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Where is Dopamine and How Do Immune Cells See It?: Dopamine-Mediated Immune Cell Function in Health and Disease

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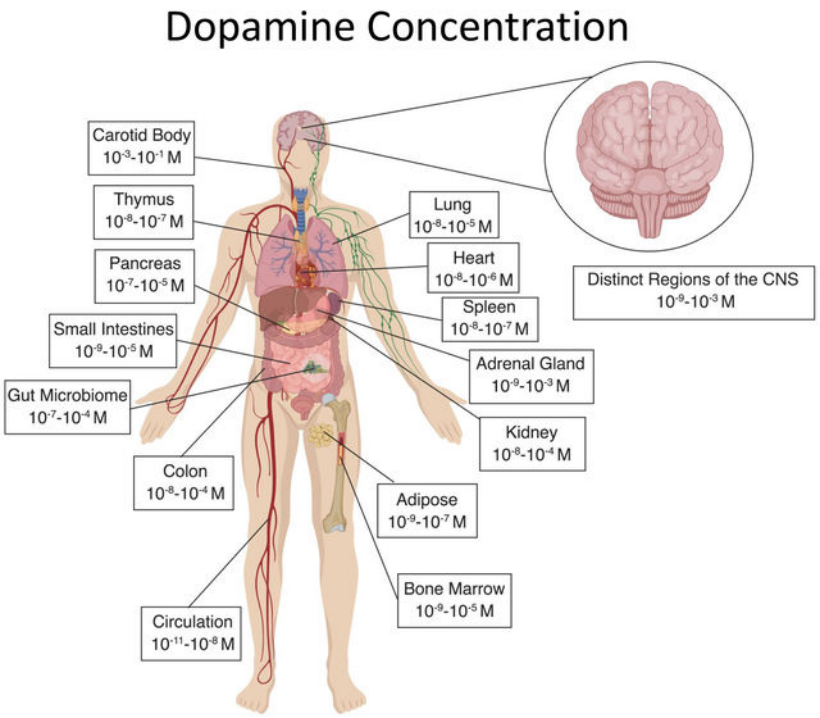
Abstract

Dopamine is well recognized as a neurotransmitter in the brain, and regulates critical functions in a variety of peripheral systems. Growing research has also shown that dopamine acts as an important regulator of immune function. Many immune cells express dopamine receptors and other dopamine related proteins, enabling them to actively respond to dopamine and suggesting that dopaminergic immunoregulation is an important part of proper immune function. A detailed understanding of the physiological concentrations of dopamine in specific regions of the human body, particularly in peripheral systems, is critical to the development of hypotheses and experiments examining the effects of physiologically relevant dopamine concentrations on immune cells. Unfortunately, the dopamine concentrations to which these immune cells would be exposed in different anatomical regions are not clear. To address this issue, this comprehensive review details the current information regarding concentrations of dopamine found in both the central nervous system and in many regions of the periphery. In addition, we discuss the immune cells present in each region, and how these could interact with dopamine in each compartment described. Finally, the review briefly addresses how changes in these dopamine concentrations could influence immune cell dysfunction in several disease states including Parkinson's disease, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, as well as the collection of pathologies, cognitive and motor symptoms associated with HIV infection in the central nervous system, known as NeuroHIV. These data will improve our understanding of the interactions between the dopaminergic and immune systems during both homeostatic function and in disease, clarify the effects of existing dopaminergic drugs and promote the creation of new therapeutic strategies based on manipulating immune function through dopaminergic signaling.

Graphical Abstract



Keywords

Dopamine; neuroimmunology; immune system; catecholamine

Introduction

Dopamine, or 3-hydroxytyramine, is a catecholamine neurotransmitter that is associated with a variety of neurological processes, including motor control, cognition, learning and reward. In addition to these and other central nervous system (CNS) processes, dopamine influences numerous peripheral functions including gastrointestinal motility, hormone release, blood pressure and sodium balance. While dopamine was first synthesized in 1910 (Hornykiewicz 1986), it wasn't until 1957 that dopamine was found in the human brain (Montagu 1957). Prior to this discovery, dopamine had only been found in peripheral tissues and body fluids of mammalian animals (Euler and Hellner 1951; Goodall 1951) and was assumed to be just a precursor to other catecholamines. This changed in 1958, when Arvid Carlsson found that dopamine acted as a neurotransmitter (Carlsson, Lindqvist, Magnusson, & Waldeck, 1958), and was primarily concentrated in the basal ganglia of both humans and rodents (Bertler and Rosengren 1959; Sano et al. 1959). Soon after, the development of fluorescent histochemical visualization of monoamines enabled observation of neuronal pathways containing dopamine (Carlsson et al. 1962), establishing an independent role for dopamine and leading to the identification of specific dopamine receptors (Kebabian et al. 1972; Seeman et al. 1976) and their signaling pathways (Kebabian and Calne 1979).

The immunomodulatory activities of dopamine were first proposed in the 1980's and 1990's, when a number of studies suggested immune cells contain components of the

dopaminergic system (Cosentino et al. 1999; Le Fur et al. 1980; Musso et al. 1996; Santambrogio et al. 1993). Many studies now show that dopamine functions as an immunomodulatory regulator and is pivotal for neuroimmune communication, with recent studies finding dopamine-induced changes in the functions of lymphocytes, macrophages, neutrophils and monocytes (Calderon et al. 2017; Dos-Santos-Pereira et al. 2018; Fan et al. 2018; Gaskill et al. 2014; Kawano et al. 2018; Nolan et al. 2018). Significant progress has also been made in understanding the specific dopaminergic signaling mechanisms in a variety of cell types other than neurons, indicating that immune cells interact with dopamine centrally and peripherally, in both homeostatic and pathological conditions.

However, the physiological concentrations of dopamine in specific regions of the human body, particularly in peripheral systems, remain unclear due to a relative scarcity of data on this topic, and the large variability among those studies which have been done. Further, most studies comparing distinct effects of dopamine between tissues focus on the expression of dopamine receptors, but not the concentration of dopamine itself. This presents a significant problem in the field, as lack of information prevents the development of hypotheses and experiments examining the effects of physiologically relevant dopamine concentrations on immune function. The purpose of this review is to fill this knowledge gap, providing a comprehensive summary of the available data regarding dopamine concentrations and activities throughout the body in both humans and animal models. Recognizing the heterogeneity of dopamine concentrations and the cells that regulate it across distinct tissue milieu is critical to defining the complex role of this neurotransmitter in the immune response. Further, many dopaminergic drugs are currently in use as therapeutics for a variety of disorders including depression, Alzheimer’s disease, and Parkinson’s disease, so a more comprehensive understanding of the immunologic actions of dopamine could initiate drug repurposing and the development of new therapeutic strategies based on manipulating dopaminergic immunology.

Overview of the Dopaminergic System

Dopamine Receptors

Dopamine primarily mediates its effects through activation of dopamine receptors (DRs), which are members of the G protein-coupled receptor (GPCR) superfamily. Dopamine receptors are divided into 2 subgroups, D1-like (D1 and D5), and D2-like (D2, D3 and D4) (Beaulieu and Gainetdinov 2011; Missale et al. 1998), which have different affinities for dopamine (Mittal et al. 2017). Greengard and colleagues showed that dopamine acts on D1-like receptors to increase the formation of cAMP (Hemmings Jr et al. 1984), and this pathway now serves as the basis for the distinction between DR subtypes. The D1-like receptors couple to Gαs/olf and stimulate cAMP production, while D2-like DR couple to $G_{\alpha i/o}$ and inhibit cAMP production. In addition to regulating cAMP, DRs can act through several alternative signaling pathways. The most studied is the Gq/11 mediated activation of phospholipase C (PLC) which induces calcium release from the endoplasmic reticulum through activation of IP_3 receptors (Felder et al. 1989; Jin et al. 2001; Wang et al. 1995). Dopamine also mediates β-arrestin 2 induced activation of Akt, and the transactivation of tyrosine receptor kinases (RTKs) such as BDNF and TrkB (Beaulieu et al. 2015). Additional

signaling complexity is generated by the formation of oligomeric complexes with other GPCR, such as D2-D4 or D2 with the adenosine A_2A receptor (Borroto-Escuela et al. 2011; Fiorentini et al. 2008; Fuxe et al. 2010; Lee et al. 2002; Łukasiewicz et al. 2016; Perreault et al. 2010; Perreault et al. 2014), although formation of some of these heteromers is controversial (Frederick et al. 2015). A more detailed discussion of DR signaling and pharmacology can be found in Beaulieu and Gainetidinov (Beaulieu and Gainetdinov 2011).

Dopamine Synthesis, Metabolism, Storage, and Transport

This has been covered extensively in other recent reviews (Arreola et al. 2016; Nolan and Gaskill 2018), so we will only briefly cover this topic. Dopamine is derived from a two-step process starting with the hydroxylation of L-tyrosine by the enzyme tyrosine hydroxylase (TH) (Meiser et al. 2013), followed by the decarboxylation of the resulting product, L-DOPA, by aromatic amino acid decarboxylase (AADC). This process primarily occurs in dopaminergic neurons, although immune cells (Nolan and Gaskill 2018) and other cells from peripheral tissues (Mezey et al. 1998; Nurse and Fearon 2002; Pilipović et al. 2008) also express enzymes for dopamine synthesis (Rubí and Maechler 2010; Ugrumov 2009). In neurons, once dopamine is produced, it is either stored in synaptic vesicles at high concentrations (mM) (Omiatek et al. 2013; Scimemi and Beato 2009) for future release, or hydroxylated to form norepinephrine if the cell contains dopamine-β-hydroxylase (DBH). Dopamine is released into the synaptic cleft upon neuronal excitation, and excess dopamine in the cleft is returned to the cell by reuptake through the dopamine transporter (DAT), located at the presynaptic membrane. The norepinephrine transporter (NET) can also take-up dopamine in areas where the concentration of DAT is low (Moron et al. 2002). After returning to the neuron, dopamine is translocated from the cytoplasm to storage vesicles by vesicular monoamine transporter 2 (VMAT2), located on vesicular membranes. Dopamine remaining in the cytoplasm is inactivated through multiple pathways including oxidative deamination by monoamine oxidase (MAO) and *O*-methylation by catechol-*O*-methyl transferase (COMT), leading to the formation of dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) (Kopin 1985; Korf et al. 1976). In addition, formation of dopamine sulfate, the predominant form of dopamine in circulation, is catalyzed by phenolsulfotransferases (PSTs) and glucuronidation is catalyzed by uridine diphosphoglucuronosyltransferases (UGTs) to form their respective inactive conjugates (Suominen et al. 2015; Suominen et al. 2013; Uutela et al. 2009). Dopamine is also susceptible to oxidation, producing reactive quinones and reactive oxygen species that can cause cell damage and neurodegeneration (Delcambre et al. 2016; Meiser et al. 2013).

Dopaminergic Interaction with Immune Cells

The immune and nervous systems participate in extensive bidirectional crosstalk, mediated by a wide array of neurotransmitters, hormones, cytokines, and other factors, including dopamine. Dopamine regulates a variety of immune functions including cytokine secretion, cell adhesion, cytotoxicity, and chemotaxis (Besser et al. 2005; Cosentino et al. 2007; Gaskill et al. 2012; Kipnis et al. 2004; Nolan et al. 2018; Watanabe et al. 2006a), and these immune functions in turn can affect dopaminergic signaling both centrally and peripherally (Kabiersch et al. 1998; Kumai et al. 2000; Song et al. 2006). The effects are likely mediated by activation of DRs, as both human and rodent immune cells express multiple DR subtypes,

however, DRs on distinct immune cell types may have different sensitivities to dopamine (Ferrari et al. 2004). These cells may also respond to different dopamine concentrations than those required for classical dopamine signaling in neurons (Meredith et al. 2006). The specific effects of dopamine on immune function have been described in recent articles (Gaskill et al. 2013; Levite 2016; Nolan and Gaskill 2018; Pinoli et al. 2017), therefore this section will only briefly discuss the immune cells in the CNS and periphery which could respond to dopamine.

Dopamine-Immune Interactions in CNS Immune cells—In the CNS, microglia are the predominant immune effector cells and they express functional DRs (Farber et al. 2005; Huck et al. 2015; Kopec et al. 2017; Mastroeni et al. 2009), as well as other dopaminergic proteins (Fan et al. 2018; Myohanen et al. 2010). Microglia are heterogeneously located throughout the brain, and are likely to encounter dopamine in any brain region where it is elevated. In addition to microglia, different types of CNS macrophages including perivascular, juxtavascular, meningeal and choroid plexus macrophages are active in the CNS immune response in their cognate regions (Corraliza 2014; Nayak et al. 2012). Human monocyte-derived macrophages have been shown to express active DRs and other dopamine-related proteins, suggesting that the brain specific macrophages may also express dopaminergic machinery (Gaskill et al. 2009; Gaskill et al. 2012; Nolan et al. 2018).

Although they are not immune cells, astrocytes are the most abundant glial cells in the CNS and extensively modulate immune function within the brain. Astrocytes from different brain regions show heterogeneity in DR expression, with expression found in cells in dopaminergic areas like the basal ganglia or striatum but not in other regions such as the cerebellum (Bal et al. 1994; Khan et al. 2001; Reuss and Unsicker 2001; Zanassi et al. 1999). Astrocytes also express DAT (Takeda et al. 2002), MAO-B, and COMT (Levitt et al. 1982; Myohanen et al. 2010; Winner et al. 2017), suggesting that they can take up and metabolize dopamine.

Dopamine-Immune Interactions in Peripheral Immune Cells—T-lymphocytes were first shown to express DRs in 1980 (Le Fur et al. 1980), and since then many other studies have shown that T cells express all DRs (Besser et al. 2005; Huang et al. 2010; Kirillova et al. 2008; Levite et al. 2001; McKenna et al. 2002; Ricci et al. 1995; Santambrogio et al. 1993; Watanabe et al. 2006a). The binding profiles of dopaminergic ligands in these cells were similar to those in neuronal membranes, suggesting the receptors act similarly to those found in neurons (Takahashi et al. 1992). T-cells also express TH, DAT, VMAT2, and COMT, suggesting they have the capacity to take up, synthesize, store, and release dopamine (Bergquist et al. 1994; Cosentino et al. 2007; Qiu et al. 2004; Tsao et al. 1998). The particular expression and function of the T-cell dopaminergic system is heterogeneous among T cell subsets, and some studies show expression is dependent on activation state and/or differentiation (Cosentino et al. 2007; Mignini et al. 2013; Nakano et al. 2009), which is extensively reviewed elsewhere (Pacheco et al. 2009). There is much less data regarding the dopaminergic system in B-lymphocytes and natural killer cells, but both cell types have also been shown to express all subtypes of DRs (McKenna et al. 2002; Meredith et al. 2006;

Santambrogio et al. 1993; Watanabe et al. 2006b) and B-cells have dopamine stores (Ferrari et al. 2004).

Human myeloid cells, such as monocytes and macrophages, also express all subtypes of DRs, as well as DAT, VMAT2, TH, and AADC (Coley et al. 2015; Gaskill et al. 2009; Gaskill et al. 2012; Nolan et al. 2018). Other studies have found that human monocytes/macrophages can store and produce dopamine as well (Cosentino et al. 2000; Flierl et al. 2009; Josefsson et al. 1996; Marino et al. 1999). Monocyte-derived dendritic cells express DRs, primarily D1-like DR, and expression MAO and VMAT2, while expression of DAT is not clear (Nakano et al. 2008). These cells were also shown to contain intracellular dopamine, which is released upon antigen presentation to T cells (Nakano et al. 2009). Fewer studies have focused on granulocytes, but all five DR subtypes have been found on neutrophils (Boneberg et al. 2006; McKenna et al. 2002; Sookhai et al. 1999) and eosinophils (McKenna et al. 2002). Neutrophils and eosinophils contain intracellular dopamine (Cosentino et al. 1999) and eosinophils can also release dopamine (Withers et al. 2017). Further, human neutrophils and eosinophils can respond to dopamine (Pinoli et al. 2017). To our knowledge, there is no data on DR expression in basophils or mast cells.

Neural-immune Interactions Between Central/Peripheral Dopaminergic Systems—In addition to directly responding to dopamine, immune cells can be indirectly influenced by dopaminergic regulation in distant tissues, including the CNS (Basu and Dasgupta 2000). For example, hypoactivation of central dopamine increases the risk of inflammation during infection or tissue injury (Engler et al. 2009), and animals with hyperdopaminergic systems showed increased lipopolysaccharide (LPS)-induced cytokine production in macrophages (Kavelaars et al. 2005; Teunis et al. 2004). In rats, elevation of CNS dopamine levels using L-DOPA caused peripheral T cells to exhibit similar characteristics to those of dopamine activated T cells *in vitro* (Ilani et al. 2004). In addition, direct activation of dopaminergic neurons in the mouse VTA using DREADDs led to enhanced phagocytic activity of splenic dendritic cells and macrophages (Ben-Shaanan et al. 2016). These data suggest dopaminergic neurotransmission is important to immunoregulation, and suggest that consideration of the immunologic impact of dopamine across the body is an important step in evaluating therapeutic efficacy of dopaminergic drugs.

Caveats Regarding the Comparison of Dopamine Concentrations

This review consolidates the data from a large number of studies describing dopamine concentrations both within the CNS and in the periphery. Despite the amount of research cited here, there were a number of additional studies that examined dopamine which were not included due to the inability to determine the precise dopamine concentrations being reported. For example, studies that only reported percent changes in dopamine relative to baseline (Dunn et al. 1987; Floresco et al. 2003; Hu et al. 2015; Jackson and Moghaddam 2001; Kao et al. 1994; Keefe et al. 1993; Tanda et al. 1997), only reported levels of dopamine metabolites (Dahlin et al. 2012; Geracioti et al. 1998; Kilpatrick et al. 1986), or found dopamine to be below the limit of detection (Markianos et al. 2009; Nagler et al. 2018) were not included. To more effectively compare dopamine concentrations between

studies, all values were converted to relative molar concentrations by dividing original values by the molecular weight of dopamine (153.18 g/mol) if not already in a molar value, and multiplying the density of tissues or fluids which we averaged to be around 1 kg/L or kg/m^3 for all tissues or fluids. Additionally, if the values reported were not usable in this calculation, for instance concentrations of dopamine over time or concentration of a tissue with undefined mass, these values were not included (Basson et al. 1997; Di Chiara and Imperato 1988; McCarty et al. 1986; Reith et al. 1997; Yoshimoto et al. 1992). All the calculated values are reported alongside the original measurements in Tables 1–4 for reference. While this enables a more standardized comparison, it does not account for substantial variability resulting from differences in species, age, cell type or sex (Arvidsson et al. 2014; Bourque et al. 2011; Cosentino et al. 2000; Pilipović et al. 2008; Wahlstrom et al. 2010). An additional consideration when comparing the concentrations of dopamine found in corresponding regions of different species, even though we limited reporting studies from only mammals, is that while dopamine pathways are functional similarly among rodent species (Bhagwandin et al. 2008; Calvey et al. 2016; Calvey et al. 2015; Kruger et al. 2012; Limacher et al. 2008), there are major variations between these pathways in different mammalian orders (Manger et al. 2004; Maseko et al. 2013). There may also be significant variation resulting from experimental differences such as detection technique, preparation of tissue, type of analysis used or physical state of the animal (i.e. freely moving versus anesthetized) (Jackowska and Krysinski 2013; Peaston and Weinkove 2004; Wanat et al. 2009; Wightman and Robinson 2002). Important examples include the fact that almost all researchers do not report free versus conjugated dopamine, and some experiments utilize additional reagents to increase dopamine to the level of detection (Hauber and Fuchs 2000; Ripley et al. 1997), which are useful in detecting small changes in dopamine in response to pharmacological agents, but give artificial values that confound our understanding of the true concentrations of dopamine that immune cells could be exposed to in a particular tissue. Further, research groups without experience examining dopamine tended to show more extreme values than those laboratories with extensive experience with studying this neurotransmitter, suggesting that research experience should also be considered when evaluating the cited studies.

