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Specificity and impact of adrenergic projections to the midbrain dopamine system

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Abstract

Dopamine (DA) is a neuromodulator that regulates different brain circuits involved in cognitive functions, motor coordination, and emotions. Dysregulation of DA is associated with many neurological and psychiatric disorders such as Parkinson's disease and substance abuse. Several lines of research have shown that the midbrain DA system is regulated by the central adrenergic system. This review focuses on adrenergic interactions with midbrain DA neurons. It discusses the current neuroanatomy including source of adrenergic innervation, type of synapses, and adrenoceptors expression. It also discusses adrenergic regulation of DA cell activity and neurotransmitter release. Finally, it reviews several neurological and psychiatric disorders where changes in adrenergic system are associated with dysregulation of the midbrain DA system.

Norepinephrine (NE) and epinephrine (E) enhance or dampen neural activity by acting through G-coupled receptors. Adrenoceptors α_1 and β_1, β_2, and β_3 are classified as activators, as binding of agonist to these receptors leads to $G\alpha_q$- and $G\alpha_s$-mediated signaling. Adrenoceptor α_2, and in some cases β_2, can be classified as inhibitors, as binding of agonist to these receptors leads to leads to $G\alpha_i$-mediated signaling. The adrenergic system is incredibly complex with adrenoceptors ubiquitously present at postsynaptic and presynaptic elements of neurons, glia, and blood vessels. This complexity makes it difficult to determine how NE and E modulate the activity of brain circuits. The goal of this review is to summarize experimental data on how NE and E modulate the activity of midbrain dopamine (DA) neurons, what the substrates of their actions are and how these may relate to neurological diseases and neuropsychiatric disorders.

Anatomy of midbrain DA regions

Midbrain DA neurons are clustered into three groups originally described by Dahlstrom and Fuxe (1964). In the original description, DA neurons were identified by their green fluorescence induced by a formaldehyde treatment and were named under an A

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nomenclature. Three clusters were segregated by their location in association to anatomical landmarks. Cells located within the midbrain reticular formation were named A8, those at the substantia nigra (SN) were named A9, and those dorsal and lateral to the interpeduncular nucleus were named A10. Boundaries among these clusters are not well defined; especially in the anteriorlateral part of A10 and the ventromedial part of group A8, and the lateral part of SN and the lateral A8, where DA neurons formed a continuum (Dahlstroem and Fuxe, 1964).

Current anatomical atlases locate A8 in the retrorubral field (RRF). A9 is divided into SN pars compacta and pars lateralis, but with some DA neurons are scattered in the SN pars reticulata. The A10 encompasses many subregions in the midbrain. It is usually associated with the ventral tegmental area (VTA), but it extends to other regions including dorsal raphe, caudal linear nucleus of the raphe (CLi), rostral linear nucleus of the raphe (RLi), interfascicular nucleus (IF), and medial supramammillary nucleus (Phillipson, 1979; Swanson, 1982). In rats, the distribution of DA neurons in the midbrain is 6% in A8, and 47% in A9 and 47% in A10 (German and Manaye, 1993).

DA neurons have a differentiated output with few axon collaterals. With the exception of cell in the medial part of the SN and lateral parts of the VTA, most midbrain DA neurons tend to send axons to discrete brain regions (Fallon, 1981; Fallon and Loughlin, 1982; Swanson, 1982). The axons of DA neurons follow two topographical arrangements. On one hand, DA neurons located medially project to the medial and somewhat anterior sectors of the forebrain, while DA neurons located laterally project to the lateral and somewhat posterior sectors of the forebrain (Fallon, 1988). On the other hand, ventral SN and VTA neurons project preferentially to dorsal structures such as caudate-putamen and septum whereas dorsal SN and VTA neurons project preferentially to ventral structures such as the amygdala and olfactory tubercle (Fallon, 1988). It is important to note that DA neuron topographical segregation also correlates to distinct physiological features and have become important feature in our understanding on how DA might be altered under different psychopathologies (Lammel et al., 2011; Margolis et al., 2008; Mejias-Aponte et al., 2015).

It is important to recognize that in addition to DA neurons, GABA and glutamate neurons are also major cell types within the midbrain DA regions (Steffensen et al., 1998; Yamaguchi et al., 2011; Yamaguchi et al., 2013). These neurons synapse onto DA neurons providing local inhibitory and excitatory inputs to DA neurons (Dobi et al., 2010; van Zessen et al., 2012; Yamaguchi et al., 2013). Recently two pathways with preferential inputs to non-DA neurons have been described; a GABAergic input by nucleus accumbens (NAcc) medium spiny neurons (Xia et al., 2011), and GABAergic and glutamatergic inputs from the bed nucleus of the stria terminalis (Jennings et al., 2013). This organization provides a path to selectively affect DA neuron function through feed forward excitation or inhibition.

Another feature of GABA and glutamate neurons is that they also send afferents to many of the same brain regions that DA neurons innervate (Brown et al., 2012; Carr and Sesack, 2000; Taylor et al., 2014; Yamaguchi et al., 2011). Some of these neurons co-transmit DA (Li et al., 2013; Stuber et al., 2010; Tecuapetla et al., 2010; Tritsch et al., 2014; Zhang et al., 2015). In the case of glutamate neurons, DA release occurs in different subcellular domains

to those of glutamate (Zhang et al., 2015). These studies highlight that, in addition to DA, GABA and glutamate are also major neurotransmitters of the system.

Anatomy of adrenergic innervation to midbrain DA regions

Adrenergic innervation to midbrain DA regions arises from locus coeruleus (LC) and brainstem adrenergic nuclei (Mejias-Aponte et al., 2009; Robertson et al., 2013)(Figure 1). The major NE afferents originate from areas A1, A2, and the LC, whereas the major E afferents originate from area C1. The A1 NE group is located in the caudal ventrolateral medulla, A2 is located in the nucleus of the solitary tract, and C1 is located in the rostral ventrolateral medulla (Dahlstroem and Fuxe, 1964; Hokfelt et al., 1974; Ungerstedt, 1971). The NE and E innervation is topographically distributed. Retrorubral field (RRF, area A8) receives the highest innervation followed by the VTA and midline DA nuclei of A10 (RLi, CLi, IF), and SN (area A9). There is also a small group of DA neurons that belong to A10 within the periaqueductal gray in the dorsal raphe; their source of adrenergic innervation includes the LC and area C1 (Card et al., 2006; Kim et al., 2004).

At the ultrastructure level, adrenergic axons within the VTA terminals are primarily associated with synaptic appositions without making synaptic contacts (Liprando et al., 2004). These appositions represent 77% and 49% of samples analyzed from rat and monkey, respectively. The second most frequent synaptic arrangement is synaptic appositions separated by glia processes; 27% on samples analyzed from rat and 40% on samples analyzed from monkey. Lastly, adrenergic terminals with junctional specializations, constituting 7% and 11% in samples analyzed from rat and monkey, respectively. These junctional specializations are often symmetric (associated with inhibitory synapses), but some are asymmetric (associated with excitatory synapses). Furthermore, it was also observed by Liprando and colleagues that some adrenergic terminals were associated with non-DA dendrites; indicating that non-DA neurons within the VTA also receive adrenergic innervation. Taken together, the higher prevalence of synaptic appositions over junctional specializations observed in the ultrastructure indicates a paracrine release of neurotransmitter, where neurotransmitter release occurs extrasynaptically and produces changes in nearby cells (Figure 2). This system of neurotransmitter release is also known as volume transmission (Fuxe et al., 2010).

