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The effect of striatal dopamine depletion on striatal and cortical glutamate: A mini-review

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ABSTRACT

Understanding the interplay between the neurotransmitters dopamine and glutamate in the striatum has become the highlight of several theories of neuropsychiatric illnesses, such as schizophrenia. Using in vivo brain imaging in humans, alterations in dopamine and glutamate concentrations have been observed in several neuropsychiatric disorders. However, it is unclear a priori how alterations in striatal dopamine should modulate glutamate concentrations in the basal ganglia. In this selective mini-review, we examine the consequence of reducing striatal dopamine functioning on glutamate concentrations in the striatum and cortex; regions of interest heavily examined in the human brain imaging studies. We examine the predictions of the classical model of the basal ganglia, and contrast it with findings in humans and animals. The review concludes that chronic dopamine depletion (>4 months) produces decreases in striatal glutamate levels which are consistent with the classical model of the basal ganglia. However, acute alterations in striatal dopamine functioning, specifically at the D_2 receptors, may produce opposite affects. This has important implications for models of the basal ganglia and theorizing about neurochemical alterations in neuropsychiatric diseases. Moreover, these findings may help guide a priori hypotheses for ^{1}H-MRS studies measuring glutamate changes given alterations in dopaminergic functioning in humans.

1. Introduction

Dopamine and glutamate interact with each other in the basal ganglia and prefrontal cortex, intimately regulating each other's function and release (David et al., 2005; Del Arco and Mora, 2008; Jones, 2012). Abnormalities in these dopaminergic and glutamatergic systems have been observed in numerous neuropsychiatric disorders, including Parkinson's disease (Griffith et al., 2008; Loane and Politis, 2011; Pavese et al., 2011), depression (Musazzi et al., 2012; Treadway and Zald, 2011), drug addiction (Martinez et al., 2009; Yang et al., 2009; Yucel et al., 2007), and schizophrenia (de la Fuente-Sandoval et al., 2013a,b; de la Fuente-Sandoval et al., 2011; Kegeles et al., 2010). The classical model of the basal ganglia developed in the 1980s (Obeso and Lanciego, 2011) predicts that loss of striatal dopamine will decrease extracellular levels of glutamate in the striatum and cortex (Albin et al., 1989, 1995; Jones, 2012). Similarly, it predicts that increasing levels of striatal dopamine should increase levels of glutamate in the striatum and cortex. However, the classical model of the basal ganglia is an incomplete one. For instance, it does not take into account the influence of the cholinergic system, and has been criticized for offering a better understanding of pathology rather than normal functioning (Obeso et al., 2008; Obeso et al., 2000). Undoubtedly, the in vivo environment in which dopamine–glutamate interactions take place in the basal ganglia is far more complex than suggested by the classical model.

Positron emission tomography (PET) and proton magnetic resonance spectroscopy (^{1}H-MRS) are two non-invasive brain-imaging techniques, which allow for quantification of biochemical information about the living human brain. PET employs the use of radiolabelled probes, termed radiotracers or radioisotopes (Baron, 2005; Das, 2015). These radiotracers are positron emitting isotopes which are chemically incorporated into a biologically active molecule (Das, 2015). For example, the accumulation of ^{18}F-labeled 3,4-dihydroxy-6-[18F]fluoro-L-phenylalanine ([^{18}F]F-DOPA) in the brain measured with PET can be used as a quantitative index of dopamine synthesis capacity (Nanni et al., 2007; Pretze et al., 2014). Moreover, dopamine $D_{2/3}$ receptor availability, as well as changes in dopamine concentrations at these receptors, can be measured with ^{11}C- and ^{18}F-labeled compounds such as [^{11}C]-raclopride, [^{11}C]-(+)-PHNO, and [^{18}F]-fallypride. ^{1}H-MRS allows for quantification of concentrations of several neurometabolites, which are characterized by their unique set of ^{1}H chemical shifts (Rae, 2014). These include glutamate, glutamine, glutamate + glutamine

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(Glx), creatine (Cr), myo-inositol (Myo), and N-acetyl-aspartate (NAA), among several others (Rae, 2014).