Dopamine in the Central Nervous System

There are four main dopaminergic pathways in the mammalian brain; the nigrostriatal, mesolimbic, mesocortical, and tuberoinfundibular pathways. The nigrostriatal pathway is involved in motor control and starts in the substantia nigra (SbN), where dopaminergic neurons give rise to ascending fibers densely innervating the caudate and putamen (dorsal striatum). Both the mesolimbic pathway and mesocortical pathways are associated with the reward system (Wise 2004). The mesolimbic pathway connects the ventral tegmental area (VTA) to the limbic regions of the brain (nucleus accumbens, ventral striatum and amygdala), and the mesocortical pathway links the VTA to the cortex (medial, prefrontal, cingulate and entorhinal cortex). The tuberoinfundibular pathway is important in the inhibitory control of prolactin (Ben-Jonathan and Hnasko 2001) and runs from the arcuate and periventricular nuclei of the hypothalamus to the intermediate lobe of the pituitary and the median eminence. In addition to these regions, there are smaller amounts of dopamine in

other areas in which immune cells are active, such as the CSF (Hubbard et al. 2009; Louveau et al. 2015) and the retina (Silverman and Wong 2018; Witkovsky 2004), but this review focuses on the major dopaminergic pathways.

Dopamine neurons represent only a fraction of the total CNS neuronal population, even within these regions, but they influence significant areas of the brain through networks of branching fibers and display diverse electrophysiological properties (Hauber 2010; Marinelli and McCutcheon 2014; Roeper 2013). These neurons operate in two distinct temporal modes, a “phasic” mode producing fast, transient dopamine release (seconds) through synchronized burst firing, and a tonic mode, which produces slow (minutes – hours), widespread dopamine release through non-synchronous spontaneous firing (Hauber 2010). Dopamine release is regulated by interactions with other neurons such as glutamatergic, cholinergic as well as GABAergic cells (Morikawa and Paladini 2011). The local dopamine concentration is also regulated by the relative rates of dopamine release and uptake, as they are regionally specific (Calipari et al. 2012; Cass and Gerhardt 1995; Cragg et al. 2000; Garris and Wightman 1994; Letchworth et al. 2001; Sulzer et al. 2016; Trout and Kruk 1992).

Dopamine neurons can communicate through either one-to-one synaptic wiring transmission, or through a one-to-many volume transmission. Modeling dopamine spillover during neurotransmission indicates that short distance volume transmission is the primary mode of dopamine-mediated communication (Agnati et al. 2010; Borroto-Escuela et al. 2018; Peters and Michael 2000; Venton et al. 2003). Additionally, the largest dimension of the dopamine synaptic cleft is small (300 nm) (Pickel et al. 1996), suggesting it was designed to promote dopamine efflux. This is also supported by ultrastructural studies showing many DRs and transporters are extrasynaptic (Caille et al. 1996; Levey et al. 1993; Nirenberg et al. 1996). These and other studies indicate that during volume transmission, a cloud of released dopamine spills out of the synapse in three dimensions and permeates the surrounding area (Cragg et al. 2001; Garris and Wightman 1994), exposing adjacent immune cells to elevated dopamine during neuronal communication. The dopaminergic tone in humans is unclear, but in rodents, tonic dopamine concentrations are commonly thought to be in the nanomolar range (Floresco et al. 2003; Keefe et al. 1993; Parsons and Justice 1992), while phasic dopamine concentrations can be as high as in the micromolar range (Garris et al. 1994; Kawagoe et al. 1992; Wanat et al. 2009). As the concentration of dopamine to which immune cells will be exposed depends on the regional dopaminergic tone, this section examines the concentrations of dopamine within these pathways (Table 1), the mechanisms contributing to these dopamine levels and the immune cells that could be exposed to dopamine in these regions under homeostatic and drug-using conditions.

Nigrostriatal, Mesolimbic and Mesocortical Dopamine Levels

The midbrain dopamine neurons making up the nigrostriatal, mesolimbic and mesocortical pathways are largely localized in the SbN and the VTA, with efferents reaching to the striatum, accumbens and several regions in the cortex. The basal dopamine levels in the rodent and primate striatum are thought to be around 10 – 30 nM (Owesson-White et al. 2012; Sulzer et al. 2016), although the estimates vary widely depending on the model and

analytic technique used (Table 1, Figure 1). Although measuring the spatiotemporal dynamics of dopamine *in vivo* is difficult, models of dopamine release in the SbN suggest that during phasic firing, dopamine concentrations of 1 μM can be found up to 2 μm from the synapse, while concentrations of 10 nM can be found 8.2 um away (Cragg and Rice 2004). The distances in the striatum are suggested to be 2 – 7 μm for 1 uM dopamine, and 7 – 20 μm for 10 nM dopamine (Beyene et al. 2017; Cragg and Rice 2004; Staal et al. 2004; Sulzer et al. 2000), while models of the primate prefrontal cortex suggest that 10 nM dopamine can reach as far as 10 – 15 μm from the synapse during tonic firing, with concentrations as high as 90 nM during phasic output (Spühler and Hauri 2013). Examination of the nucleus accumbens suggests dopamine could reach 6 – 10 μm from the synapse at 10 nM concentrations (Cragg et al. 2001; Garris et al. 1994; Stamford et al. 1988). Some studies suggest that more extensive dopamine volume transmission may occur due to dopaminergic terminal-receptor mismatches in the retina, nucleus accumbens shell, and amygdala, reaching as far as 30 – 50 μm (Bjelke et al. 1996; Fuxe et al. 2003; Jansson et al. 1999).

These “spheres of influence” are significantly affected by DAT function in these regions (Sulzer et al. 2016), and in the case of diseases that dysregulate DAT function, such as Parkinson’s Disease (Mackie et al. 2018) or HIV (Gaskill et al. 2017), the area exposed to dopamine could be much larger. An important caveat to these models is that they generally assume the only DAT taking up dopamine are those on dopaminergic neurons, whereas numerous studies have shown DAT is also present on immune cells and astrocytes, which may also influence dopamine concentrations. Further, the distances and concentrations modeled here are based on quantal release from a single synapse, and depending on the stimulus, the firing pattern and the number of synapses involved, the concentration of dopamine could be significantly greater (Arbuthnott and Wickens 2007). For instance, dopamine neurons projecting to the dorsal striatum and the nucleus accumbens shell show classical slow firing properties, whereas dopamine neurons in the medial VTA projecting to the amygdala or nucleus accumbens core have unconventional fast-firing properties that include an almost doubled basal firing rate and maximal firing rate (Hauber 2010; Lammel et al. 2008).

Thus, when microglia and macrophages in these regions are in close proximity to dopaminergic neurons, they would be exposed to dopamine concentrations ranging from 10 nM to 1 μM or higher. Microglia are particularly likely to encounter elevated dopamine in this way, as the density of these cell is particularly high in the SbN (Kim et al. 2000; Lawson et al. 1990; Yang et al. 2013), and both ultrastructural analysis and two-photon imaging studies show microglial processes contact neuronal cell bodies and dendritic spines (Tremblay et al. 2010; Wake et al. 2009). Similarly, all types of CNS macrophages have been shown to interact with neurons in different brain regions (Faraco et al. 2017). By participating in the ‘tripartite’ synapse (Farhy-Tselnicker and Allen 2018), astrocytes can also regulate synapses by direct contact (Hama et al. 2004; Nishida and Okabe 2007), and are interconnected with each other to expand the range and magnitude of synaptic regulation. Localization of substantial D1R on fine processes of astrocytes within the SbN and D2R in the prefrontal cortex suggest that they are a likely recipient for dopamine (Khan

et al. 2001; Nagatomo et al. 2017), and that dopamine could impact large astroglial networks within these regions.

Tuberoinfundibular Dopamine

Studies indicate that the regions in this pathway contain high levels of dopamine, ranging from 1 μM to around 100 μM in the in both the hypothalamus and the pituitary (Table 1). While most neurons release dopamine into the synaptic cleft and bind to postsynaptic receptors, the majority of tuberoinfundibular dopaminergic neurons (TIDA) lack true synaptic contacts and are categorized as secretory neurons (Ben-Jonathan and Hnasko 2001). As such, dopamine diffuses away from the terminals through the perivascular space and is transported by portal blood to the pituitary. The rate of dopamine release from neurons of this pathway appears to be slower than from classical neurons, but the basal activity is high, making the dopaminergic environment within this pathway quite unique. Maintaining low circulating prolactin levels requires a continuous high input of dopamine and a high but sustainable rate of synthesis, but also a mechanism to allow for rapid decreases in dopamine to enable prolactin release during situations that result in massive changes in hormones like pregnancy. This is accomplished by hypothalamic TH activity that is basally constitutive but can be transiently inactivated, unlike TH in most tissues, which can rapidly generate dopamine for immediate release (Haycock and Haycock 1991). Both microglia and macrophages are active in the hypothalamus, mediating the inflammatory response to obesity (Valdearcos et al. 2017). Studies have also identified both dendritic cells (Glennon et al. 2015) and macrophages (Fujiwara et al. 2017) in the pituitary that may play a role in communicating immune activation to the hypothalamic pituitary adrenal (HPA) axis. As local dopamine concentrations fluctuate to regulate prolactin production (Lyons et al. 2012; Stagkourakis et al. 2016) or in response to diet (Volkow et al. 2011), immune cells located in this pathway could be exposed to significant dopamine fluctuations.

CNS Dopamine During Drug Abuse

The effects of drug abuse on CNS dopamine has been discussed in detail in a number of excellent recent reviews (Fox and Wightman 2017; Nutt et al. 2015; Solinas et al. 2018; Volkow and Morales 2015).

Therefore, this section will only briefly discuss these effects, focusing particularly on how drug abuse changes regional dopamine concentrations and the impact this may have on immune cell interactions. This is important, as recent research has revealed that CNS immune signaling may substantially contribute to dopamine signaling induced by drugs of abuse (Hutchinson and Watkins 2014; Lacagnina et al. 2017). The dopaminergic system, particularly the mesolimbic and mesocortical pathways, is activated by many of types of drugs of abuse, including psychostimulants, opioids, nicotine and alcohol (Di Chiara and Imperato 1988; Pierce and Kumaresan 2006; Volkow and Morales 2015). The specific pharmacological effects of these drugs are wide-ranging but many act, at least partially, by interfering with dopamine reuptake through antagonism or reversal of DAT (Sulzer 2011; Torres et al. 2003; Volkow et al. 1997). Despite the differences in mechanisms, all drugs of abuse increase extracellular DA levels, generally to the high nanomolar to low micromolar range (Table 2).

These increases in dopamine concentrations would expand the volume of the brain permeated by dopamine, and also increase the distance from the synapse at which higher concentrations of dopamine are present (Peters and Michael 2000; Spühler and Hauri 2013; Venton et al. 2003). This could substantially increase the number of immune cells which interact with dopamine, with larger increases in tissues that have proportionately greater responses to drug use. The largest drug-induced elevations in dopamine concentrations generally occur within the basal ganglia, specifically in the striatum and nucleus accumbens (Fadda et al. 2003; Shou et al. 2006; Stuber et al. 2005; Wightman et al. 2007). In both striatum and prefrontal cortex, increased dopamine concentrations induced by blockade of dopamine reuptake using cocaine, methylphenidate or nomifensine enhance the diffusion of dopamine, increasing the volume of tissue exposed to this neurotransmitter by as much as 50% (Peters and Michael 2000; Spühler and Hauri 2013; Venton et al. 2003). Changes in dopamine reuptake could also enhance heterogeneity in dopaminergic tone, and create local “hot spots” with unusually high dopamine concentrations (Peters and Michael 2000; Spühler and Hauri 2013). Another factor influencing the interaction of dopamine with immune cells is that different types of drugs have a regionally distinct impact on dopamine diffusion and reuptake, suggesting the changes in immune cell exposure could differ in magnitude across the brain (Cass et al. 1992; Cragg and Greenfield 1997; Jones et al. 1995; Porrino et al. 2004; Salinas et al. 2016). There are also regional differences in the homeostatic rate of uptake that could affect immune cell responses. For example, cocaine mediated inhibition of uptake in a region where it tightly controls extracellular DA such as the striatum would have a different effect on extracellular levels than in a brain region where uptake does not regulate DA as closely such as in the nucleus accumbens shell (Wu et al. 2001).

Drug-induced increases in dopamine likely have a large impact on CNS immune cells and astrocytes, as many drugs of abuse increase expression of microglial and astrocytic markers, increase cytokine/chemokine release, and promote pro-inflammatory glial phenotypes (Alfonso-Loeches et al. 2010; Cadet and Bisagno 2014; Schwarz and Bilbo 2013; Wang et al. 2012). Specifically, glial inhibitors and cytokines can augment drug-induced dopamine release (Bland et al. 2009; Hutchinson et al. 2008; Nakajima et al. 2004; Zhang et al. 2006), demonstrating that CNS immune cells could modulate the effects of drugs of abuse and interact with dopamine during drug exposure. Synaptic remodeling may also occur during increased exposure to dopamine during drug abuse, which could contribute to the persistent behavioral effects typical of substance abuse disorders (Coller and Hutchinson 2012; Kovacs 2012). Importantly, the changes in dopaminergic tone evoked by drug abuse will also depend on the timing, method of delivery and length of drug exposure. There are large differences in dopamine response between chronic drug abusers and intermittent or naive users (Sklair-Tavron et al. 1996; Volkow et al. 2010; Wu and French 2000), and some studies show that chronic drug use decreases drug-induced dopamine release (Volkow et al. 1996; Wilson et al. 1996a). Thus, it is important to consider not only the neurological effects of the drug being used, but also the epidemiological context of the substance abuser in order to develop a complete picture of how the changes in CNS dopamine induced in a particular drug abuser impact the immune cells in the CNS.

Dopamine in Peripheral Systems

It has been more than five decades since a peripheral role for dopamine was first described (Goldberg 1972), and while dopamine is most often studied in the context of its actions in the CNS, this neurotransmitter is also present throughout the periphery. Peripheral dopamine plays an important regulatory role in a variety of functions including hormone secretion, vascular tone, sympathetic regulation, immune activation, gastrointestinal motility, blood pressure, respiration, and renal functions (Arreola et al. 2016; Goldstein et al. 1995; Rubí and Maechler 2010). Dopamine can be released from sympathetic nerves and the adrenal medulla, as well as from other peripheral organs, where dopamine can act as an autocrine/paracrine regulator of local organ function. This section focuses on the available research showing the concentrations of dopamine in peripheral compartments (Table 3), and discusses how the dopaminergic machinery found in peripheral systems affects the amount of dopamine seen by immune cells in these regions. Specifically, the tissues discussed here are those in which multiple studies have reported measurable dopamine concentrations that could interact with resident immune cells. Tissues that are not discussed may also express sufficient dopamine to affect immune cells, but either the reports of this were scarce or to our knowledge it has not be demonstrated yet. For example, very few studies have reported dopamine concentrations in the liver. However, the liver receives both parasympathetic and sympathetic input (Yi et al. 2010), and is known to have some of the highest expression of COMT in the body (Männistö and Kaakkola 1999; Myohanen et al. 2010), suggesting it plays a major role in metabolizing dopamine (Eisenhofer et al. 1995). Therefore, more research is warranted to further characterize additional sources of dopamine and dopaminergic regulation throughout the body.

Adrenals

The adrenal glands are one of the more well-known sources of peripheral dopamine, and express both D1-like and D2-like DRs (Pivonello et al. 2004). Specifically, the adrenal medulla, located at the center of the gland and surrounded by the cortex, is innervated by the greater splanchnic nerve and regulates secretion of catecholamines into systemic circulation (Bloom et al. 1988). However, both medulla and cortex seem to be important for dopamine production (McCarty et al. 1986). Adrenocortical dopamine appears to derive from DOPA removed from the circulation and decarboxylated in non-catecholaminergic cells (Buu and Lussier 1990). Recently, studies showed that electroacupuncture in the sciatic nerve of mice increased the production of dopamine in the adrenal medulla, and vagotomy abolishes this, suggesting that dopamine from the adrenals relies on both neuronal and non-neuronal inputs (Torres-Rosas et al. 2014). Many studies have shown that resident neuroendocrine chromaffin cells release dopamine (Fhaner et al. 2013; Leszczyszyn et al. 1991; Podvin et al. 2015), and the vesicular concentration of dopamine in these cells has been estimated to be as high as 300 mM (Wightman et al. 1991) which is comparable to that found in midbrain neurons (Pothos et al. 1998), although a range of studies estimate the dopamine concentration in the adrenals to be in the nanomolar to milimolar range (Table 3).

Many types of immune cells, in particular macrophages, dendritic cells, mast cells, and lymphocytes, can be found in the adrenals (Kanczkowski et al. 2016; Schober et al. 1998).

Close cell–cell localization between immune cells and surrounding adrenocortical, chromaffin, or endothelial cells has been observed (Gonzalez-Hernandez et al. 1994; Wolkersdorfer et al. 1999), indicating that immune cells are likely to be in close contact with dopamine-releasing cells and exposed to high concentrations of dopamine. The catecholaminergic machinery in immune cells themselves can also be altered by the adrenal environment, as adrenalectomy increases TH and decreases MAO-A expression in macrophages (Stanojevic et al. 2013). The dopamine released from the adrenals is likely to influence other peripheral regions as well, as the hormones and catecholamines they release can regulate cytokine expression and immune cell activation (Deak 2008; Kanczkowski et al. 2016). Further, mature dendritic cells exposed to dopamine in the adrenals migrate from their residence in the adrenal cortex into the bloodstream and lymph nodes to present antigen to lymphocytes (Deak 2008).

