Heterogeneity of the mesotelencephalic dopamine fibers: physiology and pharmacology

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Abstract

The mesotelencephalic dopamine (DA) system is heterogeneous with respect to nuclei, terminal loci, DA receptor subtypes, electrophysiological characteristics and response patterns, and neuropharmacological response to a range of agents. The majority of mesocortical and mesolimbic DA neurons originate in the ventral tegmental area. Mesostriatal DA neurons originate in substantia nigra pars compacta. DA neurons originating from the retrorubal field primarily innervate subcortical limbic and neostriatal loci. Mesostriatal terminal loci have relatively low densities of D3 and D4 receptors, compared to mesolimbic and mesocortical loci. The D1 and D2 receptors appear more homogeneously distributed. Electrophysiologically, mesostriatal DA neurons show more regularity in firing pattern (fewer bursting events), and a lower basal firing rate than mesolimbic or mesocortical neurons. Neuropharmacologically, mesocortical DA neurons are less responsive to intravenous d-amphetamine, (+)-apomorphine, and chronic antipsychotic drug treatment. Mesocortical DA neurons are also relatively insensitive to iontophoretically applied DA, a finding congruent with their reported relative lack of somatodendritic autoreceptors. Neurochemically, mesoaccumbens DA neurons are more sensitive to systemic administration of drugs with addictive liability. © 2000 Elsevier Science Ltd. All rights reserved.

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1. Introduction

The mesotelencephalic dopamine (DA) system displays considerable heterogeneity with respect to nuclei, terminal loci, DA receptor subtypes, electrophysiological characteristics and response patterns, and neuropharmacological response to a range of agents. This heterogeneity has important implications for animal models of neuropsychiatric diseases such as attention deficit/hyperactivity disorder (ADHD).

2. Anatomy, receptors, and receptor subtypes

The mesotelencephalic DA system is generally agreed to be divided into three components—the mesostriatal (also commonly called the nigrostriatal), mesolimbic, and mesocortical. The mesostriatal DA fibers predominantly arise in the substantia nigra pars compacta (SNC), although a small portion appears to arise from the ventrolateral aspect of the ventral tegmental area (VTA) [8,9]. These mesostriatal fibers project predominantly to the caudate-putamen. However, a relatively small number of mesostriatal DA fibers innervate the amygdala (fibers primarily from substantia nigra pars lateralis), prefrontal cortex (fibers from medial-most SNC), nucleus accumbens (NAC) (fibers from medial-most SNC), anterior cingulate cortex (fibers from dorsal SNC), supracallosal cortex (fibers from dorsal SNC), and olfactory tubercle (fibers from medial SNC). The mesolimbic DA fibers predominantly arise from the VTA, with a minor component originating in various parts of the substantia nigra and the retrorubal DA cell field. The mesolimbic DA fibers project predominantly to the NAc, amygdala, bed nucleus of stria terminalis, olfactory tubercle, lateral septal area, and lateral hypothalamus, with a smaller portion projecting to various thalamic, habenular, and hypothalamic loci, and to the diagonal band of Broca. The mesocortical DA fibers predominantly arise from the VTA, although some originate in the dorsal and medial aspects of the substantia nigra. These mesocortical DA fibers primarily innervate the medial prefrontal cortex, the anterior cingulate cortex, and the suprarhinal cortex. Thus, it can be appreciated that there is a significant degree of heterogeneity in...
the anatomic origins and terminal projection loci of the mesotelencephalic DA system. In terms of DA receptors, it is currently accepted that five distinct subtypes exist, within two broad families [15,20]. The D1-like DA receptors consist of the D1 and D5. The D2-like DA receptors consist of the D2, D3, and D4 subtypes. The D2 subtype is divided into D2long and D2short variants. The D1 subtype shows highest levels in the caudate-putamen, NAc, olfactory tubercle, islands of Calleja, ventral pallidum, basolateral and intercalated nuclei of the amygdala, substantia nigra pars reticulata, and VTA. Low to moderate levels of D1 receptors are found in frontal, cingulate, parietal, piriform, temporal, and entorhinal cortices, dentate gyrus, hippocampus, subiculum, lateral septal area, bed nucleus of stria terminalis, and SNc. The D2 subtype shows highest levels in olfactory tubercle, islands of Calleja, NAc, caudate-putamen, mammillary nucleus of the hypothalamus, central nucleus of the amygdala, SNc, and VTA. Low to moderate levels of D2 receptors are found in various thalamic nuclei, the above-noted neocortical regions, hippocampal loci, ventral pallidum, globus pallidus, lateral septal area, and bed nucleus of stria terminalis. The D3 subtype shows highest levels in the olfactory tubercle, islands of Calleja, and NAc. Low to moderate levels of D3 receptors are found in SNc, neocortical areas, caudate-putamen, and globus pallidus. The D4 subtype shows highest levels in frontal cortex and suprachiasmatic nucleus of hypothalamus. Low to moderate levels of D4 receptors are found in olfactory tubercle, caudate-putamen, and hypothalamus. D5 receptors are found in highest concentrations in the mammillary nucleus of the hypothalamus, and in low to moderate levels in the thalamus and hippocampus. Thus, it may be appreciated that a considerable degree of heterogeneity exists within the mesotelencephalic DA system with respect to DA receptors and receptor subtypes, and their anatomical localization.