Adrenergic receptors expression within midbrain DA regions

Actions of NE and E on midbrain DA regions are dependent on the location of adrenoceptors and the type of neurons expressing these receptors. Whereas in the SN DA and non-DA neurons are mostly segregated, this is not the case in the VTA and RRF (Figure 1). In addition to DA neurons, GABA and glutamate neurons are also present in midbrain DA regions (Yamaguchi et al., 2007; Yamaguchi et al., 2013). The heterogeneity of cell types is a challenge to the integration of the available anatomical data mostly established through in-situ hybridization, autoradiography, and immunohistochemistry, and, recently complemented with few ultrastructure studies.

In-situ hybridization studies have shown low levels or no expression of α and β adrenoceptors. RRF, VTA and SN express α_{1A} adrenoceptors, SN also expresses α_{1B} adrenoceptors (Day et al., 1997). Recently, quantitative real-time polymerase chain reaction (qPCR) was used for gene expression profiling of VTA and SN DA neurons and the α_{1B} receptor was detected with a 2-fold higher expression in the VTA than SN (Greene et al., 2005). Conversely, α_2 and β_1 mRNA expression were undetected in midbrain DA regions (Nicholas et al., 1993a; Nicholas et al., 1993b). It is important to acknowledge that most in-situ hybridization comes from whole-brain sampling studies, where the assays might not been optimized for midbrain DA region samples. This is an area that should be revisited and expanded to cover both DA and non-DA midbrain neurons.

Receptor binding autoradiography has detected mild to moderate levels of α and β adrenoceptors in SN and VTA. Using the selective α_1 antagonist, HEAT, low expression has been reported in SN and VTA (Jones et al., 1985). Figure 8 in this report also showed α_1 adrenoceptors labeling in the midline A10 nuclei, CLi and IF (Jones et al., 1985). Using the selective α_2 antagonist, idaxozan, moderately high levels were detected in the RLi and VTA, and moderate levels in SN pars compacta (Boyajian et al., 1987). Similarly, moderate to low expression was detected with the α_2 antagonist, rauwolscine primarily in SN pars lateralis and to a lesser extent in SN pars compacta and VTA. Beta adrenoceptors were studied with the β adrenoceptor antagonist, dihydroalprenolol, revealing moderate expression in both SNc and VTA (Palacios and Kuhar, 1980).

Expression of α_{2A} and α_{2C} adrenoceptorss in midbrain DA regions has been investigated using immunohistochemistry. Moderate levels of α_{2A} were observed in both SNc and VTA. However, few DA neurons expressed the receptor, only 4% and 14% in the SNc and VTA, respectively (Rosin et al., 1993). This indicates that α_{2A} is expressed mainly on non-DA neurons, but whether is in glutamate of GABA neurons is still undetermined. In contrast to the α_{2A} adrenoceptors, α_{2C} is expressed by many DA neurons; co-expression is as high as 63% in RRF, 77–83% in SN, 67% in VTA (Lee et al., 1998).

There is abundant evidence of the presence of adrenoceptors in midbrain DA regions from in-situ hybridization, receptor autoradiography, and immunohistochemistry studies. Nevertheless, there is a lack of cellular detail of their location and their relative expression on DA versus non-DA neurons. The in-situ hybridization studies have established that there are neurons within midbrain DA regions expressing adrenoceptors. Both autoradiography and immunohistochemistry have established associations of adrenoreceptors and neurons in the midbrain DA regions, but ultrastructure studies are needed to conclusively determine whether the adrenoceptors are present at axon terminals or on postsynaptic elements. Conversely, evidence of postsynaptic expression has been supported by electrophysiological studies; these are described in the next section.

Recent ultrastructural studies have started to shed light on the cellular detail of α_1 adrenoceptors cellular location. The α_1 adrenoceptors were detected almost exclusively extrasynaptically, with <10% of these receptors found peri-synaptically or directly associated with the synaptic active zones of either asymmetric or symmetric specializations. When associated with synaptic elements, the α_1 adrenoceptors have been observed primarily

in presynaptic elements, with scarce postsynaptic labeling in VTA neurons (Mitrano et al., 2012; Rommelfanger et al., 2009). The majority of presynaptic labeling is associated with symmetric perisynaptic elements and to a lesser extent with asymmetric synapses. Importantly, α_1 adrenoceptors are present in VGluT1 and VGluT2 expressing glutamatergic terminals, and in GABAergic terminals (Mitrano et al., 2012), indicating presynaptic regulation of glutamate and GABA release.

In addition to the presence of adrenoceptors in neurons, there is also evidence of α_1 adrenoceptors in glia (Mitrano et al., 2012; Rommelfanger et al., 2009). Moreover, the noradrenergic transporter (NET) has also been detected in glia (Liprando et al., 2004). Adrenoceptors α_2 and β are also expressed by astrocytes and microglia (Fuxe et al., 2015); however, their presence within midbrain DA regions have not been studied. The separation of synaptic appositions of adrenergic axon terminals by glia suggests an important role of glia in NE neurotransmission.

In summary, the current anatomical data support preferential paracrine release of NE within midbrain DA regions indicated by the greater proportion of synaptic appositions over synaptic junctions. Many of these of synaptic appositions are separated by glia. This synaptic arrangement offers NE access to different cellular elements in the circuit, both at postsynaptic and presynaptic sites, and regulation though interaction with glia (Figure 1 and 2). Evidence of direct postsynaptic actions is supported by mRNA expression of the α_{1B} and protein detection of α_{2A} and α_{2C} adrenoceptors on VTA and SN DA neurons. The α_{2A} adrenoceptors were also found on non-DA neurons; thus, highlighting the possibility of adrenergic regulation of DA neurons indirectly by local connection of non-DA neurons with DA neurons. At the presynaptic site, α_1 adrenoceptors are present in glutamatergic and GABAergic terminals supporting presynaptic regulation of neurotransmitter release. Moreover, the presence of NET in glia indicates an active participation of glia in the regulation of NE levels.

Many aspects of the neuroanatomy of the adrenergic innervation require further research. Among these, a revision of the receptor expression is highly needed. Particularly, determining the distribution among DA neurons, non-DA neurons and glia would provide insight into the local circuitry. Moreover, ultrastructural studies focusing on the α_2 adrenoceptors are also needed. Conversely, tracing studies are needed to identify the origin of neurons that are expressing the α_1 adrenoceptors presynaptically.