Bone Marrow

The bone marrow microenvironment is critical in the maintenance of hematopoietic stem cells (HSCs), from which immune cells are derived through hematopoiesis. Signals from the sympathetic nervous system, including dopamine release, have been shown to regulate HSC development and function (Cosentino et al. 2015; Madden 2017; Mercier et al. 2011). Dopamine specifically enhances a number of cellular functions including cell polarity, migration, colony formation and metalloproteinase secretion, through stimulation of DRs expressed on these cells (Basu et al. 1993; Chakroborty et al. 2008; Spiegel et al. 2007). These and other studies suggest dopamine plays an active role in the bone marrow, a hypothesis supported by data showing nanomolar to micromolar ranges of dopamine in this compartment (Chakroborty et al. 2008; Maestroni et al. 1998; Marino et al. 1997), which is substantially more than what is typically found in circulation. Interestingly, bone marrow dopamine levels display rhythmicity, which could be disrupted by chemical sympathectomy, thereby indicating the possible role of this rhythmicity in regulation of hematopoiesis (Maestroni et al. 1998). The dopamine found in this compartment can also act on the many other immune cells present in the bone marrow, including macrophages and osteoclasts, several types of T-cells, B-cells and myeloid-derived suppressor cells. These cells are found throughout the bone marrow, circulating through the capillary network permeating this region (Mercier et al. 2011; Zhao et al. 2012), and all respond to dopamine. Thus, the dopamine present in the bone marrow could directly influence both the development of immune cell precursors, as well as indirectly affect hematopoiesis and ancillary functions, by acting on the mature immune cells hosted in this compartment. Further characterization of the role of dopamine in hematopoiesis is needed to better define how dopamine affects immune cell development, and to determine how dopaminergic effects on mature immune cells influence this process. This is of particular clinical significance as bone marrow derived stem cells are being utilized for therapies in Parkinson’s disease (Fu et al. 2015) as well as Alzheimer’s disease (Fang et al. 2018).

Carotid bodies

Carotid bodies, small clusters of chemoreceptors (type I cells) located near the bifurcation of the carotid artery, are one of the major groups of peripheral chemoreceptors in the body (Kumar and Prabhakar 2012). These cells are similar to the chromaffin cells of the adrenal

medulla, and express both pre- and post-synaptic DRs (Almaraz et al. 1991; Bairam et al. 1998; McQueen et al. 1984) as well as dense core vesicles where TH has been localized (Karasawa et al. 1982; Nurse and Fearon 2002), indicating the storage of dopamine. Although these vesicles contain approximately 20-fold less catecholamine per vesicle than larger vesicles in chromaffin cells (Wightman et al. 1991), they have around 5-fold more dopamine than the smaller vesicles found in sympathetic ganglia (Zhou and Misler 1995). These cells are synaptically connected to nerve terminals of the petrosal ganglion neurons (Iturriaga and Alcayaga 2004), and release dopamine in response to changes in the oxygenation, pH, and temperature of arterial blood (Kumar and Prabhakar 2012). The literature suggests that the amount of dopamine in this region is substantial, in the micromolar to millimolar range (Table 3). The carotid bodies contain large numbers of monocytes and macrophages (Dvorakova et al. 2000), and carotid bodies exposed to chronic hypoxia, which increases dopamine (Hanbauer et al. 1981), also show invasion of macrophages and subsequent upregulation of proinflammatory cytokines (Lam et al. 2012). Carotid bodies can also respond to a wide variety of blood-borne stimuli, including cytokines, with IL-6 inducing catecholamine release from chemoreceptors in a dose-dependent manner via elevation in intracellular Ca^{2+} (Fan et al. 2009). The dopamine concentrations found in carotid bodies are sufficient to increase macrophage-mediated inflammation, including production of IL-6 (Nolan et al. 2018), suggesting that bidirectional interaction between inflammatory stimuli and changes in chemoreceptor dopamine release could stimulate immune activation and inflammation in these regions.

Circulation

Dopamine plays an important role in the circulatory system, potentiating vasodilation in systemic arteries (Amenta et al. 2000) and enhancing blood flow in skeletal muscles (Eliasen et al. 1989). Clinically, dopamine has long been used to treat cardiovascular complications arising from shock, trauma, and sepsis (Zhang and Chen 2016), suggesting that dopamine is involved in the regulation of vascular pathologies. Circulating dopamine can originate from diet and other physiological sources that can be independent or dependent of the nervous system (Eisenhofer and Goldstein 2004; Goldstein et al. 1999). Conditions that increase sympathetic nervous system activity can increase plasma dopamine levels (Van Loon 1983), and similarly, loss of sympathetic nerve function can decrease plasma dopamine (Goldstein and Holmes 2008). Dopamine is also released directly into the circulation from chromaffin cells of the adrenal medulla, amine precursor uptake decarboxylase (APUD) cells found predominantly in the kidney and pancreas (Rubi and Maechler 2010; Wolfovitz et al. 1993), and possibly from other, as yet undefined peripheral sources. Overall, peripheral dopamine synthesis and metabolism may currently be underestimated, as the high levels of dopamine in the plasma and the urinary excretion rates of dopamine metabolites and conjugated dopamine are not well accounted for by the known sources of peripheral dopamine.

Free (non-sulfated or glucuronated) dopamine levels in the circulation are relatively low compared to the rest of the body, comprising only 5% of dopamine in plasma (Kuchel and Kuchel 1991). Most studies report free dopamine concentrations in the picomolar range, but nanomolar levels have also been found (Table 3). These levels seem to vary widely among individuals (Eisenhofer et al. 2005), and can be substantially altered during normal activity.

For instance, ingestion of a meal can increase dopamine plasma concentrations by more than 5000% (Eisenhofer and Goldstein 2004). The circulatory system is home to a wide variety of immune cells, many of which actively respond to dopamine (Scheiermann et al. 2015; Shi and Pamer 2011). Within circulation, these immune cells, including T-cells, granulocytes or monocytes, are likely to encounter large fluctuations in dopamine, with only small regions concentrated with enough dopamine to mediate the effects described for these cells (Gaskill et al. 2013; Pinoli et al. 2017). In particular, pockets of higher dopamine concentrations present on blood vessels and other tissue barriers may be critical for extravasation and trafficking of T cells and monocytes, as dopamine has been shown to both promote adhesion to extracellular matrix components and enhance chemokinesis and transmigration (Calderon et al. 2017; Coley et al. 2015; Levite et al. 2001; Watanabe et al. 2006a). Encounters with elevated dopamine could also slow down or diminish the immediate response to pathogenic insults, as dopamine decreases neutrophil adherence, phagocytosis, ROS formation and migration while increasing the apoptosis of these cells (Sookhai et al. 1999; Trabold et al. 2007; Wenisch et al. 1996).

The majority of circulating dopamine is conjugated with sulfates or glucuronides, rendering it biologically inactive (Yoneda et al. 1983). In humans, sulfation is the more important metabolic pathway (Claustre et al. 1983), Dopamine sulfate has a half-life of a few hours, compared to a few minutes for free dopamine (Eldrup 2004). Its concentration is relatively independent of sympathetic nerves and more dependent on diet and conjugation of dopamine in the gastrointestinal tract (Eldrup et al. 1997; Goldstein et al. 1999). Unlike inactivation of dopamine by deamination or O-methylation, glucuronidation and sulfoconjugation are reversible by the enzymes β-glucuronidase (Pellock and Redinbo 2017) and arylsulfatase A (ARSA) (Strobel et al. 1990), respectively, which are found in the both the CNS and peripheral tissues (Antunes et al. 2012; Borcherding et al. 2011; Richard et al. 2001; Sperker et al. 2000). The function of dopamine conjugation remains unclear. One hypothesis is that conjugation sequesters dopamine to reduce its bioactivity and prevent catecholamine buildup in circulation, while another proposes that it acts as a reservoir for free dopamine (Goldstein et al. 1999; Yamamoto et al. 1996). Higher levels of plasma dopamine are associated with congenital heart defects (Yoshizumi et al. 1998) and are a risk factor for future coronary events in patients with coronary artery disease (Abe et al. 2007), so sequestration of free dopamine might be a protective mechanism. It is not clear that immune cells have the capability to reverse sulfation or glucuronidation, but these processes would prevent circulating leukocytes from encountering high levels of free dopamine in the blood stream, thereby reducing dopamine-mediated inflammation.

Heart

Within the heart, the measured concentrations of dopamine are generally found to be in the high nanomolar range (Table 3), suggesting that dopamine could be synthesized in this compartment non-neuronally. This is supported by studies indicating that dopamine can be synthesized in the heart independent of noradrenergic nerves (Mohanty et al. 1986), possibly via chromaffin cells found in the paraganglia of the heart (Chumasov et al. 2011; Scheuermann 1993). These concentrations of dopamine are high enough to elicit activity from the immune cells present in the heart, which include resident cardiac macrophages, T-

cells and mast cells, as well as lesser numbers of neutrophils and eosinophils (Frieler and Mortensen 2015; Lavine et al. 2014). Recent studies have shown that immune cells play an important role in both homeostatic heart function and in cardiac pathology. Distinct subsets of cardiac macrophages, both directly and indirectly facilitate tissue repair after cardiac injury, through phagocytosis and the production of cytokines such as IL-1β, IL-10 and IL-6, which are important regulators of cardiomyocyte and fibroblast function (Epelman et al. 2014; Frieler and Mortensen 2015). Recent studies show that heart-resident macrophages and cardiomyocytes can be physically connected by gap junctions to allow for synchronous propagation of electrical signals that drive the heart to contract during a normal heartbeat (Hulsmans et al. 2017). Monocyte derived macrophages are also recruited to the heart after injury, and have been show to promote inflammation (Lavine et al. 2014). Different subtypes of T-cells are involved in cardiac remodeling, altering cardiac physiology and both promoting and suppressing hypertrophy (Hamrell et al. 1995; Tang et al. 2012). Mast cells are also associated with maladaptive cardiac remodeling, potentially through interactions with fibroblasts (Zhang et al. 2011b). As dopamine has been shown to regulate cytokine production, phagocytosis and chemotaxis in both macrophages and T-cells, and to inhibit T_{reg} function (Gaskill et al. 2013), the interactions of immune cells with dopamine in the heart could certainly promote or exacerbate cardiac inflammation and pathology. Exogenous changes in dopamine levels due to therapeutics or drug abuse could also disrupt non-pathologic cardiac function.

Kidney

Dopamine regulation in the kidney is one of the better characterized systems in the periphery, with dopamine levels reaching nanomolar to micromolar concentrations in this organ (Table 3). DRs in the kidney contribute to the control of renal electrolyte balance and blood pressure, as well as renin production (DiBona 1990; Gildea 2009; Harris and Zhang 2012; Hussain and Lokhandwala 2003). The primary source of dopamine in the kidney are renal peritubular cells (RPTs). These cells express AADC but not TH or DBH, so dopamine can only be produced from L-DOPA and can't be converted into norepinephrine. Peritubular L-DOPA is transported into the RPTs via the Na^+-independent and pH-sensitive L-type amino acid transporters (LAT) or related to $b^{0,+}$ amino acid transporters (rBAT) from the circulation or following filtration at the glomerulus (Harris and Zhang 2012). This dopamine can then be secreted into the lumen from the same transporter, acting as a paracrine agent along nephron segments, circulating throughout the kidney (Carey 2001; Hussain and Lokhandwala 2003) or metabolized due to the high activity of COMT in this organ (Vieira-Coelho and Soares-da-Silva 1996). In addition to metabolizing dopamine, recent research has identified another enzyme, a FAD/NADH-dependent amine oxidase known as renalase, that is expressed in the kidney and secreted into blood, where it may metabolize catecholamines (Luft 2005). Renalase knockout mice have increased urinary and circulating dopamine, which is thought to result from an enhanced availability/uptake of l-DOPA in RPTs (Quelhas-Santos et al. 2015; Sizova et al. 2013). Interestingly, renalase is expressed in other tissues such as the brain, heart, and pancreas (Fedchenko et al. 2013; Guo et al. 2016), so although it is not well known it could be hypothesized that this enzyme has an important regulatory role in metabolizing dopamine throughout the body.

The primary immune cells in a healthy kidney are several discrete subpopulations of tissue resident macrophages, resident dendritic cells and a small number of lymphocytes and mast cells. The dendritic cells are found in the interstitium and extend dendrites into the tubular lumen, while the macrophages are also found in the interstitium, as well as the renal medulla and capsule and to a lesser extent in the glomeruli. The lymphocytes and mast cells can also be found in the interstitium (Kawakami et al. 2013; Kurts et al. 2013; Weisheit et al. 2015). High levels of dopamine are present in all these regions; therefore, kidney immune cells are likely to regularly interact with high levels of this neurotransmitter. Because of this regular interaction, it is likely that the impact of dopamine on the function of these cells is part of homeostatic kidney function. Indeed, mice with intrarenal dopamine deficiency show increased oxidative stress and inflammatory infiltration, and reduced intrarenal dopamine synthesis is associated with increased detrimental effects of angiotensin II on renal injury (Yang et al. 2012; Zhang et al. 2011a).

Lung

A number of cells within the lung may be capable of producing dopamine, including alveolar type II epithelial cells (Adir et al. 2004) and pulmonary neuroendocrine cells (Scheuermann et al. 1988). Additionally, dopamine is taken up and metabolized in lungs from rats (Bryan-Lluka et al. 1992; Scarcella and Bryan-Lluka 1995) and humans (Russell et al. 1982). There is evidence that dopamine is physiologically produced and distributed in the lungs in a process similar to that found in the kidney, although stimulation of DRs has opposite effects in these organs, increasing lung Na^+ absorption but increasing kidney Na^+ excretion (Barnard et al. 1999; Bertorello and Sznajder 2005). Further, while pulmonary endothelial cells are a site of very rapid metabolism by MAO and COMT (Russell et al. 1982) there is a lack of conversion of dopamine to norepinephrine, unlike other peripheral tissues (Scarcella and Bryan-Lluka 1995). DRs are found in airway smooth muscle (Mizuta et al. 2013), lung epithelial cells (Matsuyama et al. 2018), and lung arteries (Kobayashi et al. 1995), and lung dopamine levels are substantial enough to influence these receptors in a dose-dependent fashion (Ciarka et al. 2007). These concentrations are in nanomolar to micromolar levels (Table 3), and together these data suggest dopamine is involved in a number of pulmonary functions. Indeed, this neurotransmitter can modulate respiratory function through carotid bodies, and influence pulmonary circulation, neuromodulation of sensory pulmonary nerves, and lung water clearance (Chamorro-Marín et al. 2008; Prieto-Lloret et al. 2015; Vohra et al. 2012).

The role of the immune system in the lungs is critical, as they represent the environment most frequently targeted by pathogens (Lloyd and Marsland 2017). Alveolar macrophages make up a significant portion of immune cells within this organ during steady state, and an increase in specialized lymphocytes and neutrophils are recruited during bouts of inflammation (Cho et al. 2016; Hussell and Bell 2014). Lung immune activation can be triggered by the pulmonary neuroendocrine cells, which are the only innervated airway epithelial cells (Branchfield et al. 2016), suggesting dopamine could play a role in regulating this process. Expression of MAO and COMT in murine alveolar macrophages is regulated by LPS, suggesting lung inflammation changes their response to dopamine (Flierl et al. 2007). Pretreatment with dopamine ameliorated LPS-mediated edema formation and

lowered neutrophil infiltration in a murine lung injury model (Vohra et al. 2012). In humans, inhaled dopamine induces bronchodilation during bronchial obstruction in asthmatic patients (Cabezas et al. 2003). However, D1-like receptor antagonists suppress Th17-mediated neutrophilic airway inflammation resulting from severe asthma (Nakagome et al. 2011). As with the kidney, the relatively high baseline dopamine levels in the lung suggest that dopamine-immune interactions are a regular part of pulmonary function, and seem to have an anti-inflammatory and therapeutically beneficial effect. However, in individuals with certain conditions, or under conditions of aberrant dopamine regulation, the alterations in immune function resulting from interaction with dopamine could be dangerous (Ciarka et al. 2004).

Gastrointestinal System

Dopaminergic mechanisms are important for regulation of gastrointestinal motility, likely through stimulation of DRs found along the gastrointestinal tract (Glavin and Hall 1995; Li et al. 2006; Mittal et al. 2017). The expression and activity of TH is high throughout the gastrointestinal system, and it is thought to be a significant source of dopamine metabolism. The sources of dopamine include the enteric nervous system as well as non-neuronal cells such as stomach epithelial cells, cells in the lamina propria and gut resident immune cells (Eisenhofer et al. 1997; Mezey et al. 1998). The microbiome may also be involved in the production of gut dopamine. Germ free animals have decreased dopamine concentrations in the small intestine (Asano et al. 2012), and germ free mice also display an increased turnover rate of dopamine in the brain (Diaz Heijtz et al. 2011). Additionally, microbiome depletion by antibiotics decreases TH in the gut and cytokine inhibition in invariant NKT cells, which could be reversed by replenishing the microbiome or treating with the D1-like receptor agonist A68,930 (Xue et al. 2018). Recent data indicate that bacteria produce and recognize neurochemicals (Lyte 2013; Strandwitz 2018), and have shown micromolar concentrations of dopamine that can be detected in the bacteria themselves and their culture fluid (Nagler et al. 2018; Özoğul 2004; Shishov et al. 2009). In addition, bacteria themselves, in particular *Clostridium* species, have been shown to express β-glucuronidase, which could significantly contribute to the generation of free dopamine in the gut (Asano et al. 2012). Overall, studies show nanomolar to micromolar dopamine throughout the gastrointestinal tissues and fluids including gastric and duodenal juice, stomach, small intestine, and colon (Table 3).

The gut contains the largest number of immune cells in the body, include multiple subsets of T-cells, macrophages and dendritic cells, as well as a variety of granulocytes, many of which are specifically adapted to the GI tract (Huffnagle and Noverr 2008; Wu and Wu 2012). These cells are found throughout the gastrointestinal system, and the ubiquity of these cells suggests that they could encounter dopamine anywhere within the gastrointestinal system. Large numbers of macrophages accumulate around the submucosal and myenteric plexuses (Bogunovic et al. 2009), which contain nerve terminals for both sympathetic and parasympathetic nerve fibers connected to the CNS. Mast cells have also been shown to surround nerve terminals in these regions (Schemann and Camilleri 2013). The mucosal plexus in the mucosal layer contains nerve endings in close proximity to a high concentration of immune and epithelial cells (Benarroch 2007). In addition, a substantial

number of immune cells in the lamina propria express mRNA for DRs and TH but not DBH and PNMT, suggesting that these cells are exclusively dopaminergic (Mezey and Palkovits 1992). This demonstrates that many of the immune cells in this compartment are specifically adapted to respond to dopamine. The close proximity of other immune cells to nerve fibers and other sources of dopamine indicate many gastrointestinal immune populations interact with dopamine on a regular basis. Thus, dopamine-mediated changes in immune function are likely important to maintaining gut homeostasis, and disruptions in the gut dopaminergic system could be involved the development or exacerbation of a number of gastrointestinal disorders (Magro et al. 2004; Pacheco et al. 2014; Rooks et al. 2014; Tolstanova et al. 2015), as discussed later in this review.

