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Environment- and activity-dependent dopamine neurotransmitter plasticity in the adult substantia nigra

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ABSTRACT

The ability of neurons to change the amount or type of neurotransmitter they use, or 'neurotransmitter plasticity', is an emerging new form of adult brain plasticity. For example, it has recently been shown that neurons in the adult rat hypothalamus up- or down-regulate dopamine (DA) neurotransmission in response to the amount of light the animal receives (photoperiod), and that this in turn affects anxiety- and depressive-like behaviors (Dulcis et al., 2013). In this Chapter I consolidate recent evidence from my laboratory suggesting neurons in the adult mouse substantia nigra pars compacta (SNc) also undergo DA neurotransmitter plasticity in response to persistent changes in their electrical activity, including that driven by the mouse's environment or behavior. Specifically, we have shown that the amounts of tyrosine hydroxylase (TH, the rate-limiting enzyme in DA synthesis) gene promoter activity, TH mRNA and TH protein in SNc neurons increases or decreases after ~20 h of altered electrical activity. Also, infusion of ion-channel agonists or antagonists into the midbrain for 2 weeks results in ~10% (~500 neurons) more or fewer TH immunoreactive (TH+) SNc neurons, with no change in the total number of SNc neurons (TH+ and TH−). Targeting ion-channels mediating cell-autonomous pacemaker activity in, or synaptic input and afferent pathways to, SNc neurons are equally effective in this regard. In addition, exposing mice to different environments (sex pairing or environment enrichment) for 1–2 weeks induces ~10% more or fewer TH+ SNc (and ventral tegmental area or VTA) neurons and this is abolished by concurrent blockade of synaptic transmission in midbrain. Although further research is required to establish SNc (and VTA) DA neurotransmitter plasticity, and to determine whether it alters brain function and behavior, it is an exciting prospect because: (1) It may play important roles in movement, motor learning, reward, motivation, memory and cognition; and (2) Imbalances in midbrain DA cause symptoms associated with several prominent brain and behavioral disorders such as schizophrenia, addiction, obsessive-compulsive disorder, depression, Parkinson's disease and attention-deficit and hyperactivity disorder. Midbrain DA neurotransmitter plasticity may therefore play a role in the etiology of these symptoms, and might also offer new treatment options.

1. Introduction

Long-lasting changes in the brain or 'brain plasticity' underlie adaptive behavior or learning and memory in healthy individuals, and symptom etiology and brain repair in neurological disease or injury. Established forms of brain plasticity such as neurogenesis, neurodegeneration and synaptic plasticity arise following stimuli that trigger biochemical signaling leading to altered gene and protein expression inside cells, altered cell phenotype, and ultimately brain function and behavioral changes. Notionally, these generic mechanisms could encompass any gene or protein, so it is likely that undiscovered or less-established forms of brain plasticity exist.

Neurotransmitter plasticity, the topic of this Special Issue, is a less-established form of brain plasticity that at its core comprises altered expression of genes and/or their protein products necessary for neurons to communicate using a particular neurotransmitter. This has the potential to alter neurotransmission in the brain and thereby brain function and behavior. Indeed, Dulcis et al. (2013) recently showed that neurons in the adult rat hypothalamus up- or down-regulate dopamine (DA) synthesis and neurotransmission in response to the amount of light exposure the animal receives (photoperiod), and that this in turn affects anxiety- and depressive-like behaviors. Thus, present indications are that neurotransmitter plasticity is a legitimate new form of adult brain plasticity with significant implications for brain function and behavior.

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In this Chapter I consolidate recent evidence from my laboratory suggesting environment- and activity-dependent DA neurotransmitter plasticity occurs also in the adult substantia nigra pars compacta (SNc) and ventral tegmental area (VTA) of the midbrain. Midbrain DA plays important roles in movement, motor learning, reward, motivation, memory and cognition; therefore midbrain DA neurotransmitter plasticity could potentially affect these behaviors. Furthermore, imbalances in midbrain DA cause symptoms associated with several prominent brain and behavioral disorders such as schizophrenia, addiction, obsessive-compulsive disorder (OCD), depression, Parkinson's disease (PD) and attention-deficit and hyperactivity disorder (ADHD). Therefore midbrain DA neurotransmitter plasticity may play a previously unrecognized role in the etiology of these symptoms and, more significantly, may offer new treatment options. In these lights I also review the cytoarchitecture and neurotransmitter phenotypes of SNc neurons with a view to helping identify those cells that are capable of DA neurotransmitter plasticity. This is crucial for verifying SNc DA neurotransmitter plasticity, as well as determining its cellular mechanisms. I conclude with a catalog of outstanding questions to help guide future research on the subject, including a summary of how I believe SNc DA neurotransmitter plasticity occurs and what its neurobiological and behavioral consequences are likely to be. This is helpful for designing future experiments to test whether SNc DA neurotransmitter plasticity is neurobiologically and behaviorally relevant.

2. Terminology

Before proceeding, it is helpful to define some terminology.

I define 'DA phenotype' as cellular expression of genes and their protein products that are necessary to synthesize and handle DA as a neurotransmitter [*e.g.* tyrosine hydroxylase (TH), aromatic L-amino acid decarboxylase (AADC), guanosine triphosphate cyclohydrolase (GTPCH), vesicular monoamine transporter (vMAT), DA transporter (DAT)]. I sometimes refer to these molecules as 'DA genes' or 'DA proteins'.