Adrenergic regulation of midbrain DA neuron activity

DA neuron activity is characterized as regular with intermittent bursts (Grace and Bunney, 1984). Regular firing is characterized by constant inter-spike intervals between action potentials while bursts are identified by an increase in firing pace of action potentials clustering together for a brief time. Burst firing produces a massive DA release at terminals (Floresco et al., 2003). DA neurons fire in bursts in response to events of behavioral relevance such a conditioned stimulus or the consumption of a reward (Schultz, 2007).

Changes in firing regularity were among the first effects described for adrenergic drugs on DA neurons (Table 1). When given intravenously, clonidine, an α_2 agonist, increased firing regularity of midbrain DA neurons without changes in firing rate. Conversely, idaxozan, an α_2 antagonist, increased burst firing and prevented clonidine effects (Grenhoff and Svensson, 1988; Grenhoff and Svensson, 1989). Moreover, prazosin, an α_1 antagonist, decreased burst firing and prevented idazoxan-increased burst firing (Grenhoff and Svensson, 1993). Given that adrenergic drugs were administered systemically, these studies did not discern whether the effects are caused by direct regulation of DA neurons or regulation of inputs to DA neurons. Nevertheless, these studies established that adrenergic drugs were capable of altering burst firing of DA neurons.

Few in-vivo studies have demonstrated changes in firing activity of DA neurons by local administration of NE or adrenoceptor agonists and antagonists (Table 1). Applied iontophoretically, NE decreased DA neuron discharge activity. This effect is blocked by sulpiride, a D_2 antagonist, or piperxane and idaxozan, α_2 antagonists (Aghajanian and Bunney, 1977; Guiard et al., 2008; White and Wang, 1984); thus indicating that NE inhibits DA neurons through activation of D_2 and α_2 receptors. Moreover, iontophoresis of α_2 agonist, clonidine, weakly decreased firing rate (White and Wang, 1984). Inhibition of firing rate is also evoked by the β adrenoceptor agonist, isoproterenol (Aghajanian and Bunney, 1977; White and Wang, 1984). Contrary to the inhibitory effects of α_2 and β adrenoceptors, activation of α1 adrenoceptors by phenylephrine increased both firing rate and burst firing of DA neurons (Goertz et al., 2015).

NE modulatory effects on glutamate-evoked excitation have also been studied in-vivo (Almodovar-Fabregas et al., 2002). In this experiment glutamate-mediated excitation was evoked using short iontophoresis pulses of glutamate while local NE levels were increased using long iontophoresis pulses of NE. This produces an on and off pattern of glutamate-evoked excitation in the presence or absence of local increases in NE. Three different forms of neuromodulation were observed: potentiation (increase in glutamate-evoked excitation independent of changes in spontaneous activity), enhancement (increase in glutamate-evoked excitation relative to spontaneous activity), and suppression (decrease in glutamate-evoked excitation relative to spontaneous activity). Modulation of glutamate-evoked excitation by NE was observed in 92 % of putative VTA DA neurons. Of these 19% of neurons showed potentiation, 27% of neurons showed enhancement, and 46% of neurons showed suppression.

Electrical stimulation of brain regions containing NE and E cell bodies has also shown changes in the activity of DA neurons. Single-pulse stimulation of the LC evoked excitation followed by inhibition. This excitation was sensitive to the α1 adrenoceptor antagonist prazosin. The inhibition was insensitive to α_1, α_2 and β adrenoceptor antagonists (Grenhoff et al., 1993). Similarly, electrical stimulation of the nucleus of the solitary tract, the brain regions where A2 NE and C2 E neurons reside, also evoked responses of VTA DA neurons; some neurons are excited while others are inhibited (Kirouac and Ciriello, 1997; Mejias-Aponte and Aston-Jones, 2005). Although, A1 NE and C1 E neurons also project to midbrain DA regions, the effects of their stimulation is on the activity of DA neurons have not yet been investigated.

Postsynaptic actions of α_1 adrenoceptors have been determined in ex-vivo recordings on midbrain slices (Table 2). NE depolarized 36% of putative DA neurons, which leads to an increase in firing rate for some neurons. NE-induced depolarization is blocked by the α_1 antagonist prazosin and mimicked by phelyephrine, an α1 agonist. Phenylephrine-induced membrane depolarization persisted in the presence of tetradotoxin, a sodium channel blocker, confirming its independence from incoming inputs (Grenhoff et al., 1995). Two conductances are affected by α_1 adrenoceptors activation, calcium-activated potassium channel currents are decreased and hyperpolarization-activated cation currents are increased. Acting on theses conductances, NE increased intra-burst frequency of aspartate-evoked burst firing (Goertz et al., 2015).

Presynaptic modulation of inputs to DA neurons by NE has also been established. Activation of α_1 adrenoceptors decreased the frequency of spontaneous $GABA_A$ inhibitory postsynaptic currents. This activation is input dependent, as miniature inhibitory postsynaptic currents are unaffected. The underlying mechanism relies on phosphokinase C signaling and the activation of the voltage and calcium-activated potassium channels (Velasquez-Martinez et al., 2015). Contrary to the effect of inhibitory postsynaptic currents, activation of α1 adrenoceptors increased presynaptic glutamate release. Phenylephrine increased the amplitude of evoked and frequency of spontaneous AMPA excitatory postsynaptic currents (Velasquez-Martinez et al., 2012; Williams et al., 2014). Taken together, the presynaptic α1 actions are in accordance to an activation of DA neurons favoring glutamate over GABA inputs.

Postsynaptic modulation by α_2 adrenoceptors modulates excitation of DA neurons. Clonidine and UK14304, α_2 agonists, both inhibited the hyperpolarization-activated cation current by activating the protein kinase C signaling pathway (Inyushin et al., 2010). Similarly, NE and UK14304 activate a non-specific cationic conductance that produced a small inward current (Cathala et al., 2002). In conjunction, these two postsynaptic actions render DA neurons more excitable and might play a role in the transition to burst firing observed with systemic administration of α_2 antagonists (Grenhoff and Svensson, 1988; Grenhoff and Svensson, 1989) These action of α_2 adrenoceptors may also synergize with the postsynaptic activation of α_1 adrenoceptors (Goertz et al., 2015).

Presynaptic modulation by α_2 adrenoceptors affects both inhibitory and excitatory inputs to DA neurons. Clonidine and UK14304, both α_2 agonist, decreased the frequency of spontaneous and miniature EPSCs (Jimenez-Rivera et al., 2012; Williams et al., 2014). Conversely, both clonidine and UK14304 increased spontaneous IPSCs (Cathala et al., 2002). This suggests a net increase in inhibition by inputs into DA neurons through activation of α_2 receptors.

Another mechanism of adrenergic actions is heterosynaptic interaction with metabotropic glutamate receptor-mediated inhibitory postsynaptic potential (mGluR IPSPs). Brief exposure of aspartate or a train of electrical pulses produces burst firing on DA neurons. This stimulation also activates the mGluR resulting in a negative feedback control that regulates DA neuron burst activity. In the presence of NE, mGluR IPSPs are attenuated in an α_1-dependent manner. NE, by itself, also evoked an IPSPs through activation of the

postsynaptic α_1 receptor, but this effect was susceptible to receptor desensitization, while NE the effect on mGluR was not (Paladini and Williams, 2004). This relationship suggests that, when the coincidence of NE and glutamate inputs into DA neurons is strong enough, DA neurons will fire longer bursts of action potentials (Goertz et al., 2015).