Lymphoid Organs

Primary and secondary lymphoid organs, including the thymus, spleen, and lymph nodes, are massively innervated by sympathetic nerves that store a large amount of dopamine (Mignini et al. 2009; Weihe et al. 1991). Another source of dopamine for these regions is thought to be autocrine and paracrine secretion of dopamine by immune cells, primarily T-cells, as both regulatory $CD4^+CD25^+$ T-cells (Cosentino et al. 2007) and T follicular helper cells (Papa et al. 2017) contain and release dopamine. In addition, parasympathetic efferent nerves could also contribute to dopamine production, but their presence and function is not clear (Nance and Sanders 2007; Schafer et al. 1998). Many of the nerve fibers within the secondary lymphoid tissues are in close contact with blood vessels (Mignini et al. 2014), and DRs, TH and VMATs can be found on sympathetic nerve endings in the medulla, cortico-medullary junction, and thymic epithelial cell compartments of the thymus (Pilipović et al. 2008). Dopaminergic proteins are also found in the white pulp border and to a lesser extent in the red pulp in the spleen (Mignini et al. 2003; Mignini et al. 2009). These and other studies indicate that dopamine is present throughout the lymphoid organs, that some of it may derive from the CNS, and that dopamine is involved in the function of the lymphoid tissues. This is supported by data showing that the destruction of dopaminergic terminals in the nucleus accumbens and striatum results in depression of spleen natural killer cells and lymphocytes (Deleplanque et al. 1994).

The lymphoid organs have been shown to contain high nanomolar concentrations of dopamine, although the amounts vary between tissues (Table 3). The presence of both dopamine and dopaminergic proteins at the border of the thymic medulla, where most of single-positive ($CD4^+$ and $CD8^+$) lymphocytes reside, suggests that these immune cells may be directly exposed to dopamine from nerve terminals. Further, in the splenic white pulp, sympathetic nerve terminals are in direct apposition to T-cells and adjacent to both dendritic cells and B-cells, with a neuroimmune junction approximately 6 nm wide (Felten et al. 1987; Felten et al. 1985). These data indicate an extremely close interaction between sympathetic terminals and immune cells in these organs, demonstrating that interactions with dopamine are essential to proper tissue homeostasis and suggesting that stimuli which disrupt dopamine concentrations in these tissues could significantly impair immune function.

Pancreas

Concentrations of dopamine in the pancreas are relatively high, with reports showing dopamine content in the low micromolar range (Table 3). Dopamine in this organ is derived from sympathetic innervation and the circulation, as well as from pancreatic cells and resident immune cells (Rodriguez-Diaz et al. 2011; Zern et al. 1980). Within the endocrine tissues of the pancreas, dopamine can directly regulate insulin production (Farino et al. 2019; Rubí and Maechler 2010). In addition, dopamine release from the hypothalamus can indirectly regulate insulin and dopamine production through effects of prolactin on islet cells, which express TH (Teitelman et al. 1981) and DRs (Chen et al. 2014; Rubi et al. 2005). Dopamine from the exocrine tissues is released into the duodenum to protect it from harmful digestive enzymes. Although pancreatic exocrine cells can respond to and produce dopamine, the dopamine released from these cells likely does not contribute to dopamine in the general circulation, as there is an absence of DAT in endothelial cells of arteries but abundance in excreting ducts and veins (Mezey et al. 1996). While chemical sympathectomy does not significantly alter dopamine levels, suggesting a non-neuronal source of pancreatic dopamine (Mezey et al. 1996), neurons from the gut can send axonal projections to the pancreas (Kirchgessner and Gershon 1990), and there is a central vagal connection through the paraventricular nucleus of the hypothalamus (Davis and Smith 1985).

While the role of pancreatic immune cells is still being defined, T-cells, macrophages and dendritic cells are all though to play important roles in the development and function of this organ (Carrero et al. 2017; Hawkins et al. 1996; Homo-Delarche and Drexhage 2004). The endocrine pancreas has a highly specialized islet structure and microvascular cells that facilitates T cell infiltration, bringing these lymphocytes into close contact with dopamine-producing islet cells. The resident macrophages and dendritic cells in the islets are in close contact with blood vessels where they could encounter dopamine (Boldison and Wong 2016; Homo-Delarche and Drexhage 2004). While these and other studies indicate dopamine-immune interaction may be part of normal pancreatic function, dopamine mediated changes to insulin levels, combined with the inflammatory phenotype of dopamine-exposed immune cells, suggests that changes in pancreatic dopamine levels could contribute to development of pancreatic pathology. Further, dopamine/insulin crosstalk can occur in other organs, such as the brain (Mebel et al. 2012; Stouffer et al. 2015; Williams et al. 2007), so the pancreatic influence on dopamine concentrations could also affect immune cells in other tissues.

Adipose

As dopamine has direct inhibitory effects on the secretion of insulin, it follows that dopamine also participates in glucose homeostasis and body weight. Alterations in dopaminergic markers such as DAT are decreased in postmortem brain samples from obese subjects (Wu et al. 2017) and dopamine is decreased in the brains of obese rats (Cone et al. 2013). Dopamine can also directly affect differentiation and proliferation of adipocytes themselves (Borcherding et al. 2011). While concentrations of dopamine in adipose tissue appears to be in the lower nanomolar range (Table 3), adipocytes express DRs (Wang et al. 2018), TH (Zhu et al. 2014) and ARSA, indicative of an active sulfoconjugation mechanism in adipose tissues (Borcherding et al. 2011). And while the adrenal medulla on average had 1000 fold more TH expression than adipose tissues, considering the size of the adrenal

medulla compared to all of the adipose depots within the body, the dopamine production in adipose tissue may be comparable (Vargovic et al. 2011).

The immune composition of adipose tissue fluctuations based on the obesity of the individual and thus metabolic state of the tissue. In general, adipose tissue macrophages, which are divided into several distinct subsets, constitute 5% of the cells in adipose tissue, although the ratio of the subsets changes with body composition (Ortega Martinez de Victoria et al. 2009). In addition, dendritic cells, neutrophils, and mast cells are all relatively sparse in the adipose tissue of lean individuals, but much more common in the adipose tissue of obese individuals (Bertola et al. 2012; Elgazar-Carmon et al. 2008; Liu et al. 2009). This increase is also seen in T-cells, which are the second most common immune cell in adipose after macrophages (Wu et al. 2007). Some studies suggest that adipocytes act as antigen presenting cells during inflammation (Deng et al. 2013; Morris et al. 2013), meaning that T-cells in adipose make direct contact with dopamine-producing adipocytes. As dopamine can enhance inflammatory activity in immune cells, the immune cells in adipose that are exposed to dopamine released from adipocytes and innervating nerve fibers could be contributing to the inflammatory milieu that is now commonly associated with metabolic disorders and obesity (Huh et al. 2014). Further research on the impact of changes in dopamine on adipose tissue is important to more effectively use dopaminergic drugs to treat obesity and metabolic disorders, as well as manage metabolic symptoms associated with chronic treatment with dopaminergic drugs such as antipsychotics (Panariello et al. 2011).

Peripheral Dopamine and Drug Abuse

There is little data on the effects of drugs of abuse on peripheral dopamine concentrations, although a mouse study using positron emission tomography (PET) imaging and quantitative whole-body autoradiography (QWBAR) with [18F]FDOPA indicates that use of ketamine, cocaine and methamphetamine increase dopamine levels in the gastrointestinal tract and kidney (Yeh et al. 2014). Many of the drugs that produce increases in CNS dopamine, such as cocaine, methamphetamine, and ethanol, are associated with significant pathology in peripheral organs with higher dopamine levels, such as the lung, gut, or kidney (Dimitrijevic et al. 2008; Lineberry and Bostwick 2006; Tiwari et al. 2006). Drug induced increases in the dopamine content of these tissues could disrupt homeostatic function and/or promote inflammation through dopamine modulation of resident macrophages and other immune cells. Indeed, drugs of abuse such as opioids have been shown to modulate both peripheral innate and adaptive immune cells (Roy et al. 2011). Further, DR expression in peripheral lymphocytes is affected by cocaine (Faraj et al. 1991), opioids (Goodarzi et al. 2009), alcohol (Biermann et al. 2007), and heroin (Czermak et al. 2004) during abuse and abstinence phases. These effects could also be induced by therapeutic agents that increase dopamine or act on DRs, such as Bromocriptine, L-DOPA, Emsam or Wellbutrin (Brannan et al. 1993; Lamensdorf et al. 1999; Stahl et al. 2004). Future studies should address the impact of drugs on peripheral dopamine, as it is clear that dopamine is present throughout the periphery, and the actions of both immune cells and dopamine are necessary for proper function in many different tissues.

Clinical Implications of Dopamine Stimulation of Immune Cells

Disturbances in central and peripheral dopamine production are involved in many pathological conditions, including but not limited to Parkinson's disease, NeuroHIV, multiple sclerosis, rheumatoid arthritis, and inflammatory bowel disease. All these pathologies are also influenced by changes in immune function, suggesting that communication between the dopaminergic system and immune cells plays a substantial role in their etiology. This section briefly discusses these interactions, examining the role dopamine in several pathologies in which dopamine-mediated alterations in the immune system might impact the development of disease.

Parkinson's Disease

Parkinson's disease (PD) is the most well-known disease associated with dopaminergic dysfunction. Characterized by James Parkinson in 1817, this disease is characterized by the degeneration of dopaminergic neurons in the substantia nigra, pathological protein aggregates known as Lewy bodies, reduced CNS extracellular DA concentrations particularly in the striatum, neuroinflammation, and motor disturbances (Table 4). In addition to these neurological symptoms, Parkinson's symptoms include duodenal ulcers, GI absorptive motile functions, and generation of Lewy bodies in the gut (Glavin and Szabo 1990; Singaram et al. 1995). It is not clear whether this connection is due to dysregulation of the local dopamine levels or the influence of the damaged CNS dopaminergic system on innervated peripheral organs, although both may contribute (Pellegrini et al. 2016; Singaram et al. 1995). Of note, PD has been positively correlated with inflammatory bowel diseases (Lin et al. 2016), another group of disorders where dopamine may be an important regulator of disease progression, and it has recently been hypothesized that T-cell driven inflammation, which mediates dopaminergic neurodegeneration, is triggered in the gut (Campos-Acuña et al. 2019). Although PD itself reduces dopaminergic tone by destroying dopamine neurons in the nigrostriatal pathway, treatment for this disease involves the administration of L-DOPA and/or DR agonists, potentially leading to stimulation of DRs on immune cells. Indeed, both in both humans and Parkinson's rodent models, changes in dopamine concentrations have been found in the periphery as well as in the CNS (Eldrup et al. 1995; Kawamura et al. 1999; Winner et al. 2017). Dopamine has been shown to affect phagocytosis in myeloid cells (Gaskill et al. 2013), and microglia show greater phagocytic activity in the substantia nigra of the brain of PD patients has been reported (Barcia 2013).

Peripherally, the correlations between central and peripheral dopamine in PD patients are inconsistent (Buttarelli et al. 2009; Pontieri and Colosimo 2010), although significant correlations are more often found in patients undergoing dopamine therapy. A number of studies have reported increased dopamine in the intestines accompanying decreased CNS dopamine after treatment with 6-OHDA (Garrido-Gil et al. 2018b; Levandis et al. 2015), which is used to model Parkinson's in rodents. With regards to the specific dopamine-immune effects in PD and PD models, lymphocytes in these systems show reductions in intracellular dopamine content, as well as changes in expression of TH, DAT, and DRs (Barbanti et al. 1999; Caronti et al. 2001; Kustrimovic et al. 2016; Nagai et al. 1996). $CD4^+$ T-cells seem to play more of a role in disease progression, as these cells can infiltrate into

the substantia nigra during PD, and depletion of $CD4^+$ T-cells attenuates dopaminergic neurodegeneration in animal models of PD (Benner et al. 2008; Brochard et al. 2009). Very recently, it has also been shown that oxidized forms of α-synuclein, one of the main constituents of Lewy bodies, specifically drive $CD4^+$ T-cell responses in PD patients (Sulzer et al. 2017). A case study additionally demonstrated that treatment with L-DOPA led to neutropenia and changes in neutrophil TH and DR expression (Cordano et al. 2015). These and other studies show that PD has a significant interaction with immune function (Mackie et al. 2018), and suggest that the role of dopamine in this interaction should be studied further.

NeuroHIV

The connection between HIV infection of the CNS and dopaminergic dysfunction has been recently reviewed (Gaskill et al. 2013; Nolan and Gaskill 2018), and will therefore only be briefly discussed here. This virus attacks immune cells, primarily CD4+ T cells and myeloid cells, and in the CNS the primary targets for HIV are myeloid cells such as microglia and macrophages. Once infected these cells can produce new virus, act as viral reservoirs, and release neurotoxic factors that contribute to the constellation of pathologies and behavioral cognitive and motor symptoms known as NeuroHIV. Prior to the use of combined antiretroviral therapy (cART), greater amounts of viral DNA and elevated neuropathology were seen in regions of the brain innervated by dopaminergic neurons (Aylward et al. 1993; Fujimura et al. 1997; Kieburtz et al. 1996). With cART, the effects are subtler, but changes in the dopaminergic system are still present (Cassol et al. 2014; Gaskill et al. 2017). Drugs which increase dopamine levels exacerbate SIV-associated neuropathology in the Rhesus macaque model of NeuroAIDS (Czub et al. 2004; Czub et al. 2001), and individuals infected with HIV show alterations in CNS and CSF dopamine (Table 4). During HIV infection, dopamine could increase monocyte transmigration into the CNS (Calderon et al. 2017; Coley et al. 2015), as well as increase HIV infection of macrophages (Gaskill et al. 2009; Gaskill et al. 2014) and promote an inflammatory environment, even in infected individuals on cART (Nolan et al. 2018). As drug abuse is a common comorbidity in HIV infection (Mathers et al. 2008), and many HIV-infected individuals also suffer from neuropsychiatric disorders (Dubé et al. 2005; Gallego et al. 2011), changes in dopamine concentrations in response to both illicit and psychiatric drugs could exacerbate the impact of dopamine on HIV associated neuropathology. Overall, these and other studies indicate that the bidirectional interactions between dopamine and HIV-infected myeloid cells are an important driver of NeuroHIV.

Multiple Sclerosis

Multiple sclerosis (MS) is a progressive, neurodegenerative disease characterized by progressive loss of neurological function due to the destruction of sheath axonal myelin throughout the brain and spinal cord (Cosentino and Marino 2013; Marino and Cosentino 2016). The heightened inflammatory processes present in the CNS during MS increase the entry of circulating immune cells (Engelhardt 2006; Larochelle et al. 2011). As dopamine can increase the activation and production of inflammatory mediators, changes in CNS dopamine levels during increased immune cell entry could contribute to MS pathology. In experimental mouse models of MS such as experimental autoimmune encephalomyelitis

(EAE), changes in CNS dopamine alter the progression of disease (Bałkowiec-Iskra et al. 2007). While there are no changes in the dopamine concentrations in the immune cells of MS patients (Cosentino et al. 2002; Rajda et al. 2002), there are substantial differences in DR expression in these cells, particularly D1-like DRs (Cosentino et al. 2014; Giorelli et al. 2005; Prado et al. 2018). In an EAE model of MS, these changes promoted the production of inflammatory cytokines IL-12 and IL-23, and disrupted the balance of activity between T_{reg} and Th17 cells, while the depletion of dopamine decreased the severity of the disease (Nakano et al. 2008; Prado et al. 2012; Prado et al. 2018). While other innate immune cells that are responsive to dopamine, including monocytes, NK cells, mast cells, and neutrophils also play a role in MS (Chanvillard et al. 2013; Hernández-Pedro et al. 2013; Hertwig et al. 2016; Naegele et al. 2012), the specific dopaminergic modulation of these cells in the context of MS is not clear. One of the most common treatments for MS, IFN-β, induces the production of dopamine in human lymphocytes (Cosentino et al. 2005), and a longitudinal study in relapsing remitting MS patients undergoing IFN-β treatment for 12 months found increased D5 and decreased D2 in lymphocytes compared to untreated patients (Zaffaroni et al. 2008). Thus, IFN-β may alter the response to dopamine in these cells, promoting D1-like responses and suggesting a potential benefit for dopaminergic agents in MS (Cosentino and Marino 2013). Thus, the amount of dopamine immune cells encounter in the brains of MS patients could substantially alter the progression of disease by changing the inflammatory milieu in the CNS.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disease in which the destruction of bone tissue and the articular structures of joints leads to progressive disability. Macrophages that infiltrate the synovial tissues play a crucial role in the progression of this disease, and dendritic cells (Gierut et al. 2010; Lutzky et al. 2007), neutrophils, and NK cells (Falgarone et al. 2005) in the synovial fluid also contribute to the development of the pathology. The dopaminergic system strongly influences the progression of RA (Pacheco et al. 2014), although dopamine levels in synovial fluid are relatively low, in the picomolar to nanomolar range (Table 4). Dopamine released from dendritic cells mediates IL-6 dependent differentiation of Th17 lymphocytes, resulting in exacerbated cartilage destruction that was blocked by the a D1-like receptor antagonist (SCH23390) (Nakano et al. 2011). In addition, the D2 antagonist haloperidol, and the DR agonist cabergoline have also been shown to ameliorate disease progression (Fahmy Wahba et al. 2015; Mobini et al. 2011). These effects may be mediated through effects on synovial fibroblasts in RA patients, which express both DRs and TH, (Capellino et al. 2014; Capellino et al. 2010), or through the effect of dopamine on osteoblasts, which also express these receptors and TH (Capellino et al. 2016). Expression of TH in osteoblasts suggests dopamine locally synthesized in the bone could influence disease progression, and that dopamine may be involved in not only bone formation (Lee et al. 2015), but also bone remodeling and joint erosion in RA.