Findings from in vivo brain imaging in neuropsychiatric populations have largely supported the predictions of the basal ganglia model. For instance, Parkinson's disease is a neurodegenerative disorder characterized by progressive loss of nigral-striatal dopamine, which has been supported by in vivo brain imaging using PET (Loane and Politis, 2011; Pavese et al., 2011). Using ^{1}H-MRS, it has been observed that patients with Parkinson's disease have less glutamate-to-creatine ratios in the anterior cingulate gyrus compared to healthy controls (−46%; Cohen's d = 1) (Griffith et al., 2008). This is consistent with the predictions of the classical model: less striatal-nigral dopamine, less cortical glutamate. Notably, no studies have yet been published investigating glutamate concentrations in the striatum of persons with Parkinson's disease with ^{1}H-MRS.

Using PET it has been demonstrated that persons with cocaine addiction have reduced dopamine $D_{2/3}$ receptor ($D_{2/3}$R) availability, reduced endogenous dopamine levels at $D_{2/3}$R, and reduced evoked dopamine release (Martinez et al., 2009). Consistent with the basal ganglia model, persons with cocaine addiction have also been observed to have less glutamate-to-creatine in the rostral anterior cingulate (Yang et al., 2009), and less glutamate-to-glutamine in the dorsal anterior cingulate (Yucel et al., 2007), compared to healthy controls. Striatal concentrations of glutamate measured with ^{1}H-MRS have not yet been examined in persons with drug addiction.

In patients affected by schizophrenia, it has been demonstrated with PET that there is more endogenous dopamine occupying $D_{2/3}$R in the dorsal caudate (Caravaggio et al., 2015; Kegeles et al., 2010). In accordance with the classical model, it has been demonstrated with ^{1}H-MRS that persons at ultra-high risk for psychosis (characterized by subthreshold psychotic symptoms, a high likelihood of a family history of schizophrenia, and a decline in everyday functioning) and patients with a first episode of psychosis have increased glutamate levels in the dorsal caudate compared to healthy controls (de la Fuente-Sandoval et al., 2013a,b; de la Fuente-Sandoval et al., 2011). Note that ultra-high risk for psychosis was assessed using the Structured Interview for Prodromal Syndromes (SIPS) criteria (Miller et al., 2003). Moreover, it has been shown that four weeks of antipsychotic administration can reduce glutamate levels in the dorsal caudate of schizophrenia patients similar to the levels of healthy controls (de la Fuente-Sandoval et al., 2013a,b). Importantly, in ultra-high risk persons, higher glutamate levels in the striatum were predictive of transitioning into psychosis (de la Fuente-Sandoval et al., 2013a,b).

The aforementioned in vivo brain imaging findings in neurological and neuropsychiatric populations are notably prima facie observations. That is to say that the observed differences in dopamine and glutamate concentrations are correlational and presented as a point of reference to the predictions of the classical model of the basal ganglia. Undoubtedly the cause(s) of abnormal dopamine–glutamate interactions will differ across neurological and psychiatric disorders. For example, it has been proposed that hypofunctioning of the N-methyl-D-aspartate (NMDA) receptor may account for the increased glutamate and exacerbated psychostimulant-induced dopamine release observed in schizophrenia patients (Plitman et al., 2014; Poels et al., 2014). Like all working models, the NMDA receptor hypofunctioning model of schizophrenia requires further validation and support (Laruelle, 2014; Laruelle et al., 2005). Regardless of what the sine qua non may be for abnormal dopamine levels observed across neurological and neuropsychiatric populations, the in vivo brain imaging data suggests that decreased striatal dopamine is related to decreased striatal glutamate, and vice-versa. Future work is required to tease out the subtleties, causes, and consequences of these observed correlational changes in neurochemistry across disorders.