It is important to emphasize that NE produces a rapid desensitization of α_1 adrenoceptor-mediated IPSPs (Paladini and Williams, 2004); thus, this current is likely to be engaged during brief phasic NE release and not when there is a high NE tonic level. Importantly, high levels of NE are common throughout the brain during stress (Aston-Jones and Cohen, 2005; Valentino and Van Bockstaele, 2008), and under NET blockade by psychostimulants such as amphetamine and cocaine (Chen and Reith, 1994a; Pan et al., 1996; Pan et al., 2007; Reith et al., 1997). Under high NE levels produced by amphetamine, the α_1 adrenoceptor-mediated IPSPs should be desensitized; therefore, providing circumstances for a preferential α_1-dependent inhibition of mGluR IPSPs (Paladini et al., 2001), which could lead to the increased α_1-dependent burst firing on DA neurons observed in in-vivo recordings (Shi et al., 2000; Shi et al., 2004).

Although research has been centered on NE actions on DA neurons, one report has shown that NE also acts on local non-DA neurons. Namely, phenylephrine has been shown to depolarize non-DA neurons (Grenhoff et al., 1995). Because of the local connections of glutamate and GABA neuron with midbrain DA neurons, future studies are needed to identify other adrenergic actions on non-DA neurons that might impose a regulation on DA neurons.

In summary, there is ample evidence for adrenergic modulation of DA neural activity. This modulation is complex involving a variety of presynaptic and postsynaptic elements. In-vivo studies indicate control of firing regularity of DA neurons, where activation of α_1 adrenoceptors increases burst firing. The regulation of burst firing is associated with regulation of conductances residing in the postsynaptic site. Moreover, there is also support for presynaptic modulation, where α_1 adrenoceptors has net excitatory drive by dampening GABA and enhancing glutamate. On the other hand, α_2 adrenoceptors can enhance an inhibitory drive dampening glutamate and enhancing GABA release.

The development of optogenetics and designer receptors exclusively activated by designer drugs (DREADDs) (Bernstein and Boyden, 2011; Urban and Roth, 2015) can help decipher the specific role for each of the multiple adrenergic pathways that send afferents to midbrain DA regions. The use of transgenic animals can be very helpful; among these, the mice developed by Jensen and colleagues that allows selective targeting of LC and non-LC NE neurons (Robertson et al., 2013). Another question centers on the source of glutamatergic and GABAergic presynaptic terminals that are sensitive to adrenoceptor pharmacology. Future research should also explore in more detail adrenergic action on local non-DA neurons, as these could be a major player in the regulation of DA neural activity.

Regulation of DA release by the adrenergic system

DA levels within midbrain DA regions and at terminal sites are affected by changes in NE levels. Three factors have been identified: direct regulation of DA neurons, presynaptic regulation of DA terminals, and clearance and release of DA through NE terminals. Most of the mechanisms of direct regulation of DA neurons were reviewed in the previous section. Here, I discuss experiments where DA levels were measured locally within midbrain DA regions or at terminal sites while manipulating NE levels at midbrain DA regions.

There is clear evidence that altering brain NE levels changes DA release. Chemical lesions of the LC or its afferents decreased DA levels in the NAcc, caudate, and prefrontal cortex (PFC) (Carboni et al., 1990; Haidkind et al., 2002; Lategan et al., 1990; Lategan et al., 1992; Masana et al., 2011). Similarly, chronic inhibition of NE synthesis by genetic lesion of DA-beta hydroxylase (DBH), the enzyme responsible for converting DA into NE in adrenergic neurons, also decreased DA levels in NAcc and caudate-putamen, but not in the PFC (Schank et al., 2006). Taken together, these findings suggest that NE exerts an excitatory tone on DA levels.

A limited number of studies have provided insight on how altering local NE levels in midbrain DA regions affect the local DA levels. In these studies NE levels were increased by blocking NET or α_2 adrenoceptors. Reverse dialysis of desipramine in the VTA, a selective NET blocker, and cocaine and amphetamine, non-selective monoamine blockers, increased NE (Chen and Reith, 1994a; Pan et al., 1996; Pan et al., 2007; Reith et al., 1997). Similarly, reverse dialysis of yohimbine, an α_2 antagonist, increased NE release (Chen and Reith, 1994b). This increase on NE levels by antagonizing the α_2 adrenoceptor was associated with the blockade of α_2 autoreceptor at adrenergic axon terminals. These findings indicate that NE tone exists at the VTA and it is susceptible to regulation at terminal sites. Concomitant to the increase in NE levels, NET blockers and α_2 antagonists, also increased local DA levels (Chen and Reith, 1994a; Pan et al., 1996; Pan et al., 2007; Reith et al., 1997). These results are in accordance with an excitatory effect of NE on DA neurons. Although in the case of cocaine and amphetamine, DAT blockade as the mechanism contributing to the increased DA levels cannot be rule out, the increase in DA levels observed with desipramine and yohimbine indicate a NE-mediated activation of DA neurons.

Despite a thorough search of the literature, few experiments have sought to answer how local changes of NE within midbrain DA regions affect DA output at terminal sites. Intra-VTA infusion of cocaine, which increases NE, DA and 5-HT, decreased DA in the NAc and PFC (Chen et al., 1996; Pan et al., 1996). This decrease in extracellular DA levels is associated with heightened local increases of DA in the VTA that can lead to D_2 autoreceptor regulation (Brodie and Dunwiddie, 1990; Chen and Reith, 1994b). However, it is important to note that DA PFC projecting neurons lacks the D2 autoreceptor rendering them non-responsive to the inhibitory actions of DA (Lammel et al., 2008). Therefore, a DA-independent mechanism must underlie the decrease of DA in the PFC.

In contrast to cocaine, intra-VTA infusion of amphetamine, increased DA at the PFC. This increase in PFC DA is associated to a heightened increase in local VTA NE over DA as

amphetamine induced a 5-fold increase in NE levels compare to those of cocaine (Pan et al., 2007). Because these findings are drawn on the bases of non-specific monoamine transporter inhibitor, future studies using selective NET blockers or α_2 adrenoceptors antagonists may provide a better insight on how increasing NE levels at midbrain DA regions affect DA release at terminal sites. Furthermore, a more direct approach could be selective activation of NE terminals utilizing optogenetics or DREADDs. This later approach could also be used to investigate different adrenergic inputs by selective targeting of areas A1, A2, C1 or LC.