Inflammatory Bowel Diseases

The autoimmune disorders known as inflammatory bowel diseases (IBDs) are categorized as chronic inflammatory conditions of the gastrointestinal system, with the two main categories including Crohn’s disease and ulcerative colitis. In both rodent models and humans with

IBD, dopamine is decreased in the colon (Magro et al. 2004; Magro et al. 2002) (Table 4), and rodent models of IBD show the disease is enhanced by treatment with the peripheral dopamine antagonist domperidone, and ameliorated by the dopamine agonist bromocriptine (Herak-Perkovic et al. 2001). A number of similar studies in rodent models show that treatment with D2 agonists (Tolstanova et al. 2015), D2 antagonists (Kim D, Kim W, et. al, 2019), and the herbal alkaloid berberine, which acts as a pan-DR antagonist (Kawano et al. 2015) all decreased the severity of IBD. The link between the dopaminergic system on IBD is also supported by a rat study showing that ulcerative colitis correlated with enhanced inflammatory and damaging effects of LPS on dopaminergic neurons in the nigrostriatal pathway (Villaran et al. 2010). In human IBD patients, impaired synthesis or cellular storage of dopamine was observed in enteroendocrine cells and the enteric nervous system, suggesting aberrant intestinal cellular synthesis and storage of dopamine could stimulate inflammation in nearby immune cells (Magro et al. 2002). These data show that the inflammatory responses triggering IBD are connected to both local and distal dopaminergic systems, and that changes in dopamine may be central to disease development.

Conclusion

The data presented here demonstrate that the dopaminergic system is active in many tissues, both in the CNS and the periphery. This activity is seen not only in the concentrations of dopamine found in these tissues, but in the variety of functions that are affected by this neurotransmitter. Dopamine has been shown to regulate immune cells in the brain and throughout the periphery, and dopamine displays complex regulatory effects on immune responses, depending on dopamine concentration, time of exposure, subtype of receptors, type of immune cells and immune cell activation state. The concentrations required to induce these effects on immunity are found in many compartments, where dopamine and the immune cells it can affect contribute to both homeostatic function and pathological responses. A better understanding of dopaminergic regulation of immune function is critical to understanding its role in both tissue homeostasis and many disease states associated with abnormal dopaminergic signaling and an altered/imbalanced immune response. Overall, a better appreciation of the broad immunomodulatory effects of this neurotransmitter is critical to the advancement of a number of fields, as it will likely demonstrate new pathways and mechanisms involved in many seemingly well understood processes, along with the development of new and better therapeutics and health strategies.

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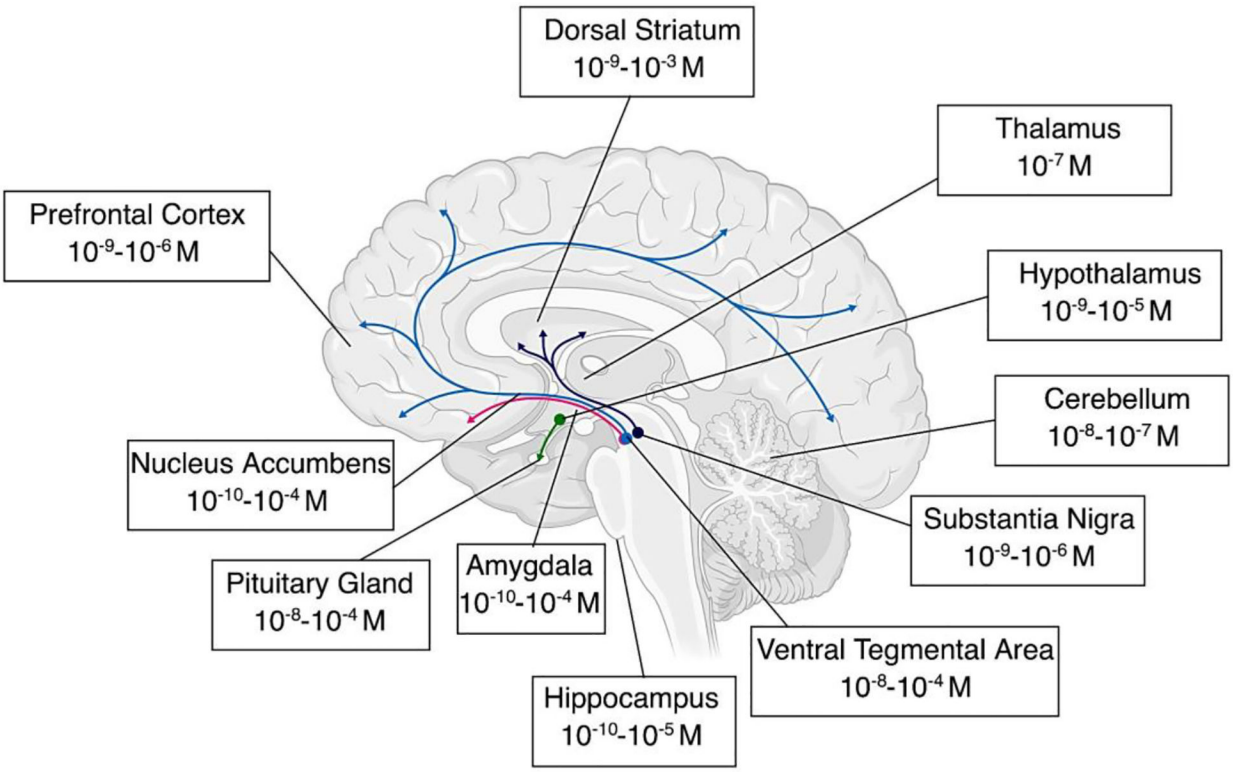

Figure 1 - Concentrations of Dopamine Throughout the Central Nervous System.

Range of dopamine concentrations found throughout the central nervous system, based on the summary of literature in Table 1. These values represent the range of calculated absolute molar values, which provide a simplified way to compare relative physiologically relevant concentrations across the brain. The dopaminergic pathways of the brain in which dopamine concentrations are the highest are highlighted; the nigrostriatal pathway starts in the substantia nigra and innervates the dorsal striatum (**purple**), the mesocortical pathway connects the ventral tegmental area to the cortex (**blue**), the mesolimbic pathway connects the ventral tegmental area to the limbic regions of the brain such as the amygdala and hippocampus (**red**), and the tuberoinfundibular pathway which runs from the hypothalamus to the pituitary (**green**). Concentrations in these regions change significantly during the use of illicit drugs (Table 2) and in different disease states (Table 4). For clarity, data showing concentrations that were outliers in the calculated range of concentrations for each region are excluded.

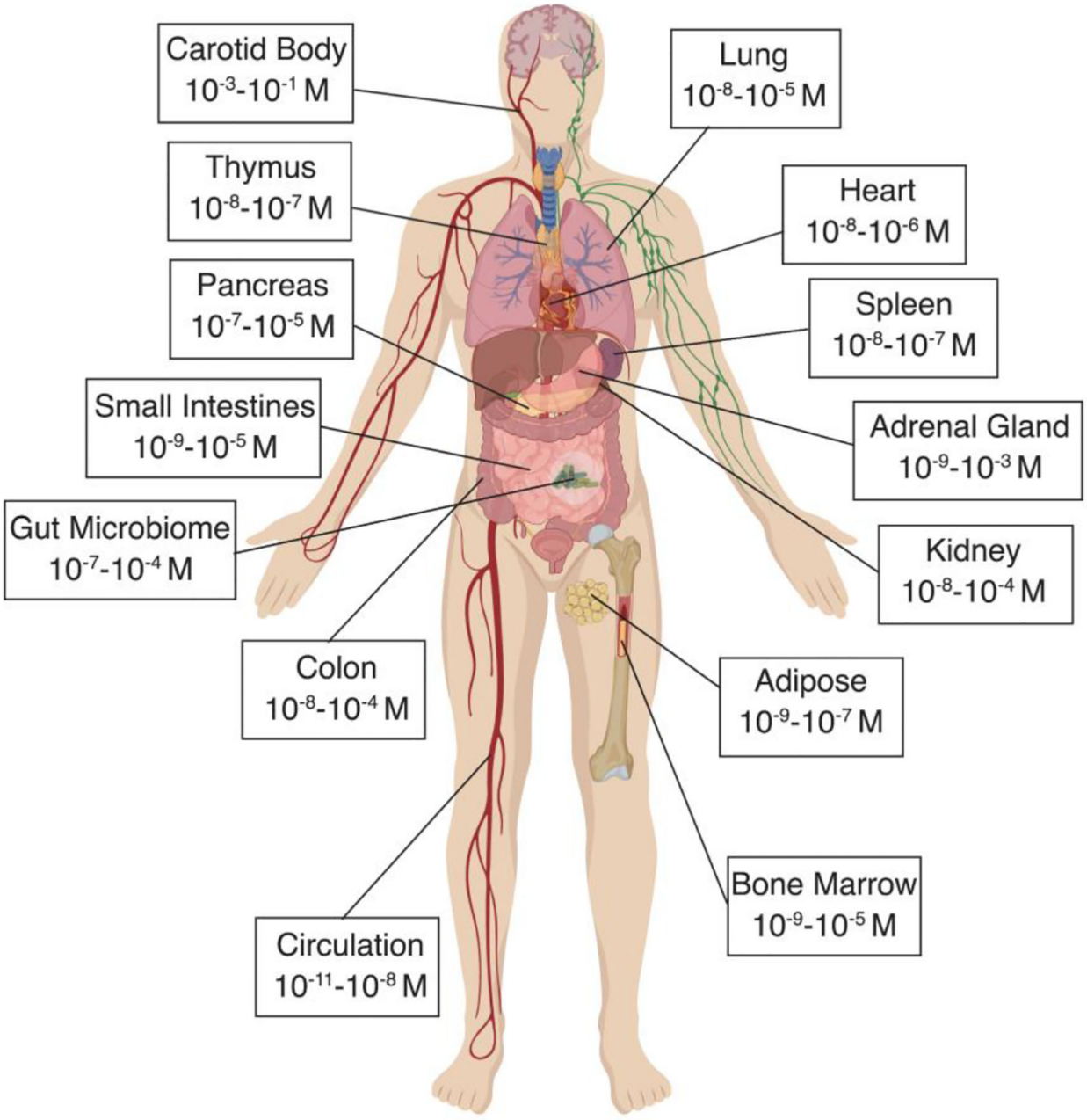

Figure 2 - Concentrations of Dopamine Throughout the Periphery.

A graphical representation of the various concentrations of dopamine throughout the periphery, based on the summary literature contained in findings in Table 3. These values represent the range of calculated absolute molar values, which provide a simplified way to compare relative physiologically relevant concentrations across peripheral systems. These concentrations can change during different disease states (Table 4). For clarity, data showing concentrations that were outliers in the calculated range of concentrations for each region are excluded

Table 1:

Dopamine Concentrations in the Central Nervous System.

A summary of human and animal studies that have examined concentrations of dopamine within the central nervous system. We have also included concentrations of dopamine in the retina and both anterior and posterior pituitary. Both original values and calculated relative molar values are reported to enable the comparison of dopamine concentrations between studies.

Original Dopamine Concentration	Dopamine Concentration (M)	Location	Species	Method	Reference
20 ng/g	1.3×10^{-7} M[a]	Amygdala	Human	HPLC	(Musshoff et al. 2000)
0.11 pmol/mg	1.1×10^{-7} M[a]	Amygdala	Human	HPLC	(Ebinger et al. 1987)
2.17 nmol/g	2.2×10^{-6} M[a]	Amygdala	Primate	HPLC	(Elchisak et al. 1983)
1.9 ng/mg[b]	1.2×10^{-5} M[a]	Amygdala	Rat	HPLC	(Carvalho et al. 2005)
1.7 ng/mg[c]	1.1×10^{-5} M[a]	Amygdala	Rat	HPLC	(Bradbury et al. 1985)
0.15 fmol/µl	1.5×10^{-10} M[a]	Amygdala	Rat	Microdialysis	(Inglis and Moghaddam 1999)
0.9 pg/10 µl[b]	5.8×10^{-10} M[a]	Amygdala	Rat	Microdialysis	(Tor-Agbidye et al. 2001)
0.67 pg/µl[c]	4.4×10^{-9} M[a]	Amygdala	Rat	Microdialysis	(Adachi et al. 2013)
0.79 nM[c]	7.9×10^{-10} M[a]	Amygdala	Rat	Microdialysis	(Weiss et al. 2000)
16 ng/mg[b]	1×10^{-4} M[a]	Amygdala (Basolateral)	Rat	HPLC	(Fadok et al. 2010)
7.95 pg/µg	5.2×10^{-5} M[a]	Arcuate Nucleus	Rat	HPLC	(MohanKumar e al. 1999)
238.5 pg/mg	1.6×10^{-6} M[a]	Arcuate Nucleus	Rat	HPLC	(Bromek et al. 2013)
2.92 pg/g log10	1×10^{-9} M[a]	Basal Ganglia	Human	HPLC	(Kumar et al. 2009)
116.1 pg/mg	7.6×10^{-7} M[a]	Brainstem	Rat	HPLC	(Rysz et al. 2015)
65 pg/mg[b]	4.2×10^{-7} M[a]	Brainstem	Rat	HPLC	(Bromek et al. 2011)
200 ng/g[b]	1.3×10^{-6} M[a]	Brainstem	Rat	HPLC	(Nikishina et al. 2016)
201.1 ng/g	1.3×10^{-6} M[a]	Brainstem	Rat	HPLC	(Meshki Baf et al. 1994)
3.43 ng/g	2.2×10^{-5} M[a]	Caudate Nucleus	Human	HPLC	(Wilson et al. 1996b)
6.62 ng/mg	4.3×10^{-5} M[a]	Caudate Nucleus	Human	HPLC	(Wilson et al. 1996a)
10,352 fmol/mg	1×10^{-5} M[a]	Caudate Nucleus	Human	HPLC	(Goldstein et al. 2011)

Original Dopamine Concentration	Dopamine Concentration (M)	Location	Species	Method	Reference
3 ng/mg[b]	2×10^{-5} M[a]	Caudate Nucleus	Human	HPLC	(Davis and Sparks 1995)
3.9 pg/g log10	2.9×10^{-6} M[a]	Caudate Nucleus	Human	HPLC	(Kumar et al. 2009)
4833 ng/g	3.2×10^{-5} M[a]	Caudate Nucleus	Human	HPLC	(Rajput et al. 2008)
2470 ng/g	1.6×10^{-5} M[a]	Caudate Nucleus	Human	HPLC	(Musshoff et al. 2000)
20.32 pmol/mg	2×10^{-5} M[a]	Caudate Nucleus	Human	HPLC	(Ebinger et al. 1987)
127 ng/mg	8.3×10^{-4} M[a]	Caudate Nucleus	Primate	HPLC	(Elsworth et al. 2008)
58.2 nmol/g	5.8×10^{-5} M[a]	Caudate Nucleus	Primate	HPLC	(Elchisak et al. 1983)
200nM	2×10^{-7} M	Caudate Nucleus (Synapse Interface)	Rat	FSCV	(Kawagoe et al. 1992)
1.68 fmol/μl	1.7×10^{-9} M[a]	Caudate Nucleus	Rat	Microdialysis	(Inglis and Moghaddam 1999)
10.9 μg/g	7.1×10^{-5} M[a]	Caudate Nucleus	Sheep	HPLC	(Juorio and Chedrese 1990)
6 nM	6×10^{-9} M	Caudate Nucleus (Extrasynaptic Region)	Rat	FSCV	(Kawagoe et al. 1992)
1.2 nM	1.2×10^{-9} M	Caudate/Putan en	Mouse	Microdialysis	(Bosse and Mathews 2011)
168.4 pg/μg	1.1×10^{-3} M[a]	Caudate/Putamen	Rat	HPLC	(MohanKumar et al. 1999)
8.4 ng/mg[c]	5.5×10^{-5} M[a]	Caudate/Putan en (Anterior)	Rat	HPLC	(Bradbury et al. 1985)
5 ng/mg[c]	3.3×10^{-5} M[a]	Caudate/Putam en (Lateral)	Rat	HPLC	(Bradbury et al. 1985)
200 nM[b]	2×10^{-7} M	Caudate/Putam en (Phasic Value)	Rat	FSCV	(Venton et al. 2003)
30 nM	3×10^{-8} M	Caudate/Putam en (Tonic Value)	Rat	FSCV	(Venton et al. 2003)
8 ng/g	5.2×10^{-8} M[a]	Cerebellum	Human	HPLC	(Musshoff et al. 2000)
19 ng/g	1.2×10^{-7} M[a]	Cerebellum	Mouse	HPLC	(Sasa and Blank 1977)
0.03 nmol/g	3×10^{-8} M[a]	Cerebellum	Primate	HPLC	(Elchisak et al. 1983)
0.29 nmol/g	2.9×10^{-7} M[a]	Cerebellum	Rat	HPLC	(Swiercz et al. 2009)
3.4 pg/mg[b]	2.2×10^{-8} M[a]	Cerebellum	Rat	HPLC	(Bromek et al. 2011)
57.3 ng/g	3.7×10^{-7} M[a]	Cerebellum	Rat	HPLC	(Meshki Baf et al. 1994)
1.19 ng/mg	7.8×10^{-6} M[a]	Cingulate Cortex	Primate	HPLC	(Elsworth et al. 2008)
0.641 nmol/g	6.4×10^{-7} M[a]	Cingulate Gyrus	Primate	HPLC	(Elchisak et al. 1983)

Original Dopamine Concentration	Dopamine Concentration (M)	Location	Species	Method	Reference
0.481 nmol/g	4.8×10^{-7} M[a]	Corpus Callosum	Primate	HPLC	(Elchisak et al. 1983)
15 fmol/mg	1.5×10^{-8} M[a]	Cortex	Human	HPLC	(Goldstein et al. 2011)
3.7 nmol/g	3.7×10^{-7} M[a]	Cortex	Rat	HPLC	(Swiercz et al. 2009)
377.4 pg/mg	2.5×10^{-6} M[a]	Cortex	Rat	HPLC	(Rysz et al. 2015)
0.01 ng/ml	6.5×10^{-11} M[a]	CSF	Human	HPLC	(Eldrup et al. 1995)
89.4 pg/ml	5.8×10^{-10} M[a]	CSF	Human	HPLC	(Berger et al. 1994)
15 pg/ml[b]	9.8×10^{-11} M[a]	CSF	Human	HPLC	(Scheller et al. 2010)
0.05 nM	5×10^{-11} M	CSF	Human	HPLC	(Andersen et al. 2017)
0.32 ng/ml	2.1×10^{-9} M[a]	CSF	Human	HPLC	(Engelborghs el al. 2003)
0.02 ng/ml	1.3×10^{-10} M[a]	CSF	Human	HPLC	(Raskind et al. 1999)
2 log pg/ml	1×10^{-9} M[a]	CSF	Human (MDD patients)	HPLC	(King et al. 1986
0.91 nmol/g	9.1×10^{-7} M[a]	Diencephalon	Rat	HPLC	(Swiercz et al. 2009)
19 ng/g	1.2×10^{-7} M[a]	Frontal cortex	Human	HPLC	(Musshoff et al. 2000)
2.186 pg/g log10	1×10^{-9} M[a]	Frontal Cortex	Human	HPLC	(Kumar et al. 2009)
0.0975 nmol/g	9.8×10^{-8} M[a]	Frontal Cortex	Primate	HPLC	(Elchisak et al. 1983)
291.7 pg/mg	1.9×10^{-6} M[a]	Frontal Cortex	Rat	HPLC	(Rysz et al. 2015)
225 pg/mg[b]	1.5×10^{-6} M[a]	Frontal Cortex	Rat	HPLC	(Bromek et al. 2011)
210.2 fmol/mg	2.1×10^{-7} M[a]	Frontal Cortex	Rat	HPLC	(Wisman et al. 2008)
2.91 pg/g log10	1×10^{-9} M[a]	Globus Pallidus	Human	HPLC	(Kumar et al. 2009)
1.59 nmol/g	1.6×10^{-6} M[a]	Globus Pallidus	Primate	HPLC	(Elchisak et al. 1983)
490 ng/g	3.2×10^{-6} M[a]	Globus Pallidus (External)	Human	HPLC	(Rajput et al. 2008)
75 ng/g	4.9×10^{-7} M[a]	Globus Pallidus (Internal)	Human	HPLC	(Rajput et al. 2008)
1.53 pmol/mg	1.5×10^{-6} M[a]	Globus Pallidus (Lateral)	Human	HPLC	(Ebinger et al. 1987)
1.46 pmol/mg	1.5×10^{-6} M[a]	Globus Pallidus (Medial)	Human	HPLC	(Ebinger et al. 1987)

