduction cascades

Stimulation of D1-like (D1 and D5) DRs is coupled with $G_s/_{olf}$ proteins, which activate adenylate cyclase (AC), cyclic adenosine monophosphate (cAMP) and PKA pathway (Neve et al., 2004; Cadet et al., 2010). During physiologic DA stimulation, D1-like DR-induced increase in AC activity is balanced by the inhibitory effects of D2-like (D2, D3 and D4) DRs. This is key to maintain physiologic levels of cAMP and PKA, which in turn has a broad array of targets (Greengard, 2001). These include DA- and cAMP-regulated phosphoprotein (DARPP-32), voltage-gated ion channels, and NMDA and AMPA glutamate receptors. Other proteins such as cyclin-dependent kinase 5 (CDK5), counterbalance the effects of PKA upon DARPP-32. In turn, this allows the activation of Phosphatase Protein 1 (PP1), which can surveil phosphorylation levels of all PKA targets. It is remarkable that the UPS regulates the levels of AC, cAMP, and PKA and in turn, these components modulate UPS activity within a feedback regulatory loop (Willeumier et al., 2006; Rinaldi et al., 2015). Such a mechanism is key to balance the levels of AC, cAMP, and downstream kinases, which are indeed non-canonically operating to serve METH-induced behavioral sensitization (Cole et al., 1995; Guigoni and Bezard, 2009; Bosse et al., 2015; Limanaqi et al., 2018a; Fig. 2). In detail, following METH administration, an abnormal stimulation of D1DR over-activates AC, which enhances the production of cAMP and over-activates PKA to trigger a non-canonical transduction pathway. A failure in UPS activity enhances AC (Naviglio et al., 2004), cAMP-PKA (Dong et al., 2008), and the non-receptor striatal-enriched phosphatase (STEP), which acts a mediator of the effects of PKA-phosphorylated DARPP-32 (Kurup et al., 2010). Thus, an increase of PKA-phosphorylated DARPP-32 leads to PP1 inhibition. In this case, CDK5 cannot face the massive PKA activation to counterbalance such an effect. This leads to a feedback loop in which an increase in CDK5 fuels the effects of PKA to sustain METH-induced behavioral sensitization (Nishi et al., 2000; Limanaqi et al., 2018a). Remarkably, CDK5 is an additional target of UPS degradation (Takasugi et al., 2016), which supports the role of UPS dysfunctions in behavioral sensitization. Thus, all PKA targets, including NMDA and AMPA receptors are abnormally phosphorylated and activated, which is magnified upon UPS inhibition, since these receptors are both UPS substrates. In addition, such a cascade leads to increased levels of extracellular signal–regulated kinases 1/2 (ERK1/2) (Valjent et al., 2005), where both DA- and glutamate-induced signaling pathways converge to promote phosphorylation of cytosolic and nuclear UPS substrates, including transcription factors and epigenetic enzymes. These encompass: i) cAMP-responsive element binding protein (CREB) (Upadhya et al., 2004) ii) Nuclear factor kB (Nf-kB); iii) activator protein 1 (AP) family proteins such as c-Fos and c-Jun (Stancovski et al., 1995; Hershko and Ciechanover, 1998); and iv) histone and DNA epigenetic modifying enzymes (Bach and Hegde, 2016; Scott et al., 2014). When the UPS is occluded under the effects of METH or DA, these events converge to alter the responsivity of post-synaptic neurons to both DA and glutamate, inducing changes in the neuronal phenotype that could lead to addictive behavior. As far as it concerns D5DRs, it is generally accepted that these latter share agonists and antagonists with D1DRs, and are coupled to the same transduction cascades which are elicited by D1DRs. Nonetheless, a few studies carrying out selective genetic ablation of D5DRs uncovered novel effects related with either METH administration or UPS. In detail, METH administered to D5DR knock-out mice produces enhanced locomotor activity and most remarkably, it increases DAT phosphorylation compared with wild-type animals (Hayashizaki et al., 2013). These effects are prevented by DAT blockade, suggesting a yet unexplored role of D5DRs in potentiating METH-induced DA release via DAT regulation (Hayashizaki et al., 2013). Again, by using antisense oligonucleotides selective for D5DRs, it was shown that D5DRs but D1DRs, are able to induce UPS-dependent degradation, though this was explored in the context of autonomous-related effects of DA (Li et al., 2008; Gildea et al., 2008).