Interestingly, contrary to the decrease in DA levels in the NAc and PFC levels by local infusion of cocaine into the VTA, systemic administration of cocaine increased NAc and PFC DA levels (Tanda et al., 1997). This discrepancy is expected as cocaine, which blocks DAT at terminals, leads to local increases in DA at terminal sites. However, DAT blockade is not the only mechanism regulating DA release after systemic cocaine administration. Cocaine increases in DA levels at terminal sites also requires DA neurons being active (Mejias-Aponte et al., 2015; Sombers et al., 2009). Importantly, two mechanisms linking activation of α_1 adrenoceptors has been described. Local intra-VTA administration of prazosin, an α_1 antagonist, blocked cocaine-evoked DA release in the NAcc shell by regulating burst activity of DA neurons (Goertz et al., 2015). NE regulation also includes presynaptic activation of α_1 adrenoceptors at NAc shell DA terminals; local infusion of α_1 antagonist, terazosin, blocked cocaine-induced increase in DA extracellular levels (Mitrano et al., 2012).

There are aspects of the regulation of DA release by NE that require further research. Most intra-VTA reverse dialysis experiments were performed using a single dose of the drugs. Future experiments using several doses are needed. This is of special interest as NE actions often follow an inverted-U shape that reflect different states of activity of NE neurons (Aston-Jones and Cohen, 2005; Berridge and Waterhouse, 2003).

DA uptake and release by NE terminals

Another mechanism regulating DA levels is reuptake and release of DA by NE terminals. Taking advantage of the differential distribution of DA and NE terminals, and DAT and NET expression in the cortex of rats, a series of studies have provided evidence of NE terminals as a source of DA. In rats, DA innervation is preferential to PFC while there is very small innervation at other cortices such as the occipital cortex (OCC) (Descarries et al., 1987). In contrast to DA innervation, NE innervation is much higher and ubiquitous throughout cortical regions (Morrison et al., 1978). If the source of DA is from DA terminals, few outcomes are expected: including increases of extracellular DA by DAT blockers and D_2 antagonist. However, local infusion of the selective DAT antagonist GBR12909 in either PFC or OCC did not increase extracellular DA, while only small increases were observed with the D_2 antagonist haloperidol (Devoto et al., 2004). The outcome of these experiments argues against DA terminals as the source of DA.

It is possible to argue that the lack of an effect by DAT blockers and the small effect of D_2 antagonist on extracellular DA can be explained by low expression of DAT and D_2 DA autoreceptors or lack of a functional D_2 receptor in cortical projecting neurons (Chiodo et

al., 1984; Lammel et al., 2008; Sesack et al., 1998). However, noradrenergic pharmacology supports that DA reuptake and release is occurring at the NE terminals. Extracellular DA and NE are increased in PFC and OCC after local infusion of the NET blocker desipramine (Devoto et al., 2004). Conversely, inhibition of LC activity by local infusion of the α_2 adrenoceptor agonist clonidine decreased extracellular DA and NE in the PFC and OCC (Devoto et al., 2003). Because of the scarce DA innervation in the OCC, these findings indicate that reuptake and release of DA occurs at NE terminals.

Another line of evidence supporting DA reuptake by NE terminals comes from genetic studies. Synaptosomes harvested from PFC of NET knock-out mice showed a 55% reduction in DA uptake. A similar reduction on DA uptake effect was also observed on synaptosomes harvested from PFC of wild-type mice treated with the selective NET inhibitor nisoxitine (Moron et al., 2002).

NE terminals are a source of neurotransmitter acting on D1 and D4 receptors

Support for NE terminals as the source of neurotransmitter for both, the activation of D1 receptor in the hippocampus and D4 receptors in the lateral habenula, has been recently demonstrated (Root et al., 2015; Smith and Greene, 2012). In the hippocampus, D1-dependent amphetamine enhancement of glutamate signaling is blocked by blockade NET or NE transmission from LC terminals, but not by blockade DAT or DA transmission from VTA terminals. Similarly, D4-mediated current in lateral habenula are susceptible to lesion of NE terminals, but not DA terminals.

These two studies highlight NE terminals as the source of neurotransmitter. In the experiment performed in the habenula, both DA and NE evoked the D4-mediated current (Root et al., 2015); thus indicating that NE itself could be the agonist. However, in the hippocampus, NE did not evoke the D1-mediated enhancement of glutamate signaling (Smith and Greene, 2012). The authors proposed that amphetamine increases intracellular DA at NE terminals by inhibiting the vesicular monoamine transporter-2 (VMAT2) and monoamine oxidase (MAO). The inhibition of VMAT2 prevents the transport of DA into presynaptic vesicles where DBH convert DA to NE, whereas inhibition of MAO prevents DA conversion to DOPAC. These two effects lead to the increases in intracellular DA that is reversely transported by NET.

Adrenergic and dopaminergic receptor cross-activation by catecholamines

NE inhibits DA neurons via D_2 DA receptor activation(Aghajanian and Bunney, 1977). Both NE and E are agonists at] of D_2 DA receptors (Lanau et al., 1997; Onali and Olianas, 1987). It worth noticing a gradient in the expression of the D_2 DA receptors, higher in the SN and lateral parts of VTA and lower or absent in DA neurons in the medial parts of the VTA, RLi, CLi and IF (Li et al., 2013); thus, regulation of NE and E of DA neuronal activity through the D2 DA receptor is more likely to affect a subgroup of neurons. Moreover, given the fact that NE and E affinity to the D2 receptor is 20–30 fold lower than DA (Werle et al., 1988),

activation of D2 receptor will depend on circumstances were NE levels are high such as in the presence of psychostimulants.

Another possible cross-activation of DA receptors by NE and E is at the D_4 DA receptors (Lanau et al., 1997). NE and E have affinities in the nanomolar range similar to that of DA for the D_4 receptor. In functional assays, based on GTPγS stimulation and changes cAMP levels, NE and E were 2–5 fold less potent than DA (Czermak et al., 2006; Lanau et al., 1997). Recently, NE was shown to be the neurotransmitter that activates D_4 receptors in the lateral habenula (Root et al., 2015), supporting NE cross-talk through D_4 receptors. Another brain region in which NE D_4 receptor activation may be of importance is the PFC, where D_4 DA receptors are highly expressed (de Almeida and Mengod, 2010).

There is biochemical evidence of α_2 adrenoceptors present in axon terminals of DA neurons (Lahdesmaki et al., 2003); although anatomical confirmation is still lacking. Given that DA binds to α_2 adrenoceptors (Cornil and Ball, 2008), the contribution of DA versus NE or E will be dependent on the presence of NE or E axons terminals in areas innervated by DA neurons. For example, dorsal striatum has scarce adrenergic input and the agonist to the α_2 adrenoceptors is most likely to be DA.

Adrenergic adrenoceptors α_{1B} and β_1 form heteromers with D_4 DA receptors. Functional activation of these heteromers has been characterized in the pineal gland, where D_4 DA receptors follow a circadian expression (Gonzalez et al., 2012). At hours of dark, when D_4 DA receptor expression is high, synthesis of melatonin was blocked by activation of D4 agonist site on heteromers preventing the adrenergic agonist-mediated effects. Conversely, at hours of light, in the absence D4 expression and formation of hetoromers, synthesis of melatonin was increased by adrenergic agonists. By changing the adrenoceptor signaling, hetoromers provide a functional switch in the pineal gland physiology. It will be important to find what other brain regions express heteromers, as they may provide novel targets for targeted receptor-mediated signaling.