Original Dopamine Concentration	Dopamine Concentration (M)	Location	Species	Method	Reference
11 ng/g	7.2×10^{-8} M[a]	Hippocampus	Human	HPLC	(Musshoff et al. 2000)
0.27 pmol/mg	2.7×10^{-7} M[a]	Hippocampus	Human	HPLC	(Ebinger et al. 1987)
9.06 pmol/mg	9.1×10^{-6} M[a]	Hippocampus (Dorsal)	Mouse	HPLC	(Kempadoo et al 2016)
0.1 ng/mg[b]	6.5×10^{-7} M[a]	Hippocampus (Dorsal)	Rat	HPLC	(Carvalho et al. 2005)
2.03 pg/μg	1.3×10^{-5} M[a]	Hippocampus	Rat	HPLC	(MohanKumar e al. 1999)
116.7 ng/g	7.6×10^{-7} M[a]	Hippocampus	Rat	HPLC	(Meshki Baf et al. 1994)
7.7 nmol/g	7.7×10^{-7} M[a]	Hippocampus	Rat	HPLC	(Swiercz et al. 2009)
65.2 fmol/mg	6.5×10^{-8} M[a]	Hippocampus	Rat	HPLC	(Wisman et al. 2008)
14.4 pg/mg	9×10^{-8} M[a]	Hippocampus	Rat	HPLC	(Rysz et al. 2015)
0.11 nM	1.1×10^{-10} M	Hippocampus	Rat	Microdialysis	(Borgkvist et al. 2012)
186 ng/g	1.2×10^{-6} M[a]	Hypothalamus	Human	HPLC	(Musshoff et al. 2000)
1301 pg/mg[c]	8.5×10^{-6} M[a]	Hypothalamus	Mouse	HPLC	(Nagler et al. 2018)
111.9 ng/g	7.3×10^{-7} M[a]	Hypothalamus	Mouse	LC-MS	(Kim et al. 2014)
2.71 nmol/g	2.7×10^{-6} M[a]	Hypothalamus	Primate	HPLC	(Elchisak et al. 1983)
11 ng/mg[b]	7.2×10^{-5} M[a]	Hypothalamus	Rat	HPLC	(De Laurentiis e al. 2002)
200 ng/g[b]	1.3×10^{-6} M[a]	Hypothalamus	Rat	HPLC	(Nikishina et al. 2016)
241.2 pg/mg	1.6×10^{-6} M[a]	Hypothalamus	Rat	HPLC	(Rysz et al. 2015)
304.8 ng/g	2×10^{-6} M[a]	Hypothalamus	Rat	HPLC	(Meshki Baf et al. 1994)
32.85 ng/g	2.1×10^{-7} M[a]	Hypothalamus	Rat	HPLC	(Hu et al. 2014)
0.34 ng/g	2.2×10^{-9} M[a]	Hypothalamus	Rat	LC-MS/MS	(Tareke et al. 2007)
0.21 ug/g	1.4×10^{-6} M[a]	Hypothalamus	Sheep	HPLC	(Juorio and Chedrese 1990'
150 pg/mg[b]	9.8×10^{-7} M[a]	Hypothalamus (Anterior Slices	Rat	HPLC	(Shintani et al. 1993)
7.7 pg/μg[b]	5×10^{-5} M[a]	Medial Preoptk Area	Rat	HPLC	(MohanKumar e al. 1999)
50.8 pg/μg[b]	3.3×10^{-5} M[a]	Median Eminence	Rat	HPLC	(MohanKumar e al. 1999)

Original Dopamine Concentration	Dopamine Concentration (M)	Location	Species	Method	Reference
15 ng/mg[b]	9.8×10^{-5} M[a]	Median Eminence	Rat	HPLC	(Nagy et al. 1998)
30 pg/μg[b]	2×10^{-4} M[a]	Median Eminence	Rat	HPLC	(Lafuente et al. 2005)
127 ng/mg[c]	8.3×10^{-4} M[a]	Median Eminence	Rat	Radioenzymatic Assay	(Demarest et al. 1982)
102 ng/g	6.7×10^{-7} M[a]	Medulla Oblongata	Human	HPLC	(Musshoff et al. 2000)
0.259 nmol/g	2.6×10^{-7} M[a]	Medulla Oblongata	Primate	HPLC	(Elchisak et al. 1983)
36.4 pg/mg	2.4×10^{-7} M[a]	Medulla Oblongata	Rat	HPLC	(Rysz et al. 2015)
0.6 nmol/g	6×10^{-7} M[a]	Mesencephaloi	Rat	HPLC	(Swiercz et al. 2009)
59.8 ng/g	3.9×10^{-7} M[a]	Midbrain	Mouse	LC-MS	(Kim et al. 2014)
0.5 nmol/g	5×10^{-7} M[a]	Midbrain	Primate	HPLC	(Elchisak et al. 1983)
104.76 ng/g	6.8×10^{-7} M[a]	Midbrain	Rat	HPLC	(Song et al. 2006)
600 ng/g[b]	3.9×10^{-6} M[a]	Midbrain	Rat	HPLC	(Nikishina et al. 2016)
180.2 ng/g	1.2×10^{-6} M[a]	Motor Cortex	Rat	HPLC	(Meshki Baf et al. 1994)
2.44 ng/mg	1.6×10^{-5} M[a]	Nucleus Accumbens	Human	HPLC	(Wilson et al. 1996a)
986 ng/g	6.4×10^{-6} M[a]	Nucleus Accumbens	Human	HPLC	(Musshoff et al. 2000)
14.93 pmol/mg	1.5×10^{-5} M[a]	Nucleus Accumbens	Human	HPLC	(Ebinger et al. 1987)
150 ng/mg[b]	9.8×10^{-4} M[a]	Nucleus Accumbens	Mouse	HPLC	(Winner et al. 2017)
4.77 ng/mg	3.1×10^{-5} M[a]	Nucleus Accumbens	Mouse	HPLC	(Bengamini et al 2018)
16.7 fmol/35 μl	4.8×10^{-10} M[a]	Nucleus Accumbens	Mouse	Microdialysis	(Airavaara et al. 2004)
75.7 ng/mg	4.9×10^{-6} M[a]	Nucleus Accumbens	Primate	HPLC	(Elsworth et al. 2008)
2 μM	2×10^{-6} M	Nucleus Accumbens	Rat	FSCV	(Kurlu et al. 2018)
0.59 μM	5.9×10^{-7} M	Nucleus Accumbens	Rat	FSCV	(Wakabayashi e al. 2016)
71.5 ng/mg	4.7×10^{-4} M[a]	Nucleus Accumbens	Rat	HPLC	(Fadok et al. 2010)
11 ng/mg	7.2×10^{-5} M[a]	Nucleus Accumbens	Rat	HPLC	(Carvalho et al. 2005)
4535.8 pg/mg	3×10^{-5} M[a]	Nucleus Accumbens	Rat	HPLC	(Rysz et al. 2015)

Original Dopamine Concentration	Dopamine Concentration (M)	Location	Species	Method	Reference
45.51 ng/mg	3×10^{-4} M[a]	Nucleus Accumbens	Rat	HPLC	(Choi et al. 2012)
8700 pg/mg[b]	5.7×10^{-5} M[a]	Nucleus Accumbens	Rat	HPLC	(Bromek et al. 2011)
4.9 μg/g[bd]	3.2×10^{-5} M[a]	Nucleus Accumbens	Rat	HPLC	(Lucas and McMillen 2002)
3.3 nM[b]	3.3×10^{-9} M	Nucleus Accumbens	Rat	Microdialysis	(Hemby et al. 1995)
1.48 fmol/μl	1.5×10^{-9} M[a]	Nucleus Accumbens	Rat	Microdialysis	(Yan 1999)
0.14 pmol/25 μl	5.6×10^{-9} M[a]	Nucleus Accumbens	Rat	Microdialysis	(Anagnostakis and Spyraki 1994)
0.01 pmol/20 μl	5×10^{-10} M[a]	Nucleus Accumbens	Rat	Microdialysis	(Pothos et al. 1991)
3.45 nM	3.5×10^{-9} M	Nucleus Accumbens	Rat	Microdialysis	(Weiss et al. 1996)
1.14 nM	1.1×10^{-9} M	Nucleus Accumbens	Rat	Microdialysis	(Borgkvist et al. 2012)
7 pg/20 μl	2.3×10^{-9} M	Nucleus Accumbens	Rat	Microdialysis	(Hernandez anc Hoebel 1988)
9.75 nM	9.8×10^{-9} M	Nucleus Accumbens	Rat	Microdialysis	(Pettit et al. 1990)
58.7 fmol/40 μl	1.5×10^{-9} M	Nucleus Accumbens	Rat	Microdialysis	(Chen et al. 1993)
4.2 nM	4.2×10^{-9} M	Nucleus Accumbens	Rat	Microdialysis	(Parsons and Justice 1992)
10.8 nM[b]	1.1×10^{-8} M	Nucleus Accumbens	Rat	Microdialysis	(Smith et al. 2006)
17.4 nM	1.7×10^{-8} M	Nucleus Accumbens	Rat	Microdialysis	(Moghaddam and Bunney 1989)
2.4 nM[c]	2.4×10^{-9} M	Nucleus Accumbens	Rat	Microdialysis	(Weiss et al. 2000)
9.4 nM	9.4×10^{-9} M	Nucleus Accumbens	Rat	Microdialysis	(Yim and Gonzales 2000)
1.24 fmol/μl	1.2×10^{-9} M[a]	Nucleus Accumbens	Rat	Microdialysis	(Inglis and Moghaddam 1999)
73.8 ng/mg[c]	4.8×10^{-4} M[a]	Nucleus Accumbens	Rat	Radioenzymatic Assay	(Demarest et al. 1982)
50 nM	5×10^{-8} M	Nucleus Accumbens (Core)	Rat	FSCV	(Wightman et al 2007)
40 nM	4×10^{-8} M	Nucleus Accumbens (Core)	Rat	FSCV	(Stuber et al. 2005)
20 nM	2×10^{-8} M	Nucleus Accumbens (Core)	Rat	FSCV	(Owesson-White et al. 2012)
15 nM[b]	1.5×10^{-8} M	Nucleus Accumbens (Core)	Rat	FSCV	(Vander Weele et al. 2014)
20.4 nM[b]	2×10^{-8} M	Nucleus Accumbens (Shell)	Rat	FSCV	(Roitman et al. 2008)
41 nM	4.1×10^{-8} M	Nucleus Accumbens (Shell)	Rat	FSCV	(Johnson et al. 2018)
30 nM[b]	3×10^{-8} M	Nucleus Accumbens (Shell)	Rat	FSCV	(Vander Weele et al. 2014)

Original Dopamine Concentration	Dopamine Concentration (M)	Location	Species	Method	Reference
0.47 nM	4.7×10^{-10} M	Nucleus Accumbens (Shell)	Rat	LC-MS/MS	(Hows et al. 2004)
66.8 fmol/50μl	1.3×10^{-9} M[a]	Nucleus Accumbens (Shell)	Rat	Microdialysis	(Fadda et al. 2003)
0.59 pg/μl[c]	3.9×10^{-9} M[a]	Nucleus Accumbens (Shell)	Rat	Microdialysis	(Adachi et al. 2013)
0.884 nmol/g	8.8×10^{-7} M[a]	Occipital Cortex	Primate	HPLC	(Elchisak et al. 1983)
40.6 ng/g	2.7×10^{-7} M[a]	Olfactory Bulb	Mouse	LC-MS	(Kim et al. 2014
0.192 μg/g	1.3×10^{-6} M[a]	Olfactory Bulb	Primate	HPLC	(Pifl et al. 2017)
75 pg/mg[b]	4.9×10^{-7} M[a]	Olfactory Bulb	Rat	HPLC	(Bromek et al. 2011)
6.87 nmol/g	6.9×10^{-6} M[a]	Olfactory Cortex	Primate	HPLC	(Elchisak et al. 1983)
11 ng/g	7.1×10^{-8} M[a]	Olfactory Tubercle	Human	HPLC	(Musshoff et al. 2000)
0.34 μM	3.4×10^{-7} M	Olfactory Tubercle	Rat	FSCV	(Wakabayashi e al. 2016)
4.1 ng/mg[c]	2.7×10^{-5} M[a]	Olfactory Tubercle	Rat	HPLC	(Bradbury et al. 1985)
39.7 ng/mg[c]	2.6×10^{-4} M[a]	Olfactory Tubercle	Rat	Radioenzymatic Assay	(Demarest et al. 1982)
6 ng/mg[b]	3.9×10^{-5} M[a]	Paraventricula Nucleus	Mouse	HPLC	(Sakic et al. 2002)
14.4 pg/μg	3.1×10^{-5} M[a]	Paraventricula Nucleus	Rat	HPLC	(MohanKumar e al. 1999)
346.2 pg/mg	2.3×10^{-6} M[a]	Paraventricula Nucleus	Rat	HPLC	(Bromek et al. 2013)
0.01 ng/g	6.5×10^{-11} M[a]	Parietal Cortex	Rat	LC-MS/MS	(Tareke et al. 2007)
48.9 ng/g	3.2×10^{-7} M[a]	Pituitary Gland	Mouse	LC-MS	(Kim et al. 2014
0.29 ng/g	1.9×10^{-9} M[a]	Pituitary Gland	Rat	LC-MS/MS	(Tareke et al. 2007)
0.01 ng/mg[b]	6.5×10^{-8} M[a]	Pituitary Gland (Anterior Inner Zone)	Rat	HPLC	(Nagy et al. 1998)
0.2 ng/mg[b]	1.3×10^{-6} M[a]	Pituitary Gland (Anterior Outer Zone)	Rat	HPLC	(Nagy et al. 1998)
0.33 ng/mg[b]	2.2×10^{-6} M[a]	Pituitary Gland (Anterior)	Rat	HPLC	(De Laurentiis e al. 2002)
0.45 ng/mg[c]	2.9×10^{-6} M[a]	Pituitary Gland (Anterior)	Rat	HPLC	(DeMaria et al. 1998)
20 pg/μg[b]	1.3×10^{-4} M[a]	Pituitary Gland (Anterior)	Rat	HPLC	(Lafuente et al. 2005)
0.2 ng/mg[c]	1.3×10^{-6} M[a]	Pituitary Gland (Anterior)	Rat	Radioenzymatic Assay	(Demarest et al. 1982)

Original Dopamine Concentration	Dopamine Concentration (M)	Location	Species	Method	Reference
5 ng/mg[b]	3.3×10^{-5} M[a]	Pituitary Gland (Intermediate)	Rat	HPLC	(Nagy et al. 1998)
25 ng/mg[c]	1.6×10^{-4} M[a]	Pituitary Gland (Intermediate)	Rat	HPLC	(DeMaria et al. 1998)
7.5 ng/mg[c]	4.9×10^{-5} M[a]	Pituitary Gland (Posterior)	Rat	HPLC	(DeMaria et al. 1998)
6 ng/mg[b]	3.9×10^{-5} M[a]	Pituitary Gland (Posterior)	Rat	HPLC	(De Laurentiis e al. 2002)
1 ng/mg[b]	6.5×10^{-6} M[a]	Pituitary Gland (Posterior)	Rat	HPLC	(Nagy et al. 1998)
6 pg/µg[b]	3.9×10^{-5} M[a]	Pituitary Gland (Posterior)	Rat	HPLC	(Lafuente et al. 2005)
7.8 ng/mg[c]	5.1×10^{-5} M[a]	Pituitary Gland (Posterior)	Rat	Radioenzymatic Assay	(Demarest et al. 1982)
0.176 nmol/g	1.8×10^{-7} M[a]	Pons	Primate	HPLC	(Elchisak et al. 1983)
0.1 pmol/mg	1×10^{-7} M[a]	Postcentral Gyrus	Human	HPLC	(Ebinger et al. 1987)
15 ng/g	9.8×10^{-8} M[a]	Precentral Gyrus	Human	HPLC	(Musshoff et al. 2000)
0.08 pmol/mg	8×10^{-8} M[a]	Precentral Gyrus	Human	HPLC	(Ebinger et al. 1987)
113.51 ng/g	7.4×10^{-7} M[a]	Prefrontal Cortex	Rat	HPLC	(Hu et al. 2014)
0.08 ng/mg[b]	5.2×10^{-7} M[a]	Prefrontal Cortex	Rat	HPLC	(Carvalho et al. 2005)
0.05 µg/g[b]	3.3×10^{-7} M[a]	Prefrontal Cortex	Rat	HPLC	(Lucas and McMillen 2002)
79.95 nmol/l	8×10^{-8} M[a]	Prefrontal Cortex	Rat	Microdialysis	(Pistis et al. 2002)
0.92 ng/mg	6×10^{-6} M[a]	Prefrontal Cortex (Dorsolateral)	Primate	HPLC	(Elsworth et al. 2008)
0.475 ng/mg	3.1×10^{-6} M[a]	Prefrontal Cortex (Medial	Rat	HPLC	(Choi et al. 2012)
2.7nM	2.7×10^{-9} M	Prefrontal Cortex (Medial	Rat	Microdialysis	(Moghaddam and Bunney 1989)
0.23 fmol/µl	2.3×10^{-10} M[a]	Prefrontal Cortex (Medial	Rat	Microdialysis	(Inglis and Moghaddam 1999)
1.27 ng/mg	8.3×10^{-6} M[a]	Prelimbic Cortex	Primate	HPLC	(Elsworth et al. 2008)
3.98 µg/g	2.6×10^{-5} M[a]	Putamen	Human	HPLC	(Pifl et al. 2014)
4.04 ng/g	2.6×10^{-5} M[a]	Putamen	Human	HPLC	(Wilson et al. 1996b)
7.16 ng/mg	4.7×10^{-5} M[a]	Putamen	Human	HPLC	(Wilson et al. 1996a)
16.96 pmol/mg	1.7×10^{-5} M[a]	Putamen	Human	HPLC	(Ebinger et al. 1987)