Also, in literature on the subject of neurotransmitter plasticity generally, the term 'neurotransmitter switching' is sometimes used. I view neurotransmitter switching as an extreme form of neurotransmitter plasticity, wherein expression of neurotransmitter genes or proteins is up-regulated from zero, *i.e.* 'switched on', or down-regulated to zero, *i.e.* 'switched off'. Nonetheless, any distinction between plasticity and switching is incidental because: (1) Current technologies are not sufficiently sensitive to distinguish whether a gene or protein has been switched completely on or off *versus* regulated above or below detection threshold; and (2) Either way there are large changes in the amounts of neurotransmitter genes or proteins in cells, which are likely to lead to large changes in neurotransmission and therefore brain function and behavior. In the interests of accuracy, clarity and consistency I will use 'neurotransmitter plasticity' rather than 'neurotransmitter switching' throughout most of this Chapter, although the two are sometimes interchangeable.

Another important point is 'neurotransmitter switching' can mean switching one (or more) neurotransmitter(s) on or off in a cell independent of changes in a different neurotransmitter(s) in the same cell, or it can mean a cell switching between different neurotransmitters, *e.g.* switching one neurotransmitter off and another neurotransmitter on. In our work so far we have evidence only of DA neurotransmitter plasticity in midbrain neurons, so it is presently unclear which of these two possibilities pertain.

3. Possible dopamine neurotransmitter plasticity following 6-OHDA susbstantia nigra lesions in rodents and in Parkinson's disease

I begin here because my laboratory's interest in DA neurotransmitter plasticity developed out of my colleagues' studies of axon sprouting by SNc neurons that survive partial 6-hydroxy-DA (6-OHDA; a neurotoxin that specifically kills DA neurons and is often used to model PD) SNc lesions in adult rats (Stanic et al., 2003). In addition to sprouting, they reported an early-phase loss of ~2500 TH immuno-positive (TH+) and concurrent gain of ~2500 TH immuno-negative (TH−) SNc neurons [2–16 weeks after lesion in Fig. 4b of (Stanic et al., 2003)], as well as a later-phase gain of ~2500 TH+ and concurrent loss of ~2500 TH− neurons [16–32 weeks after lesion in Fig. 4b of (Stanic et al., 2003)]. Both phases are consistent with changes or plasticity in the amount of TH protein in cells, specifically loss then re-acquisition of TH by the same SNc neurons. Transient loss of TH immunoreactivity in SNc neurons has also been reported following striatal infarction subsequent to transient focal cerebral ischemia (Soriano et al., 1997). Combinations of neurodegeneration and neurogenesis are unlikely to account for these changes because the weight of evidence indicates neurogenesis does not occur in the adult rodent SNc [(Aponso et al., 2008; Chen et al., 2005; Frielingsdorf et al., 2004; Lie et al., 2002; Peng et al., 2008; Yoshimi et al., 2005) but see (Zhao et al., 2003)].

In adult humans, and particularly those with PD, there is also evidence of SNc DA neurotransmitter plasticity. TH mRNA levels vary in different SNc neurons in both normal and PD brains (Javoy-Agid et al., 1990; Kingsbury et al., 1999). While low TH expression could be a pre-morbid state (Javoy-Agid et al., 1990), the similar number of cells with low TH in normal and PD brains (Kingsbury et al., 1999) suggests low TH has physiological significance. In normal brains the number of SNc cells expressing DA markers (TH, DAT and GTPCH) progressively decreases with age (Chen et al., 2000; Chu et al., 2002; Emborg et al., 1998; Ma et al., 1999) whereas the number of SNc cells containing neuromelanin (another marker of DA cells) does not change (Chu et al., 2002), indicating TH expression can be lost independent of neurodegeneration. With respect to up-regulation of DA genes and proteins, neuromelanin-negative cells have more TH mRNA in PD than control brains (Kingsbury et al., 1999), and surviving SNc neurons have increased TH but decreased DAT mRNA in PD compared with control brains (Joyce et al., 1997). Note that increased TH and decreased DAT appear also in SNc neurons following 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, another neurotoxin that specifically kills DA neurons and is often used to model PD) administration in cats, and is associated with recovery of motor function in these animals [(Rothblat et al., 2001), see also (Blanchard et al., 1995)]. Thus, plasticity of DA genes may reflect compensatory upregulation of DA neurotransmission by fewer SNc neurons.

4. Substantia nigra dopamine neurotransmitter plasticity is activity-dependent

Prompted by the above suggestions of plasticity of TH expression in SNc neurons, we documented the functional properties, *i.e.* electrophysiology, of SNc neurons undergoing putative DA neurotransmitter plasticity following 6-OHDA lesions in mice (Aumann et al., 2008). We performed whole-cell patch clamp recordings of individual SNc cells in *ex vivo* midbrain slices that were acutely prepared at different times after 6-OHDA. Their TH expression status was determined by single-cell reverse transcriptase polymerase chain reaction (RT-PCR) of a sample of cytoplasm that was aspirated into the tip of the recording