Again, D5DRs act as key regulators of neurogenesis by inhibiting glycogen synthase kinase 3 beta (GSK3β) pathway, and by increasing brain-derived neurotrophic factor (BDNF) and GAD67, which are dysregulated in both METH-induced addiction and schizophrenia (Perreault et al., 2013; Ren et al., 2015). The effects of BDNF are critical within the nucleus accumbens shell, where BDNF modulates the expression of a variety of glutamate and DA receptors, and mostly D3DRs,

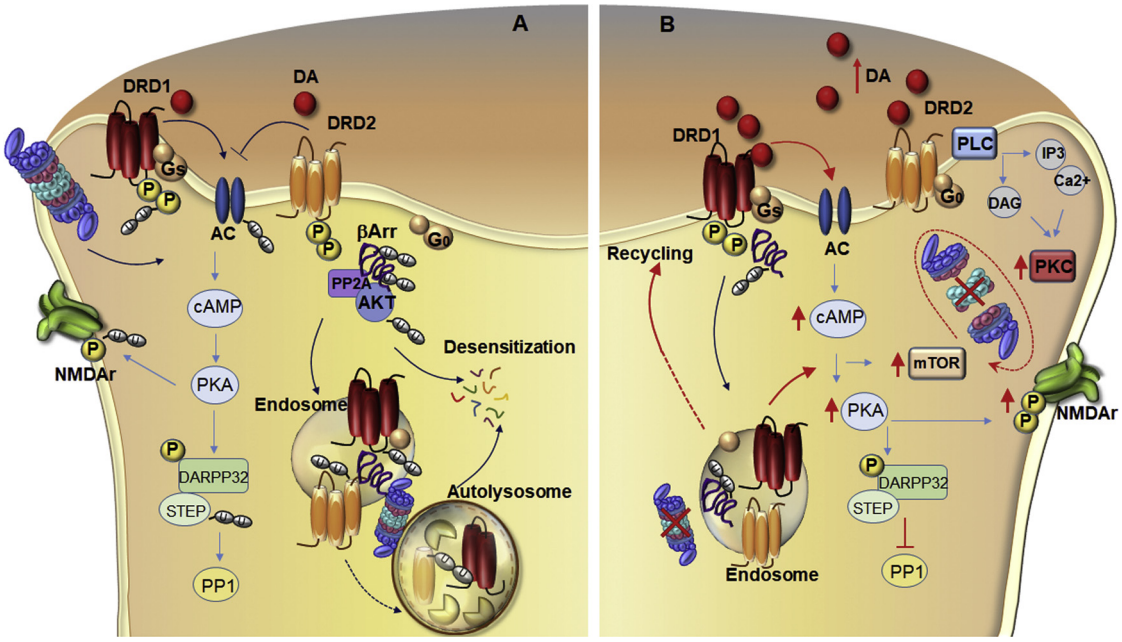

Fig. 2. Proteasome modulates DA receptor-dependent biochemical cascades.
The figure roughly summarizes the roles of UPS at post-synaptic level under baseline conditions of DA release **(A)** and following METH **(B)**.
In physiological conditions of DA stimulation **(A)**, the UPS operates at post-synaptic sites to degrade D1- and D2-like receptors (DRD1 and DRD2, respectively) by targeting either phosphorylated G-proteins or β-Arr complex, which includes PP2A and AKT. This is key for DRs desensitization, which follows their internalization within endosomes and subsequent degradation by either UPS or autolysosomes. The UPS also degrades AC, which is stimulated by DRD1. This is key to balance the levels of cAMP, PKA and its downstream targets DARPP-32 and NMDA glutamate receptors. Again, the UPS degrades NMDA glutamate receptors and the DARPP-32 effector STEP, which allows PP1 to surveil phosphorylation levels of PKA targets. In this way, the UPS guarantees canonical transduction of the cascades placed downstream of DRs.
Following the massive release of DA which is induced by METH **(B)**, abnormal stimulation of DRs contributes to impair UPS activity. In detail, DRD1 trigger an abnormal activation of AC, cAMP and PKA, which in turn over-activate mTOR and NMDA glutamate receptors. Both these events directly affect UPS activity. In addition, abnormal stimulation of DRD2s over-activates PLC and PKC, which again impairs UPS. In this way, DA and NMDA receptors degradation is occluded. This produces two effects: DRD1s transduce cAMP-PKA signaling even from the endocytic intermediate thus amplifying a non-canonical pathway where DARPP-32 inhibits PP1; in absence of degradation, DRs are rapidly recycled back to the plasma membrane to fuel both non-canonical biochemical cascades and UPS dysfunction. Therefore, METH-induced UPS inhibition is detrimental for those gene-expression changes, which sustain maladaptive plasticity and addiction.