3. Electrophysiology

With respect to electrophysiological properties, the DA cells of the mesotelencephalic system are characterized by firing patterns of irregular single spikes or bursts of spikes with short interspike intervals [17]. Within the bursts, individual spikes show progressively decreasing amplitude and progressively increasing duration and interspike interval. Each burst is followed by a quiescent period before spiking begins again. The burst patterns have functional significance, as electrical stimulation of these neurons in a pattern which mimics natural burst firing produces a significantly greater DA release in forebrain areas innervated by these neurons compared with stimuli delivered at the same overall frequency but with a constant interstimulus interval [12]. In anesthetized animals, clear heterogeneity within the mesotelencephalic DA system is seen with respect to burst firing—approximately 73% of mesolimbic/mesocortical DA neurons display burst firing as opposed to only 18% of mesostriatal DA neurons [13]. DA neurons projecting to prefrontal and cingulate cortices display a greater degree of bursting and a higher basal discharge rate compared to DA neurons projecting to piriform cortex [5]. Work by Schultz and colleagues suggests that DA burst firing within the mesotelencephalic DA system is related, albeit in a complex fashion, to the occurrence of salient environmental stimuli with positive reinforcing value [19]. Electrophysiological studies have examined whether or not the cell bodies and dendrites of DA neurons projecting to different telencephalic targets show differences with regard to somatodendritic autoreceptors. The mesocortical DA neurons projecting to the prefrontal and cingulate cortices are insensitive to low to moderately high doses of intravenous apomorphine or microiontophoretically applied DA (even at high ejection currents) [7]. In addition, DA neurons projecting to these two cortical areas are also significantly less sensitive to bolus injections of d-amphetamine. However, DA neurons projecting to piriform cortex show a relatively high degree of sensitivity to intravenous apomorphine and microiontophoretically applied DA. Mesostrialtal and mesoaccumbens DA neurons display a pharmacologic response pattern similar to that shown by mesopiriform DA neurons. Furthermore, in vivo electrophysiological data from anesthetized rats indicate that a positive correlation exists between the firing rate of VTA DA neurons and the intravenous dose of apomorphine required to suppress the firing rate by 50% [22]. These data are consistent with the hypothesis that DA neurons projecting to the prefrontal and cingulate cortices lack somatodendritic DA autoreceptors, while DA neurons projecting to the caudate-putamen and NAc possess them. In addition, evidence exists that meso-prefrontal DA neurons have a higher DA turnover rate than either mesostriatal or mesolimbic DA neurons [2].

4. Neuropharmacology

A significant degree of heterogeneity also appears to exist within the mesotelencephalic DA system with respect to response to antipsychotic drugs. For example, in vivo electrophysiological studies show that acute administration of classical antipsychotic drugs (e.g. haloperidol, chlorpromazine) significantly increases the number of spontaneously active VTA and SNc DA neurons in anesthetized rats. In contrast, atypical antipsychotics (e.g. clozapine) selectively increase the number of spontaneously active VTA DA neurons while generally not affecting SNc DA neurons [1,5,6,21]. Chronic administration of classical antipsychotic drugs produces a significant decrease in the number of spontaneously active SNc and VTA DA neurons. In contrast, chronic administration of atypical antipsychotics decreases the number of spontaneously active DA neurons selectively in VTA, an effect known to result from depolarization
inactivation. However, the subset of VTA neurons projecting to prefrontal cortex do not display depolarization inactivation [6]. Lesion experiments indicate that feedback pathways from forebrain to ventral mesencephalon may be differentially important for the maintenance of antipsychotic drug-induced inactivation of mesostriatal versus mesolimbic/mesocortical neurons. Thus, on day 21 of repeated chlorpromazine administration, acute microknife cuts between mesencephalon and telencephalon immediately reverse the depolarization inactivation of mesostriatal but not mesolimbic DA neurons [6]. Experiments using in vivo brain microdialysis and in vivo voltammetric electrochemistry to measure DA release from mesostriatal and mesolimbic DA terminal fields also show that these two subcomponents of the mesotelencephalic DA system respond differently to classical and atypical antipsychotics. Thus, acute administration of the atypical antipsychotic clozapine preferentially alters DA release in NAc as opposed to caudate-putamen [14]. Also, chronic administration of classical versus atypical antipsychotics differentially decreases dopamine release in the mesostriatal versus mesolimbic DA system [3]. Using in vivo brain microdialysis, chronic administration with the atypical antipsychotic clozapine selectively decreases basal DA release in NAc (apparently due to depolarization blockade) but not in caudate-putamen [4,11]. Other microdialysis studies suggest that the atypical antipsychotic clozapine preferentially increases DA release in prefrontal cortex, as compared to its inhibitory actions in NAc and as compared to the inhibitory actions of the classical antipsychotic haloperidol in prefrontal cortex [16,18]. The mesotelencephalic DA system also appears to show heterogeneity with respect to the actions of addictive drugs. Thus, in vivo microdialysis studies show that addictive drugs selectively enhance extra-cellular DA overflow in NAc as compared to other telencephalic DA terminal loci [10]. Intracerebral microinjection studies show that animals preferentially self-administer addictive drugs into mesolimbic (VTA, NAc, lateral hypothalamus) DA loci and prefrontal cortex, as compared to other brain loci [10].

5. Conclusion

In summary, based on evidence from a wide variety of experimental paradigms and approaches, the mesotelencephalic DA system appears to show substantial anatomical, receptor localization, neurophysiological, and neuropharmacological heterogeneity. This heterogeneity—and the heterogeneity and complexity of behavioral and central information processing functions subserved by the mesotelencephalic DA system that it implies—is far too often ignored by behavioral and cognitive neuroscientists developing models of mesotelencephalic DA function to explain human neuropsychiatric diseases such as schizophrenia, mania, drug addiction, and attention deficit/hyperactivity disorder (ADHD). To the extent that such models presume that the mesotelencephalic DA system subserves simple and/or homogeneous behavioral and cognitive functions, they must perforce be incomplete and/or incorrect.

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