Associations of adrenergic modulation of the midbrain DA system and neurological and psychiatry disorders

The direct association of the adrenergic modulation of the midbrain DA system and diseases is scarce. As reviewed in previous sections, there is ample evidence of adrenergic modulation of midbrain DA systems; however, a causal link between disease-related changes in DA as a consequence of changes in NE function is an ongoing area of research. Nevertheless, several animal models suggest that this association is of importance.

Parkinson’s disease (PD) is mostly associated with degeneration of DA neurons of the SN. However, the disease also affects NE neurons (German et al., 1992). A protective role of NE has been observed in animals showing that lesion of the LC exacerbate PD pathology and symptomology (Rommelfanger and Weinshenker, 2007). Moreover, in rodents, motor deficits associated with PD require NE depletion and can be ameliorated with DA agonist; thus indicating a dysregulation of DA by depleting NE (Rommelfanger et al., 2007).

Another interaction between NE and DA that is beneficial for PD patients is blockade of α_2 adrenoceptors. L-DOPA, a precursor of DA, is one effective treatment for delaying PD. However, L-DOPA also produces dyskinesia after long-term use. Notably, L-DOPA-induced dyskinesia can be treated with α_2 adrenoceptors antagonists (Rascol et al., 2001), which have been linked to a decrease in extracellular DA (Buck et al., 2010), supporting the notion that NE regulation of DA relates to the improvement of motor dyskinesia.

Similar to Parkinson's disease, neurodegeneration of DA innervation is observed in animals after prolonged exposure or high doses of methamphetamine (Ferrucci et al., 2013). In amphetamine users, low level of DA, TH and DAT have been observed in postmortem tissue (Wilson et al., 1996). Midbrain D_2/D_3 DA receptors binding positively correlates with grey-matter striatal volume suggesting a compromised DA function relates to a smaller striatum (Morales et al., 2015). Moreover, methamphetamine use is correlated with an enhanced risk to develop PD (Callaghan et al., 2012). The methamphetamine-induced damage of the DA system is exacerbated in animals with lesions of LC-NE axons. Moreover, DA damage is exacerbated in NE deficient mice and in mice where NE synthesis is pharmacologically blocked (reviewed by (Ferrucci et al., 2013; Weinshenker et al., 2008).

It is unclear how NE exerts a neuroprotective role against methamphetamine toxicity. One possibility is anti-inflammatory actions of NE by suppressing tumor necrosis factor, interleukin-1b, and the inducible nitric oxide synthase (Feinstein et al., 2002). Conversely, a possible link is the activation of the α_{1B} adrenoceptors. In both, α_{1B} knock-out and prazosin pretreated wild-type mice, methamphetamine damage of DA axons is reduced (Battaglia et al., 2003).

The interaction of DA and NE has also been described in the development of antidepressants that selectively target NET and DAT. One of the most studied of these antidepressants is bupropion. Given systemically, bupropion increased NE and DA at terminals in the NAcc and PFC (Cooper et al., 1994; Li et al., 2002). The antidepressant effect of bupropion is associated with NE. In mice lacking DBH, the enzyme that converts DA into norepinephrine in adrenergic neurons, bupropion fails to exhibit any effects in the tail suspension test (Cryan et al., 2004). Conversely, increased motivation is associated with bupropion-induced increase in DA (Randall et al., 2014). Interestingly, a study has linked the activity of DA neurons to depressive phenotypes in rodents (Chaudhury et al., 2013). Phasic activation of DA neurons projecting NAcc leads to a susceptible phenotype whereas inhibition of this projection promotes a resilience phenotype. Conversely, inhibition of DA neurons that projects to the PFC leads to susceptible phenotype. This research highlights a complex role of DA action in different circuits.

Attention deficit and hyperactivity disorder (ADHD), a neurodevelopmental disorder associated with inattention, hyperactivity, and impulsivity symptoms, is also associated with changes in the DA and NE systems. Among the neuronal circuits affected in patients with ADHD are prefrontal cortices and basal ganglia (Nakao et al., 2011; Valera et al., 2007). The treatment of choice for ADHD is psychostimulants, methylphenidate and amphetamine (Elia et al., 1999). By acting at DAT and NET, methylphenidate and amphetamine increase DA and NE at terminal sites.

Doses of methylphenidate that are clinically effective produce blood plasma levels between 8–40 ng/ml (Swanson and Volkow, 2002). Equivalent doses in animal studies produced improvements on working memory and sustain attention, without enhanced locomotion as would be produced by higher doses of psychostimulants (Berridge et al., 2006; Kuczenski and Segal, 2002). Behavioral improvements correlate with preferential changes in NE and DA and increase in neuronal responsiveness in the PFC (Berridge et al., 2006; Devilbiss and Berridge, 2008). Working memory improvement can also be obtained with local dorsal medial PFC injection of methylphenidate (Spencer et al., 2015), indicating that methylphenidate actions at terminal sites is sufficient to improve working memory. Methylphenidate effects on working memory are mediated through activation of PFC α_2 adrenoceptors and D_1 DA receptors; these are blocked by intra-PFC co-infusion of α_2 and D_1 receptor antagonists (Spencer et al., 2015).

Association between DA and NE is also shown in the substance abuse literature. Although a DA centered view of addiction is predominant, regulation of NE has been highlighted for certain aspects of addition (Weinshenker and Schroeder, 2007). The reinforcing properties of psychostimulants are greatly attenuated or abolished by interventions of the midbrain DA system, but not the adrenergic system (Roberts et al., 1977; Yokel and Wise, 1975; Yokel and Wise, 1976). Early literature focuses on the maintenance phase of self-administration, but latter studies show a contribution of NE adrenoceptors in extinction as well as in reinstatement of drug taking behavior evoked by drug priming, cues associated with the drug environment, and stress (review by (Schmidt and Weinshenker, 2014; Weinshenker and Schroeder, 2007).

Chronic inhibition of NE synthesis with inhibitors of DBH attenuates cocaine seeking as measured by a reduced break point responding for cocaine in a progressive ratio schedule, and attenuated lever press responding to a cocaine-primed injection, cues associated with cocaine self-administration, and stress (Schroeder et al., 2010; Schroeder et al., 2013). The underlying mechanism for drug-primed reinstatement relates to activation of α_1 adrenoceptors, as it is attenuated by prazosin, an α_1 adrenoceptor antagonist (Zhang and Kosten, 2005). Similarly, cue-induced relapse is attenuated by a cocktail of α_1 and β adrenoceptor antagonists (Smith and Aston-Jones, 2011). Cocaine history relates a differential activation of NE areas. NE A2 and C2 neurons are activated after acute cocaine. These neurons also exhibited an enhanced activation after extinction training, but not during cocaine self-administration. However, LC was not activated in any of these conditions (Buffalari and Rinaman, 2014). These studies highlight adrenergic regulation of cocaine seeking; however, whether the mechanism of action is through regulation of DA neurotransmission has not been directly established.