Original Dopamine Concentration	Dopamine Concentration (M)	Location	Species	Method	Reference
1170 ng/g	7.6×10^{-6} M[a]	Putamen	Human	HPLC	(Musshoff et al. 2000)
15488 fmol/mg	1.5×10^{-5} M[a]	Putamen	Human	HPLC	(Goldstein et al. 2011)
3.5 ng/mg[b]	2.3×10^{-5} M[a]	Putamen	Human	HPLC	(Davis and Sparks 1995)
6475 ng/g	4.2×10^{-5} M[a]	Putamen	Human	HPLC	(Rajput et al. 2008)
4.563 pg/g log10	1.1×10^{-9} M[a]	Putamen	Human	HPLC	(Kumar et al. 2009)
13.26 μg/g	8.7×10^{-5} M[a]	Putamen	Primate	HPLC	(Pifl et al. 2014)
68.4 nmol/g	6.8×10^{-5} M[a]	Putamen	Primate	HPLC	(Elchisak et al. 1983)
0.25 ng/mg	1.6×10^{-6} M[a]	Retina	Mouse	HPLC	(Wu et al. 2015)
1.4 ng/mg[b]	9.1×10^{-6} M[a]	Retina	Mouse	HPLC	(Jackson et al. 2012)
2.125 pg/mg	1.4×10^{-8} M[a]	Retina	Mouse	HPLC	(Lahouaoui et al 2016)
0.128 nmol/g	1.3×10^{-7} M[a]	Retina	Primate	HPLC	(Elchisak et al. 1983)
10,000 pg/mg[b]	6.5×10^{-5} M[a]	Striatum	Mouse	HPLC	(Batkowiec-Iskra et al. 2007)
240 ng/mg[b]	1.6×10^{-3} M[a]	Striatum	Mouse	HPLC	(Winner et al. 2017)
0.65 nmol/mg	6.5×10^{-4} M[a]	Striatum	Mouse	HPLC	(Kita et al. 2000)
269.5 ng/mg	1.8×10^{-3} M[a]	Striatum	Mouse	HPLC	(Petzinger et al. 2007)
3463 ng/g	2.3×10^{-5} M[a]	Striatum	Mouse	LC-MS	(Kim et al. 2014)
4.2 nM[b]	4.2×10^{-9} M	Striatum	Mouse	Microdialysis	(Zhang et al. 2009)
5 fmol/μL[b]	5×10^{-9} M[a]	Striatum	Primate	Microdialysis	(Bradberry 2000
181 nM	1.8×10^{-7} M	Striatum	Rat	FSCV	(Schwerdt et al. 2018)
11.3 nmol/g	1.1×10^{-5} M[a]	Striatum	Rat	HPLC	(Swiercz et al. 2009)
6553.8 pg/mg	4.3×10^{-5} M[a]	Striatum	Rat	HPLC	(Rysz et al. 2015)
6 ng/mg[b]	3.9×10^{-5} M[a]	Striatum	Rat	HPLC	(Garrido-Gil et al. 2018b)
7 ng/mg[b]	4.6×10^{-5} M[a]	Striatum	Rat	HPLC	(Villar-Cheda et al. 2014)
1300 ng/g[b]	8.5×10^{-6} M[a]	Striatum	Rat	HPLC	(Nikishina et al. 2016)

Original Dopamine Concentration	Dopamine Concentration (M)	Location	Species	Method	Reference
9500 pg/mg[b]	6.2×10^{-5} M[a]	Striatum	Rat	HPLC	(Bromek et al. 2011)
1894.5 ng/g	1.2×10^{-5} M[a]	Striatum	Rat	HPLC	(Hu et al. 2014)
10.4 ng/g	6.8×10^{-8} M[a]	Striatum	Rat	LC-MS/MS	(Tareke et al. 2007)
20 nM[b]	2×10^{-8} M	Striatum	Rat	Microdialysis	(Shou et al. 2006)
146.4 ng/mg[c]	9.6×10^{-4} M[a]	Striatum	Rat	Radioenzymatic Assay	(Demarest et al. 1982)
3.202 pg/g log10	1×10^{-8} M[a]	Substantia Nigra	Human	HPLC	(Kumar et al. 2009)
384 ng/g	2.5×10^{-6} M[a]	Substantia Nigra	Human	HPLC	(Musshoff et al. 2000)
4.96 pmol/mg	5×10^{-6} M[a]	Substantia Nigra	Human	HPLC	(Ebinger et al. 1987)
4.89 nmol/g	4.9×10^{-6} M[a]	Substantia Nigra	Primate	HPLC	(Elchisak et al. 1983)
1000 pg/mg[b]	6.5×10^{-6} M[a]	Substantia Nigra	Rat	HPLC	(Bromek et al. 2011)
0.41 ng/g	2.7×10^{-9} M[a]	Substantia Nigra	Rat	LC-MS/MS	(Tareke et al. 2007)
1.04 ng/mg	6.8×10^{-6} M[a]	Supplementary Motor Area	Primate	HPLC	(Elsworth et al. 2008)
43 ng/g	2.8×10^{-7} M[a]	Thalamus	Human	HPLC	(Musshoff et al. 2000)
115.9 pg/mg	7.6×10^{-7} M[a]	Thalamus	Rat	HPLC	(Rysz et al. 2015)
0.45 pmol/mg	4.5×10^{-7} M[a]	Thalamus (Anterior Nuclei)	Human	HPLC	(Ebinger et al. 1987)
125 pmol/mg[b]	1.3×10^{-4} M[a]	Ventral Tegmental Area	Guinea Pig	HPLC	(Rice et al. 1994
9.2 ng/mg	6×10^{-5} M[a]	Ventral Tegmental Area	Rat	HPLC	(Salvatore et al. 2012)
46.5 fmol/40 µl	1.2×10^{-9} M[a]	Ventral Tegmental Area	Rat	Microdialysis	(Chen et al. 1993)
10 ng/g	6.5×10^{-8} M[a]	White Matter	Human	HPLC	(Musshoff et al. 2000)
800 ng/g	5.2×10^{-6} M[a]	Whole brain	Mouse	GC-MS	(Weintraub et al 1975)
6.27 pmol/mg	6.3×10^{-6} M[a]	Whole brain	Mouse	HPLC	(Quelhas-Santos et al. 2015)
46.7 pmol/mg	3×10^{-7} M[a]	Whole brain	Mouse	HPLC	(Tsao et al. 1997)
973 ng/g	6.4×10^{-6} M[a]	Whole brain	Mouse	HPLC	(Sasa and Blank 1977)

[a]Concentrations calculated by dividing values by the molecular weight of dopamine (153.18 g/mol) if not already in a molar value, and multiplying the density of tissues or fluids (kg/L or kg/m^3)

[b] Estimate obtained from graph because no values given in text, or averaged values if multiple control values were given

[c] Value obtained from one or an average of treatment groups other than control because no absolute control given

[d] Averaged male and female control groups

Table 2:

Dopamine Concentrations in the Central Nervous System in Response to Drugs of Abuse.

A summary of human and animal studies that have examined concentrations of dopamine within the central nervous system in response to drugs of abuse. Both original values and our calculated relative molar values are reported to easily compare concentrations of dopamine between studies.

Original Dopamine Concentration	Concentration of Dopamine (M)	Change from Baseline	Location	Species	Drug	Method	Reference
900 pg/10 µl[b]	5.9×10^{-7} M[a]	Increased	Amygdala	Rat	Amphetamine	Microdialysis	(Tor-Agbidye et al. 2001)
147 pg/20µl	4.8×10^{-8} M[a]	Increased	Nucleus Accumbens	Rat	Amphetamine	Microdialysis	(Hernandez and Hoebel 1988)
70nM[b]	7×10^{-8} M	Increased	Nucleus Accumbens	Rat	Amphetamine	Microdialysis	(Moghadda m and Bunney 1989)
7nM[b]	7×10^{-9} M	Increased	Prefrontal Cortex (Medial)	Rat	Amphetamine	Microdialysis	(Moghadda m and Bunney 1989)
300 nM[b] (Phasic)	3×10^{-7} M	Increased	Caudate/Putamen	Rat	Cocaine	FSCV	(Venton et al. 2003)
110 nM (Tonic)	1.1×10^{-7} M	Increased	Caudate/Putamen	Rat	Cocaine	FSCV	(Venton et al. 2003)
4175 fmol/35 µl[b]	1.2×10^{-7} M[a]	Increased	Nucleus Accumbens	Mouse	Cocaine	Microdialysis	(Airavaara et al. 2004)
65 nM	6.5×10^{-8} M	Increased	Nucleus Accumbens	Rat	Cocaine	FSCV	(Phillips et al. 2003)
36 nM[b]	3.6×10^{-8} M	Increased	Nucleus Accumbens	Rat	Cocaine	Microdialysis	(Smith et al. 2006)
122nM[b]	1.2×10^{-7} M	Increased	Nucleus Accumbens	Rat	Cocaine	Microdialysis	(Moghadda m and Bunney 1989)
85 pg/20 µl[b]	2.8×10^{-8} M[a]	Increased	Nucleus Accumbens	Rat	Cocaine	Microdialysis	(Hernandez and Hoebel 1988)
2.62 µM	2.6×10^{-6} M	Increased	Nucleus Accumbens	Rat	Cocaine	Microdialysis	(Pettit et al. 1990)
70 nM	7×10^{-8} M	Increased	Nucleus Accumbens (Core)	Rat	Cocaine	FSCV	(Wightman et al. 2007)
70 nM	7×10^{-8} M	Increased	Nucleus Accumbens (Core)	Rat	Cocaine	FSCV	(Stuber et al. 2005)
0.83 nM[b]	8.3×10^{-10} M	Increased	Nucleus Accumbens (Shell)	Rat	Cocaine	LC-MS/MS	(Hows et al. 2004)
250 fmol/50µl	4.9×10^{-7} M[a]	Increased	Nucleus Accumbens (Shell)	Rat	Cocaine	Microdialysis	(Fadda et al. 2003)
8nM[b]	8×10^{-9} M	No Change	Prefrontal Cortex (Medial)	Rat	Cocaine	Microdialysis	(Moghadda m and Bunney 1989)
35 fmol/µl[b]	3.5×10^{-8} M[a]	Increased	Striatum	Primate	Cocaine	Microdialysis	(Bradberry 2000)
60 nM[b]	6×10^{-8} M	Increased	Striatum	Rat	Cocaine	Microdialysis	(Shou et al. 2006)
3.6 nM[b]	3.6×10^{-9} M	Increased	Caudate/Putamen	Mouse	Ethanol	Microdialysis	(Bosse and Mathews 2011)
2.96 fmol/µl[b]	3×10^{-9} M[a]	Increased	Nucleus Accumbens	Rat	Ethanol	Microdialysis	(Yan 1999)

Original Dopamine Concentration	Concentration of Dopamine (M)	Change from Baseline	Location	Species	Drug	Method	Reference
6.21 nM	6.2×10^{-9} M	Increased	Nucleus Accumbens	Rat	Ethanol	Microdialysis	(Weiss et al. 1996)
13.2 nM	1.3×10^{-8} M	Increased	Nucleus Accumbens	Rat	Ethanol	Microdialysis	(Yim and Gonzales 2000)
14 nM[b]	1.4×10^{-8} M	No Change	Nucleus Accumbens	Rat	Heroin	Microdialysis	(Smith et al. 2006)
8.8 nM[b]	8.8×10^{-9} M	Increased	Nucleus Accumbens	Rat	Heroin	Microdialysis	(Hemby et al. 1995)
2.97 ng/mg	1.9×10^{-5} M[a]	Decreased	Caudate	Human	Methamphetamine	HPLC	(Wilson et al. 1996a)
1.48 ng/mg	1×10^{-5} M[a]	Decreased	Nucleus Accumbens	Human	Methamphetamine	HPLC	(Wilson et al. 1996a)
3.49 ng/mg	2.3×10^{-5} M[a]	Decreased	Putamen	Human	Methamphetamine	HPLC	(Wilson et al. 1996a)
0.1 nmol/mg	1×10^{-4} M[a]	Decreased	Striatum	Mouse	Methamphetamine	HPLC	(Kita et al. 2000)
50 nM[b]	5×10^{-8} M	Increased	Nucleus Accumbens (Core)	Rat	Morphine	FSCV	(Vander Weele et al. 2014)
0.02 pmol/20 µl	1×10^{-9} M[a]	Increased	Nucleus Accumbens	Rat	Morphine	Microdialysis	(Pothos et al. 1991)
0.21 pmol/25 µl[b]	8.4×10^{-9} M[a]	No Change	Nucleus Accumbens	Rat	Morphine	Microdialysis	(Anagnosta kis and Spyraki 1994)
50 nM[b]	5×10^{-8} M	Increased	Nucleus Accumbens (Shell)	Rat	Morphine	FSCV	(Vander Weele et al. 2014)
200 fmol/50µl	4×10^{-7} M[a]	Increased	Nucleus Accumbens (Shell)	Rat	Morphine	Microdialysis	(Fadda et al. 2003)
250 nM[b]	2.5×10^{-7} M	Increased	Nucleus Accumbens (Core)	Rat	Oxycodone	FSCV	(Vander Weele et al. 2014)
500 nM[b]	5×10^{-7} M	Increased	Nucleus Accumbens (Shell)	Rat	Oxycodone	FSCV	(Vander Weele et al. 2014)
1.5 nM	1.5×10^{-9} M	Decreased	Striatum	Mouse	Oxycodone	Microdialysis	(Zhang et al. 2009)
88 fmol/40 µl[b]	2.2×10^{-9} M[a]	No Change	Nucleus Accumbens	Rat	THC	Microdialysis	(Chen et al. 1993)
134 nmol/L[b]	1.3×10^{-7} M[a]	Decreased	Prefrontal Cortex	Rat	THC	Microdialysis	(Pistis et al. 2002)
604.5 fmol/40 µl[b]	1.5×10^{-8} M[a]	Increased	Ventral Tegmental Area	Rat	THC	Microdialysis	(Chen et al. 1993)

[a] Concentrations calculated by dividing values by the molecular weight of dopamine (153.18 g/mol) if not already in a molar value, and multiplying the density of tissues or fluids (kg/L or kg/m^3)

[b] Estimate obtained from graph because no values given in text, or averaged values if multiple control values were given

[c] Value obtained from one or an average of treatment groups other than control because no absolute control given

[d] Averaged male and female control groups

Table 3:
Dopamine Concentrations in the Periphery.

A summary of human and animal studies that have examined concentrations of dopamine within the periphery. Both original values and our calculated relative molar values are reported to easily compare concentrations of dopamine between studies.

Original Dopamine Concentration	Concentration of Dopamine (M)	Location	Species	Method	Reference
30 ng/g[b]	2×10^{-7} M[a]	Adipose (Brown)	Mouse	HPLC	(Griggio et al. 1992)
1 pg/mg[c]	6.5×10^{-9} M[a]	Adipose (Epididymal White)	Mouse	HPLC	(Nagler et al. 2018)
100 pg/mg[b]	7×10^{-7} M[a]	Adipose (Mesenteric Tissue Cells)	Rat	HPLC	(Vargovic et al. 2011)
0.0853 nmol/g	8.5×10^{-8} M[a]	Adrenal Gland	Primate	HPLC	(Elchisak et al. 1983)
430 ng/kg	2.8×10^{-9} M[a]	Adrenal Gland	Rat	HPLC	(Snider and Kuchel 1983)
94600 pmol/g	9.5×10^{-5} M[a]	Adrenal Gland	Rat	HPLC	(Kawamura et al. 1999)
51 nmol/g	5.1×10^{-5} M[a]	Adrenal Gland (Cortex)	Rat	HPLC	(Hannah et al. 1984)
0.5 ng/ml[b]	3.3×10^{-9} M[a]	Adrenal Gland (Medulla)	Mouse	HPLC	(Torres-Rosas et al. 2014)
6 nmol/g	6×10^{-6} M[a]	Adrenal Gland (Medulla)	Rat	HPLC	(Hannah et al. 1984)
0.37 mg/g	2.4×10^{-3} M[a]	Adrenal Gland (Medulla)	Rat	HPLC	(Ortega-Saenz et al. 2016)
24 pmol/mg	2.4×10^{-5} M[a]	Adrenal Gland (Medulla)	Rat	HPLC	(Favre et al. 1986)
6.1 ug/g	4×10^{-5} M[a]	Adrenal Gland (Medulla)	Rat	HPLC	(Fhaneret al. 2013)
1.1 ng/ml[c]	7×10^{-9} M[a]	Amniotic Fluid	Human	HPLC	(Jonathan and Munsick 1980)
45 pmol/g	4.5×10^{-8} M[a]	Aorta	Rat	HPLC	(Kawamura et al. 1999)
0.15 μg/g	9.8×10^{-7} M[a]	Aorta	Sheep	HPLC	(Juorio and Chedrese 1990)
0.043 μg/g	3×10^{-7} M[a]	Artery (Mesenteric)	Rat	HPLC	(Bell and Gillespie 1981)
0.15 pmol/mg	1.5×10^{-7} M[a]	Bladder	Rat	HPLC	(Favre et al. 1986)
2 nM[b]	2×10^{-9} M	Bone Marrow	Mouse	HPLC	(Maestroni et al. 1998)
250 pg/g[b]	1.6×10^{-9} M[a]	Bone Marrow	Mouse	HPLC	(Marino et al. 1997)
35 ng/mg[b]	2.3×10^{-5} M[a]	Bone Marrow	Mouse	HPLC	(Chakroborty et al. 2008)
202 ng/g[b]	1.3×10^{-3} M[a]	Carotid Body	Human (infant)	HPLC	(Perrin et al. 1984)
209.6 pmol/mg	2.1×10^{-1} M[a]	Carotid Body	Rat	HPLC	(Vicario et al. 2000)