to regulate DA-dependent behavioral sensitization (Guillin et al., 2001; Sokoloff et al., 2002). Remarkably, the molecular and behavioral effects of BDNF largely rely on UPS activity, which is seminal to degrade a key messenger implicated in BDNF-induced intracellular cascade, namely STEP61 (Saavedra et al., 2016). Again, in keeping with possible overlapping and divergent effects of D5DRs vs D1DRs, it is worth mentioning that both receptors are critical for striatal long-term potentiation (LTP) and depression (LTD), which are finely tuned by UPS. However, studies employing specific D5DR and D1DR knock-out models, suggest that DA stimulates different types of striatal neurons to induce either LTP or LTD depending on D5DRs or D1DRs (Centonze et al., 2003). In fact, D1DR stimulation mainly promotes LTP in spiny neurons through the PKA pathway, while D5DR stimulation promotes LTD in striatal nitric oxide-containing interneurons (Centonze et al., 2003). Apart from PKA mentioned above, nitric oxide also regulates UPS activity (Bal et al., 2017), and modulators of nitric oxide are being tested as a potential adjunct therapeutic strategy in both METH addiction and schizophrenia (Issy et al., 2018). Therefore, the UPS is deeply intermingled with the cascades placed upstream and downstream to a variety of DA receptors, though further studies are needed to elucidate the intricate molecular mechanisms linking UPS with each specific DA receptor in these disorders.

4.2. Overlap between non-canonical downstream pathways induced by METH and proteasome inhibition

As briefly mentioned in paragraph 3, abnormal DR stimulation inhibits UPS activity in post-synaptic neurons. This is suggested to depend mainly on D1DRs, since administration of a D1DR antagonist fully reverses UPS inhibition following over-exposure to DA agonists (Berthet et al., 2012; Barroso-Chinea et al., 2015). This suggests that a failure in UPS activity is induced by METH through abnormal activation of D1DR-dependent mechanisms (Fig. 2). In turn, this is expected to occlude the degradation of these same receptors, thus amplifying downstream signaling cascades which sustain addiction. In fact, when high extracellular DA concentrations are produced, endocytosed D1DRs continue to over-transduce D1-dependent signaling. This occurs even from the endocytic intermediate unless receptor degradation occurs (Kotowski et al., 2011). However, in this context UPS is inhibited. This is the case of METH which occludes the degradation of ubiquitinated β-arr (Fornai et al., 2008). On the other hand, such an effect is reversed by administration of D1DR antagonists. Again, UPS inhibition increases AC levels in a way which is reminiscent of METH administration (Naviglio et al., 2004). An increase in cAMP levels, in turn, hyper-activates mTOR (Kim et al., 2010). Activation of mTOR following agonist-induced D1DR stimulation also occurs via AKT (Wang et al., 2018), which is a substrate of UPS as well (Wu et al., 2011). In line with this, mTOR activation, through inhibition of UPS, enhances synaptic strength by activating the cAMP-PKA pathway and NMDA receptors (Dong et al., 2008, 2014). In fact, mTOR inhibition via rapamycin prevents such an effect (Tang et al., 2002; Cammalleri et al., 2003; Dong et al., 2008). These findings demonstrate how UPS activity is enhanced by mTOR inhibition, which prevents METH-induced behavioral sensitization (Huang et al., 2018).

4.3. Proteasome and D2-like dopamine receptors

Even mechanisms arising from D2-like DRs or D1-D2DR heterodimers, which are implicated in METH-addiction (Perreault et al., 2010; Beaulieu et al., 2011), may lead to UPS impairment. For instance, $G_{i/o}$-coupled D2DR and D1-D2 heterodimers trigger PLC activation, which in turn increases PKC levels via DAG, inositol 3 phosphate (IP3) and Ca2 + (Stanwood, 2008). Increased levels of PKC have been associated with METH-induced inhibition of UPS (Fig. 2), which in turn, can be rescued by PKC inhibitors (Liu et al., 2012). Activation of D2DR contributes to the expression of DA-dependent METH-induced behavioral alterations also via a signaling complex composed of β-arr2, AKT and protein phosphatase-2A (PP2A), which activates GSK3β (Beaulieu et al., 2004, 2005). Administration of lithium, a GSK3β inhibitor, antagonizes DA-related behavioral sensitization arising from such a cascade (Beaulieu et al., 2004). All the components of the complex which activates GSK3β, including β-arr2, AKT and PP2A are UPS substrates (Wu et al., 2011; Fan et al., 2018). Instead, the relationship between the UPS and GSK3β is yet controversial and poorly investigated. Nonetheless, similarly to METH and DA, inhibition of UPS has been shown to activate GSK3β, while GSK3β inhibition protects from UPS inhibition-induced toxicity (Choi et al., 2012; Jing et al., 2013). Furthermore, lithium blunts DA transmission by acting on other UPS targets placed downstream of DRs encompassing AC, IP3 and PKC (Malhi et al., 2013). Since lithium counteracts METH-induced behavioral sensitization as well as psychiatric disorders (Beaulieu et al., 2004; Malhi et al., 2013) it seems worthwhile to test the effects of lithium on UPS activity in specific experimental settings. This may disclose a broader effect of lithium on cell clearing pathways beyond ATG (Sarkar et al., 2005).