Recently, a link between NE terminals and DA release in PFC as a mechanism involved in the regulation of drug-primed reinstatement was established. As with chronic inhibition of DBH, acute inhibition of DBH one hour before a primed injection of cocaine blocked reinstatement (Devoto et al., 2014a). The mechanism underlying the effect of the DBH treatment relates with an increase of DA release in the PFC that leads to activation of D1 receptors; PFC blockade of D1 receptor reverted the effect of the DBH inhibitor (Devoto et al., 2014b). The source of the heightened PFC DA comes from NE terminals. It was

sensitive to α_2 adrenoceptor presynaptic modulation and it was also observed in the OCC that it almost devoid of DA terminals in rodents (Devoto et al., 2012; Devoto et al., 2014b).

A strong relationship between NE and modulation of DA release has been established for the cocaine' seeking and its psychomotor effects measured using conditioned place preference and locomotor behavior. Local depletion of NE in the PFC prevented the development of place preference and increased DA release in the NAcc, indicating that noradrenergic transmission in the PFC is a necessary condition for accumbal DA release (Ventura et al., 2007). Similarly, enhanced locomotion and increased accumbal DA release was attenuated by blockade of α1 adrenoceptors in the NAcc (Mitrano et al., 2012). Blockade of α_1 adrenoceptors in the VTA blunted cocaine-evoked increase in DA and the elevation in locomotor activity. The elevation of DA relates to an increase in burst firing through modulation of both calcium-activated potassium channel current and the hyperpolarization-activated cation currents (Goertz et al., 2015).

Summary and future directions

There is clear evidence of adrenergic regulation of midbrain DA neural activity either directly though the activation of postsynaptic adrenoceptors or regulation of inputs at presynaptic glutamaterigic or GABAergic terminals. Adrenergic modulation of DA also occurs at terminal sites, where DA release and uptake can be mediated through adrenergic terminals. This latter NE regulation might be a major player in systems where DA innervation is less dense than NE innervation such as in the cortex or hippocampus (Devoto and Flore, 2006; Smith and Greene, 2012), or in systems where DA neurons lack the machinery to effectively regulate its release, as in the case in the lateral habenula (Root et al., 2015).

Although adrenergic modulation of the midbrain DA system has been a subject of research for four decades, there are many unanswered questions. In terms of basic neurobiology, a better characterization of the receptors expressed postsynaptically, presynaptically and glia within midbrain DA regions is greatly needed. There is also a need to understand how tonic and phasic release NE and E change the activity of midbrain DA regions. This can be achieved utilizing transgenic animals to selectively express opsins and receptors activated by designer drugs in combination with electrophysiology and neurochemical measurements. Similarly with respect to translational science, it is mostly unknown when NE and E levels are altered within midbrain DA regions in different animal models or under different behavioral paradigms.

Most of the interest in adrenergic regulation of midbrain DA regions is focused on the VTA, and to a lesser extent the SN. However, the strongest adrenergic innervation is to the RRF(Mejias-Aponte et al., 2009). DA neurons of the RRF are less studied than those of VTA and SN, in part because there are fewer DA neurons and more non-DA neurons in this region (Yamaguchi et al., 2013). Nevertheless, RRF might be a better research target for understanding the fundamentals of adrenergic modulation of DA neuron activity and output.

It is important to emphasize that the E system also targets the midbrain DA regions. Of the three E groups, C1 is the most prominent (Mejias-Aponte et al., 2009). These neurons are activated by physical stressors including hypoglycemia, infection or inflammation, hypoxia, nociception and hypotension (review by (Guyenet et al., 2013). They are also activated by an acute injection of cocaine (Buffalari and Rinaman, 2014), and psychological stressors including restrain stress, noise and forced swim (Dayas et al., 2001). How activation of C1 affects the activity of DA neurons is at present an unanswered question.

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Abbreviations

CLi	caudal linear nucleus of the raphe
DA	dopamine
DBH	dopamine β-hydroxylase
E	epinephrine
IF	interfascicular nucleus
LC	locus coeruleus
MAO	monoamine oxidase
NAcc	nucleus accumbens
NE	norepinephrine
Occ	occipital cortex
PFC	prefrontal cortex
RLi	rostral linear nucleus of the raphe
RRF	retrorubral field
SN	substantia nigra
VTA	ventral tegmental area
VMAT2	vesicular monoamine transporter-2

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Highlights

- LC and medullary NE and E neurons sends afferents to midbrain DA neurons.
- Adrenergic axons mainly form synaptic appositions indicative of a parachrine release of neurotransmitter.
- Both, α1 and α2 adrenoceptor, modulates DA neurons firing.
- NE axons are one of the sources of DA in the cortex, hippocampus and lateral habenula.
- In the absence of NE, DA neurons are more susceptible to toxicity.

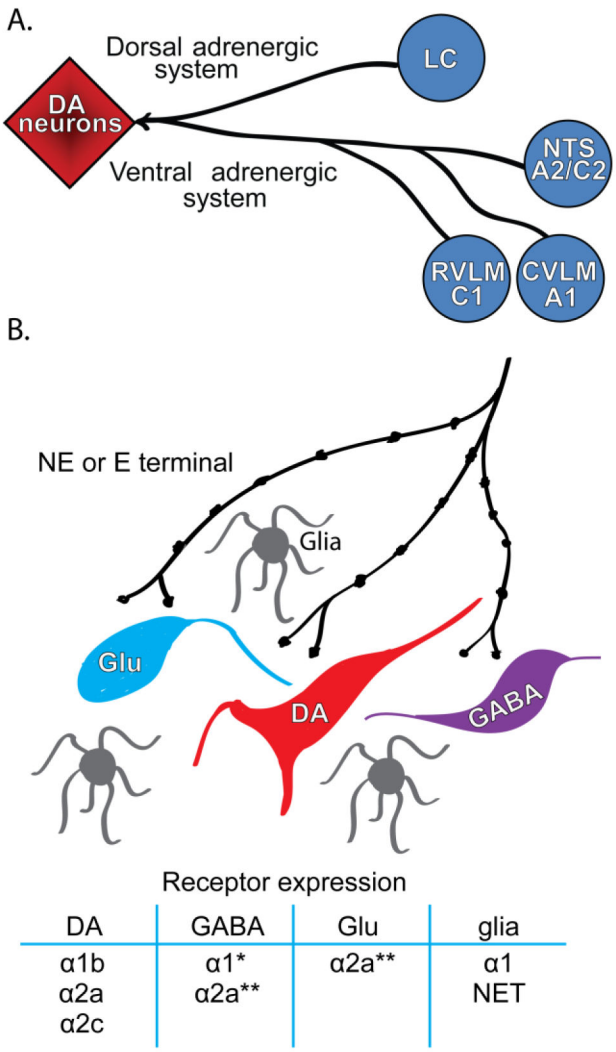

Figure 1.