One study has simultaneously examined in healthy persons striatal dopamine synthesis capacity measured with [^{18}F]-DOPA and glutamate concentrations measured with ^{1}H-MRS (Gleich et al., 2015). Importantly, a positive correlation was observed between left ventral striatal glutamate concentrations and left ventral striatal dopamine synthesis capacity ($r^2 = .17$). This is at least prima facie consistent with the notion that increased dopaminergic activity in the striatum should also result in greater glutamatergic activity therein. This also mirrors the findings in persons with schizophrenia, wherein both increased striatal dopamine and striatal glutamate levels are observed compared to healthy controls; albeit in the dorsal striatum (Caravaggio et al., 2015; Kegeles et al., 2010). However, a negative correlation was observed between glutamate concentrations in the left prefrontal cortex and dopamine synthesis capacity in the left ventral striatum ($r^2 = .17$). Future PET studies examining dopamine synthesis capacity or endogenous dopaminergic tone (Caravaggio et al., 2014; Laruelle et al., 1997; Verhoeff et al., 2001) should also examine glutamate concentrations measured with ^{1}H-MRS in the dorsal striatum and cortex; in healthy persons and persons with neuropsychiatric diseases.

The effect of dopamine depletion on the glutamatergic system has been extensively investigated in non-human primates and rodents, using a myriad of methods and techniques (David et al., 2005). However, these in vivo and ex vivo investigations have often not yielded consistent support for the classical model's predictions. The findings from these studies will be summarized below, separated by their respective method/technique.

2. Effects of dopamine depletion on tissue concentrations of free amino acids

Singh and Malhotra (1964) examined the effect of reserpine-induced (0.5 mg/kg, iv) dopamine depletion on brain tissue concentrations of numerous amino acids in adult Rhesus monkeys. They observed that reserpine significantly reduced glutamic acid/glutamate concentrations in the amygdala (390.9 ± 37.68 vs. 317.9 ± 11.4, $p < 0.001$), hippocampus (340.9 ± 18.4 vs. 292.1 ± 22.7, $p < 0.001$), and cerebellum (342.8 ± 20.38 vs. 315.2 ± 20.4, $p < 0.001$), with the largest effect observed in the cerebellum. However, concentrations in the midbrain significantly increased (155.3 ± 11.8 vs. 190.6 ± 19.7, $p < 0.001$), while there was no observed change in the frontal lobe and hypothalamus. Tanaka et al. (1986) examined the effect of unilateral 6-hydroxydopamine (6-OHDA) lesions (8 μg) in Wistar rats on striatal concentrations of glutamate. After 9 months of dopamine denervation, they observed that glutamate content was significantly decreased in the striatum (8.87 ± 0.48 vs 7.72 ± 0.76, $p < 0.05$). However, this study did not compare glutamate content between 6-OHDAtreated rats and controls. Rather, they examined striatal tissue concentrations ipsilateral and contralateral to the 6-OHDA lesion in the same rats. Lindefors and Ungerstedt (1990) demonstrated, in Sprague-Dawley rats, that unilateral 6-OHDA lesions (2 μg/μl) caused a significant increase in tissue concentrations of glutamate both ipsilateral (45%) and contralateral (39%) to the lesion compared to controls. Thus, the lack of a proper sham-lesion control group poses a major flaw in interpreting the findings from Tanaka and colleagues. Collectively, these data suggests that dopamine depletion does not change tissue concentrations of glutamate in the cortex, increases concentrations in the striatum bilaterally, and decreases concentrations in the cerebellum.

3. Microdialysis of extracellular glutamate

Lindefors and Ungerstedt (1990) showed that unilateral 6-OHDA lesions in Sprague-Dawley rats resulted in increased extracellular release of glutamate in the striatum (by 107% ipsilateral to lesion, 94% contralateral). This is in accordance with their finding of increased striatal tissue concentrations of glutamate given the same administration of 6-OHDA. Biggs and Starr (1997) investigated how multiple dopaminergic manipulations affect extracellular glutamate release in the entopeduncular nucleus (globus pallidus in humans) in Wistar rats. They found that administration of the dopamine $D_{2/3}$ agonist