Another signaling cascade through which D2-like DRs (including D2DR and D3DR) may modulate the UPS is the Akt/mTOR pathway. In fact, agonist-induced stimulation of D2DR, and mostly D3DR, induces activation of Akt-mTOR (Salles et al., 2013; La Cour et al., 2011), which in turn, negatively modulates both cell-clearing systems UPS and ATG. Nonetheless, recent studies yielded opposite results suggesting that D2DR and D3DR inhibit mTOR, contrarily to D1DR and D5DR, which instead activate mTOR (Wang et al., 2018). Thus, further studies are needed to elucidate the effects of D2-like DRs upon UPS activity. In this context, it is worth mentioning that chronic stimulation of D3DRs, also induces D1DR-dependent AC hyper-activation (Fiorentini et al., 2008; Maggio et al., 2009). In line with this, D3DRs are implicated in METH-induced behavioral sensitization and also in schizophrenia (Sokoloff et al., 2006; Zhu et al., 2012; Choi et al., 2018; Sokoloff and Le Foll, 2017). Thus, the UPS modulates behavioral sensitization by acting on both D1-like and D3DR-dependent downstream cascades. This is not surprising when considering that a functional cross-talk occurs between D1DRs and D3DRs. In fact, D1DRs and D3DRs co-localize in a large number of neurons within the striatum and nucleus accumbens shell, where they form heterodimers (Fiorentini et al., 2008). In the presence of D3DRs, DA stimulates D1DRs with higher potency. Again, heterodimerization with D3DRs abolishes D1DRs internalization and enables the internalization of D1/D3-DR complex through a mechanism involving β-arr (Fiorentini et al., 2008), which is a task of UPS. Thus, it is expected that following DA overload as induced by METH, UPS impairment antagonizes the internalization of D1/D3-DR complex to stimulate AC with higher potency and contribute to behavioral alterations.

5. Concluding remarks

The pieces of evidence here reviewed suggest that UPS is deeply intermingled with the neurochemical and molecular events which may lead to behavioral alterations induced by the widely abused and highly addictive drug METH. This suggests that METH-induced inhibition of UPS may contribute to those maladaptive plastic changes which lead to METH-induced addiction overlapping with psychiatric disorders such as schizophrenia. In fact, METH administration represents a valid experimental model of schizophrenia since it reproduces behavioral alterations associated with some abnormalities of DA and glutamate systems, which are similar to schizophrenia. Remarkably, UPS is seminal to modulate DA and glutamate transmission in baseline conditions, while the effects of DA-mediated, METH-induced inhibition of UPS overlap with DA- and glutamate-related non-canonical transduction cascades which underlie behavioral alterations. Remarkably, UPS alterations are reported in schizophrenia as well, which suggests the need for further studies aimed at investigating the UPS as a potential contributor in the neurobiology of psychiatric disease. In keeping with this, it would be worth testing the effects of UPS in the functional cross-talk between DA and glutamate. In fact, DA transmission, which is finely surveilled by the UPS, controls the presynaptic release of glutamate via both D1-like and D2-like receptors (Svenningsson and Le Moine, 2002; Ibañez-Sandoval et al., 2006; Briones-Lizardi et al., 2019). As reviewed here, compelling evidence has been provided showing that UPS is affected by abnormal stimulation, specifically of D1DRs and D5DRs. This is expected to enhance glutamate release, which cannot be restrained since UPS is impaired. In the context of D2-like DRs, it would be worth investigating the role of UPS on D3DRs. This latter receptor subtype gained growing popularity as a key player in addiction and schizophrenia due to the peculiar anatomy and synaptic localization (Sokoloff and Le Foll, 2016). D3DRs are involved in the modulation of glutamate release (Ibañez-Sandoval et al., 2006; Briones-Lizardi et al., 2019). D3DRs interact with the glutamate system, either directly at the level of striatal excitatory asymmetrical synapses co-expressing D3DRs, or indirectly, by regulating pyramidal glutamate neurons through D1DRs in the prefrontal cortex (Sokoloff and Le Foll, 2016). Exploring the role of UPS and UPS modulators on the effects of DRs upon glutamate release could provide a better understanding of the molecular events which operate in addiction and schizophrenia.

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Author contribution

FL and FB wrote the article and made art-work. CLB contributed to conceptualization. LR contributed to the literature review and artwork. FF Coordinator of the paper; he critically revised the article for intellectual content.

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