Major adrenergic inputs to midbrain DA regions. A. Both ventral and dorsal adrenergic systems innervate midbrain DA regions. The source of ventral adrenergic systems inputs include the noradrenergic and epinephrine neurons in area A2/C2 located in the nucleus of the solitary tract (NTS), noradrenergic neurons in area A1 located in the cadual vetrolateral medulla (CVLM), and epinephrine neurons in area C1 located in the rostral ventrolateral medulla (RVLM). Dorsal noradrenergic innervation arises from the locus coeruleus (LC). B. Midbrain DA regions are heterogeneous in their cellular components. GABA and glutamate neurons are abundant in the VTA and RRF, and to a lesser extent in the SN. These neurons make synapses on DA neurons. Local effects of NE and E can be mediated directly at DA neurons or through their interaction with GABA and glutamate neurons and glia. Known receptors expressed on neurons and glia are listed in the table. *, expression was suggested by electrophysiological data, but lack histological confirmation; **, α2a adrenoceptors are present in non-DA neurons, but cell type is still undetermined.

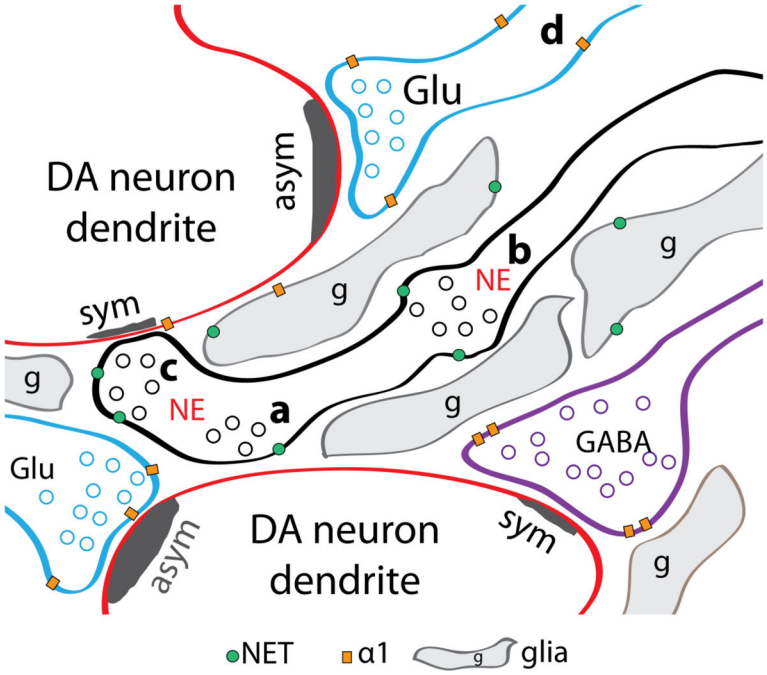

Figure 2.

Ultrastructure organization of adrenergic innervation to midbrain DA neurons. NE axons have three different synaptic specializations. The most prevalent adrenergic terminals are synaptic appositions in close proximity to synapses (a). The second most prevalent are synaptic apposition surrounded by glia (b). The less prevalent is adrenergic terminal making synaptic junctions (c). Because of the low instances of synaptic junctions, adrenergic innervation is considered a paracrine or volume transmission system. Other known detail of the adrenergic innervation is the location of NET and the α1 adrenoceptors. In addition to the expected location of NET at NE terminals, some glia also expresses NET. NE is also capable of regulating glutamate and GABA release though adrenoceptors at presynaptic terminals. The α_1 adrenoceptors are present in both glutamatergic and GABAergic terminals. It is most often found perysynaptically rather than at the synapse. Most often α_1 adrenoceptors are found extrasynaptically in unmyelinated axons (d). The α_1 adrenoceptors are also present in some glia. The ultrastructural detail of the α_2 adrenoceptors is unknown, although pharmacological and electrophysiological evidence indicate their presence in adrenergic, glutamatergic and GABAergic terminals. Abbreviations: symmetric synapse, sym; asymmetric synapse, asym; glutamate terminal, Glu; GABA terminal, GABA; NE terminal, NE.

Table 1

Adrenergic modulation of DA neuron physiology studied in in-vivo anesthetized animals

Receptor	Midbrain DA Region	Drug	Administration Route	Effect	Reference
α1	VTA	Prazosin	i.v.	Decreased burst and regulate cell firing	(Grenhoff and Svensson, 1993)
	VTA	Prazosin	i.v.	Blocked LC activation of DA neurons	(Grenhoff et al., 1993)
	VTA	Phenylephrine	Pressure	Increased firing rate and burst activity	(Goertz et al., 2015)
α2	VTA/SN	Clonidine	i.v.	Regularized firing without affecting the firing rate	(Grenhoff and Svensson, 1988; Grenhoff and Svensson, 1989)
	VTA	Clonidine	iontophoresis	Decreased firing rate	(White and Wang, 1984)
	VTA/SN	Idazoxan, Yohimbine	i.v.	Increased firing rate and burst firing	(Grenhoff and Svensson, 1988; Grenhoff and Svensson, 1993)
	VTA	Piperoxine	iontophoresis	Blocked NE inhibition on firing rate	(White and Wang, 1984)
	VTA	Idazoxan	Iontophoresis	Blocked NE inhibition on firing rate	(Guiard et al., 2008)
β	VTA/SN	Isoprotenerol	iontophoresis	Decreased firing rate	(Aghajanian and Bunney, 1977; White and Wang, 1984)
D2	VTA/SN	NE	Iontophoresis	Decreased firing rate	(Aghajanian and Bunney, 1977; White and Wang, 1984)
NET	VTA	Nisoxetine	i.v	Increased slow oscillations and burst firing	(Shi et al., 2004)

Table 2

Adrenergic modulation of DA neuron physiology studied in ex-vivo brain slices

Receptor	Site of action	Midbrain DA Region	Drug	Effect	Reference
α1	Postsynaptic	VTA	NE	Activation of calcium-activated K+ channels	(Paladini and Williams, 2004)
		VTA	Phenylephrine	Heterologous desensitization of mGluR inhibitory postsynaptic currents	(Paladini and Williams, 2004)
		VTA	Phenylephrine	Activation of inward K+ current	(Grenhoff et al., 1995; Paladini and Williams, 2004
	Presynaptic	VTA	Phenylephrine	Decrease in frequency of spontaneous IPSCs	(Velasquez-Martinez et al., 2015)
		VTA\RLi	Phenylephrine, Methoxamine	Increase in frequency of spontaneous and miniature EPSCs	(Velasquez-Martinez et al., 2012; Williams et al., 2014)
α2	Postsynaptic	VTA	Clonidine UK-14304	Inhibition of Ih current	(Inyushin et al., 2010)
		SNc	UK-14304	Activation of non-specific cationic current	(Cathala et al., 2002)
	Presynaptic	VTA	Clonidine UK14304	Decrease in frequency of spontaneous IPSCs	(Velasquez-Martinez et al., 2015)
		VTA\RLi	NE UK-14304	Increase in frequency of spontaneous and miniature EPSCs	(Velasquez-Martinez et al., 2012; Williams et al., 2014)
D2	Postsynaptic	VTA	NE	Activation of the Ih current	(Arencibia-Albite et al., 2007)