Original Dopamine Concentration	Concentration of Dopamine (M)	Location	Species	Method	Reference
84.04 mg/g	5.5×10^{-1} M[a]	Carotid Body	Rat	HPLC	(Ortega-Saenz et al. 2016)
3.3 nmol/mg	3.3×10^{-3} M[a]	Carotid Body	Rat	HPLC	(Hanbauer et al. 1981)
256.2 pmol/mg	2.6×10^{-1} M[a]	Carotid Body	Rat	HPLC	(Prieto-Lloret et al. 2015)
129 pmol/mg	1.3×10^{-1} M[a]	Carotid Body	Rat	HPLC	(Favre et al. 1986)
115.4 ng/g	7.5×10^{-7} M[a]	Cecum	Mouse	HPLC	(Asano et al. 2012)
140 pmol/g[b]	1.4×10^{-7} M[a]	Colon	Human	HPLC	(Magro et al. 2002)
177 ng/g	1.2×10^{-6} M[a]	Colon	Mouse	HPLC	(Asano et al. 2012)
26 pmol/g	3×10^{-8} M[a]	Colon	Rat	HPLC	(Magro et al. 2004)
60 pg/μg[b]	3.9×10^{-4} M[a]	Colon	Rat	HPLC	(Levandis et al. 2015)
100 pg/mg[b]	6.5×10^{-7} M[a]	Colon (Ascending)	Mouse	HPLC	(Garrido-Gil et al. 2018a)
15 pg/mg	9.8×10^{-8} M[a]	Colon (Proximal)	Rat	HPLC	(Garrido-Gil et al. 2018a)
12 pg/mg[b]	7.8×10^{-8} M[a]	Colon (Proximal)	Rat	HPLC	(Garrido-Gil et al. 2018b)
239 pmol/g	2.4×10^{-7} M[a]	Duodenum	Rat	HPLC	(Kawamura et al. 1999)
3.67 μg/g	2.4×10^{-5} M[a]	Duodenum	Sheep	HPLC	(Juorio and Chedrese 1990)
276 pg/ml	1.8×10^{-9} M[a]	Duodenum (Juice)	Rat	HPLC	(Mezey et al. 1996)
13 pmol/mg	1.3×10^{-5} M[a]	Ganglion (Coeliac)	Rat	HPLC	(Favre et al. 1986)
15 pmol/mg	1.5×10^{-5} M[a]	Ganglion (Mesenteric)	Rat	HPLC	(Favre et al. 1986)
26 pmol/mg	2.6×10^{-5} M[a]	Ganglion (Superior Cervical)	Rat	HPLC	(Favre et al. 1986)
8082 pmol/g	8.1×10^{-6} M[a]	Ganglion (Superior Cervical)	Rat	HPLC	(Kawamura et al. 1999)
14 pmol/mg	1.4×10^{-5} M[a]	Ganglion (Superior Cervical)	Rat	HPLC	(Prieto-Lloret et al. 2015)
0.52 pg/μg	3×10^{-6} M[a]	Heart	Human	HPLC	(Regitz et al. 1990)
15 ng/g[b]	1×10^{-7} M[a]	Heart	Mouse	HPLC	(Griggio et al. 1992)
55.9 ng/g	3.6×10^{-7} M[a]	Heart	Mouse	HPLC	(Amino et al. 2008)
30 ng/g	2×10^{-7} M[a]	Heart	Mouse	HPLC	(Wagner et al. 1979b)
30 ng/g[b]	2×10^{-7} M[a]	Heart	Pig	HPLC	(Schoeneman n et al. 1990)
12 ng/g[b]	8×10^{-8} M[a]	Heart	Rat	HPLC	(Schoeneman n et al. 1990)
15 ng/g	1×10^{-7} M[a]	Heart	Rat	HPLC	(Snider and Kuchel 1983)
10 ng/g[b]	6.5×10^{-8} M[a]	Heart	Rat	HPLC	(Eldrup 2004)

Original Dopamine Concentration	Concentration of Dopamine (M)	Location	Species	Method	Reference
0.11 pmol/mg	1.1×10^{-7} M[a]	Heart	Rat	HPLC	(Favre et al. 1986)
170 ng/g[b]	1.1×10^{-6} M[a]	Heart (Atrium)	Dog	HPLC	(Mohanty et al. 1986)
0.58 nmol/g	5.8×10^{-7} M[a]	Heart (Atrium)	Primate	HPLC	(Elchisak et al. 1983)
0.135 μg/g	9×10^{-7} M[a]	Heart (Atrium)	Mouse	HPLC	(Bell and Gillespie 1981)
143 ng/g	9.3×10^{-7} M[a]	Heart (Myocardium)	Human	HPLC	(Pierpont et al. 1987)
120 ng/g[b]	7.8×10^{-7} M[a]	Heart (Ventricle)	Dog	HPLC	(Mohanty et al. 1986)
0.549 nmol/g	5.5×10^{-7} M[a]	Heart (Ventricle)	Primate	HPLC	(Elchisak et al. 1983)
15.7 ng/g	1×10^{-7} M[a]	Ileum	Mouse	HPLC	(Asano et al. 2012)
30 pmol/g	3×10^{-8} M[a]	Ileum	Rat	HPLC	(Magro et al. 2004)
160 pg/μg[b]	1×10^{-3} M[a]	Ileum	Rat	HPLC	(Levandis et al. 2015)
0.03 pmol/g	3×10^{-8} M[a]	Jejunum	Mouse	HPLC	(Quelhas-Santos et al. 2015)
36 pmol/g[b]	3.6×10^{-8} M[a]	Jejunum (Epithelial cells)	Rat	HPLC	(Vieira-Coelho et al. 1998)
41 pmol/g	4.1×10^{-8} M[a]	Jejunum (Mucosa)	Rat	HPLC	(Vieira-Coelho et al. 1998)
61 pmol/g	6.1×10^{-8} M[a]	Jejunum (Mucosa)	Rat	HPLC	(Finkel et al. 1994)
13.3 ng/g	8.6×10^{-8} M[a]	Kidney	Mouse	HPLC	(Wagner et al. 1979a)
115 ng/mg[b]	7.5×10^{-4} M[a]	Kidney	Mouse	HPLC	(Zhang et al. 2011a)
0.5 ng/mg[b]	3.3×10^{-6} M[a]	Kidney	Mouse	HPLC	(Weinman et al. 2011)
33 pmol/mg	3.3×10^{-5} M[a]	Kidney	Rat	HPLC	(Wahbe et al. 1982)
5 ng/g[b]	3×10^{-8} M[a]	Kidney	Rat	HPLC	(Snider and Kuchel 1983)
50 pmol/g	5×10^{-8} M[a]	Kidney	Rat	HPLC	(Kawamura et al. 1999)
0.04 pmol/mg	4×10^{-8} M[a]	Kidney	Rat	HPLC	(Favre et al. 1986)
0.846 nmol/g	8.5×10^{-7} M[a]	Kidney (Cortex)	Primate	HPLC	(Elchisak et al. 1983)
0.017 μg/g	1×10^{-7} M[a]	Kidney (Cortex)	Rat	HPLC	(Bell and Gillespie 1981)
0.225 nmol/g	2.3×10^{-7} M[a]	Kidney (Medulla)	Primate	HPLC	(Elchisak et al. 1983)
0.092 nmol/g	9.2×10^{-8} M[a]	Liver	Primate	HPLC	(Elchisak et al. 1983)
0.011 pmol/mg	1.1×10^{-8} M[a]	Liver	Rat	HPLC	(Favre et al. 1986)
1.697 μg/g	1.1×10^{-5} M[a]	Lung	Cow	HPLC	(Eyre 1971)
0.11 μg/g	7×10^{-7} M[a]	Lung	Human	HPLC	(Aviado and Sadavongviva d1970)
0.0446 nmol/g	4.5×10^{-8} M[a]	Lung	Primate	HPLC	(Elchisak et al. 1983)

Original Dopamine Concentration	Concentration of Dopamine (M)	Location	Species	Method	Reference
40 ng/g	2.6×10^{-7} M[a]	Lung	Rat	ELISA	(Hampl et al. 2015)
34 pmol/g	3.4×10^{-8} M[a]	Lung	Rat	HPLC	(Kawamura et al. 1999)
58.8 pmol/g	5.9×10^{-8} M[a]	Lung	Rat	HPLC	(Scarcella and Bryan-Lluka 1995)
9.96 μg/g	6.5×10^{-5} M[a]	Lung	Sheep	HPLC	(Juorio and Chedrese 1990)
0.021 pmol/mg	2.1×10^{-8} M[a]	Lung/Trachea	Rat	HPLC	(Favre et al. 1986)
0.5 μmol/kg[b]	5×10^{-7} M[a]	Microbiome (Biomass)	*E coli*	HPLC	(Shishov et al. 2009)
0.1 μmol/kg[b]	1×10^{-7} M[a]	Microbiome (Supernatant)	*E coli*	HPLC	(Shishov et al. 2009)
79.4 μg/ml[b]	5.2×10^{-4} M[a]	Microbiome (Supernatant)	*E faecium*	HPLC	(Villageliu and Lyte 2018)
0.73 mg/L	4.8×10^{-6} M[a]	Microbiome (Supernatant)	*Hafnia alvei*	HPLC	(Özoğul 2004)
1.06 mg/L	6.9×10^{-6} M[a]	Microbiome (Supernatant)	*Klebsiella pneumoniae*	HPLC	(Özoğul 2004)
2.46 mg/L	1.6×10^{-5} M[a]	Microbiome (Supernatant)	*Morganella morganii*	HPLC	(Özoğul 2004)
29 pg/mg[c]	1.8×10^{-7} M[a]	Pancreas	Mouse	HPLC	(Nagler et al. 2018)
0.218 nmol/g	2.2×10^{-7} M[a]	Pancreas	Primate	HPLC	(Elchisak et al. 1983)
84 pmol/mg	8.4×10^{-5} M[a]	Pancreas	Rat	HPLC	(Mezey et al. 1996)
103 pmol/g	1×10^{-7} M[a]	Pancreas	Rat	HPLC	(Kawamura et al. 1999)
8 μmol/kg	8×10^{-6} M[a]	Pancreas (Islets)	Golden hamster	HPLC	(Zern et al. 1980)
10 pg/ml	6.5×10^{-11} M[a]	Plasma	Human	HPLC	(Saha et al. 2001)
17 pg/ml	3.5×10^{-8} M[a]	Plasma	Human	HPLC	(Mitchell et al. 2018)
10 pg/ml	6.5×10^{-11} M[a]	Plasma	Human	HPLC	(Gardner and Shoback 2007)
10 pg/ml	6.5×10^{-11} M[a]	Plasma	Human	HPLC	(Lechin et al. 1990)
38.9 pg/ml	2.5×10^{-10} M[a]	Plasma	Human	HPLC	(Scozzi et al. 2012)
22.14 ng/L	1.4×10^{-10} M[a]	Plasma	Human	HPLC	(Ambade et al. 2009)
0.02 ng/ml	1.3×10^{-10} M[a]	Plasma	Human	HPLC	(Eldrup et al. 1995)
55.5ng/L	3.6×10^{-10} M[a]	Plasma	Human	HPLC	(Iwen et al. 2017)
0.76 ng/ml	5×10^{-9} M[a]	Plasma	Mouse	HPLC	(Kavelaars et al. 2005)
0.9 ng/ml	5.9×10^{-9} M[a]	Plasma	Mouse	HPLC	(Alaniz et al. 1999)
75 pg/ml[b]	4.9×10^{-10} M[a]	Plasma	Mouse	HPLC	(Kanemi et al. 2005)
7 pmol/ml	7×10^{-9} M[a]	Plasma	Mouse	HPLC	(Quelhas-Santos et al. 2015)

Original Dopamine Concentration	Concentration of Dopamine (M)	Location	Species	Method	Reference
0.1 ng/ml[b]	7×10^{-10} M[a]	Plasma	Rat	HPLC	(De Laurentiis et al. 2002)
0.15 ng/ml[b]	9.8×10^{-10} M[a]	Plasma	Rat	HPLC	(Snider and Kuchel 1983)
0.32 nmol/L	3.2×10^{-10} M[a]	Plasma (arterial)	Human	HPLC	(Goldstein et al. 1999)
0.23 nmol/L	2.3×10^{-10} M[a]	Plasma (Hepatic Vein)	Human	HPLC	(Goldstein et al. 1999)
0.93 nmol/L	9.3×10^{-10} M[a]	Plasma (Portal Vein)	Human	HPLC	(Goldstein et al. 1999)
2 ng/ml	1.3×10^{-10} M[a]	Plasma (Umbilical Cord)	Human	HPLC	(Jonathan and Munsick 1980)
18 ng/g	1.8×10^{-7} M[a]	Salivary Gland	Rat	HPLC	(Snider and Kuchel 1983)
39 ng/g[b]	2.5×10^{-7} M[a]	Salivary Gland	Rat	HPLC	(Tomassoni et al. 2015)
211 pmol/g	2.1×10^{-7} M[a]	Salivary Gland	Rat	HPLC	(Kawamura et al. 1999)
1 pmol/mg	1×10^{-6} M[a]	Seminal Vesicles	Rat	HPLC	(Favre et al. 1986)
0.032 pmol/mg	3.2×10^{-8} M[a]	Small intestine	Rat	HPLC	(Favre et al. 1986)
1.31 ng/mg	8.6×10^{-6} M[a]	Spinal Cord (Cervical Dorsal Horn)	Rat	HPLC	(White et al. 1983)
0.65 ng/mg	4.2×10^{-6} M[a]	Spinal Cord (Cervical Ventral Horn)	Rat	HPLC	(White et al. 1983)
0.79 ng/mg	5.2×10^{-6} M[a]	Spinal Cord (Lumbar Dorsal Horn)	Rat	HPLC	(White et al. 1983)
0.67 ng/mg	4.4×10^{-6} M[a]	Spinal Cord (Lumbar Ventral Horn)	Rat	HPLC	(White et al. 1983)
2.18 ng/mg	1.4×10^{-5} M[a]	Spinal Cord (Thoracic Dorsal Horn)	Rat	HPLC	(White et al. 1983)
2.67 ng/mg	1.7×10^{-5} M[a]	Spinal Cord (Thoracic Lateral Horn)	Rat	HPLC	(White et al. 1983)
1.88 ng/mg	1.2×10^{-5} M[a]	Spinal Cord (Thoracic Ventral Horn)	Rat	HPLC	(White et al. 1983)
13.5 pmol/g	1×10^{-7} M[a]	Spleen	Mouse	HPLC	(Tsao et al. 1997)
50 ng/g[b]	3×10^{-7} M[a]	Spleen	Pig	HPLC	(Schoeneman n et al. 1990)
0.173 nmol/g	1.7×10^{-7} M[a]	Spleen	Primate	HPLC	(Elchisak et al. 1983)
10 ng/g[b]	7×10^{-8} M[a]	Spleen	Rat	HPLC	(Schoeneman n et al. 1990)
0.011 μg/g	7×10^{-8} M[a]	Spleen	Rat	HPLC	(Bell and Gillespie 1981)
0.084 pmol/mg	8.4×10^{-8} M[a]	Spleen	Rat	HPLC	(Favre et al. 1986)

Original Dopamine Concentration	Concentration of Dopamine (M)	Location	Species	Method	Reference
152 pmol/g	1.5×10^{-7} M[a]	Spleen	Rat	HPLC	(Kawamura et al. 1999)
0.078 pmol/mg	7.8×10^{-8} M[a]	Stomach	Rat	HPLC	(Favre et al. 1986)
185 pmol/g	1.9×10^{-7} M[a]	Stomach	Rat	HPLC	(Kawamura et al. 1999)
20 ng/g[b]	1.3×10^{-7} M[a]	Stomach	Rat	HPLC	(Eldrup 2004)
32.9 ng/g	3×10^{-7} M[a]	Stomach (Gastric Corpus Mucosa)	Guinea pig	HPLC	(Shichijo et al. 1997)
95.8 ng/g	6×10^{-7} M[a]	Stomach (Gastric Corpus Muscle)	Guinea pig	HPLC	(Shichijo et al. 1997)
5.41 ng/ml	4×10^{-8} M[a]	Stomach (Gastric Juice)	Human	HPLC	(Christensen and Brandsborg 1974)
1.02 nmol/g	1×10^{-6} M[a]	Testis	Primate	HPLC	(Elchisak et al. 1983)
5 pmol/g	5×10^{-9} M[a]	Testis	Rat	HPLC	(Kawamura et al. 1999)
12.7 pmol/mg	1×10^{-7} M[a]	Thymus	Mouse	HPLC	(Tsao et al. 1997)
15 pmol/g	1.5×10^{-8} M	Thymus	Rat	HPLC	(Kawamura et al. 1999)
25 ng/g[d]	1.6×10^{-7} M[a]	Thymus	Rat	HPLC	(Pilipovic et al. 2008)
0.352 μg/g	2.3×10^{-6} M[a]	Vas Deferens	Rat	HPLC	(Bell and Gillespie 1981)
2.1 pmol/mg	2.1×10^{-6} M[a]	Vas Deferens	Rat	HPLC	(Favre et al. 1986)
2466 pmol/g	2.5×10^{-6} M[a]	Vas Deferens	Rat	HPLC	(Kawamura et al. 1999)

[a]Con cent ratio ns calculated by dividing values by the molecular weight of dopamine (153 .18 g/m ol) if not already in a molar value, and multiplying the density of tissues or fluid s (kg/L or kg/m^3)

[b]Estimate obtained from graph because no values given in text, or averaged values if multiple control values were given

[c]Value obtained from one or an average of treatment groups other than control because no absolute control given

[d]Averaged male and female control groups

Table 4:

Dopamine Concentrations During Disease and Disease Models in the Central Nervous System and the Periphery.

A summary of human and animal studies that have examined concentrations of dopamine in disease states and animal models of disease in the central nervous system and periphery. Both original values and our calculated relative molar values are reported to easily compare concentrations of dopamine between studies.

Original Value	Concentration of Dopamine (M)	Change From Baseline	Location	Species	Disease	Method	Reference
133400 pmol/g	1.3×10^{-4} M[a]	No Change	Adrenal gland	Rat	6-OHDA (Parkinson's Disease Model)	HPLC	(Kawamura et al. 1999)
130 pg/ug[b]	8.5×10^{-4} M[a]	Increased	Colon	Rat	6-OHDA (Parkinson's Disease Model)	HPLC	(Levandis et al. 2015)
57 pmol/g	5.7×10^{-8} M[a]	Decreased	Duodenum	Rat	6-OHDA (Parkinson's Disease Model)	HPLC	(Kawamura et al. 1999)
35.7 fmol/mg	3.6×10^{-8} M[a]	Decreased	Frontal cortex	Rat	6-OHDA (Parkinson's Disease Model)	HPLC	(Wisman et al. 2008)
16 pmol/g	1.6×10^{-8} M[a]	Decreased	Heart	Rat	6-OHDA (Parkinson's Disease Model)	HPLC	(Kawamura et al. 1999)
86 pmol/g	8.6×10^{-8} M[a]	No Change	Heart (Aorta)	Rat	6-OHDA (Parkinson's Disease Model)	HPLC	(Kawamura et al. 1999)
17.2 fmol/mg	1.7×10^{-8} M[a]	Decreased	Hippocampus	Rat	6-OHDA (Parkinson's Disease Model)	HPLC	(Wisman et al. 2008)
165 pg/ug[b]	1.1×10^{-3} M[a]	No Change	Ileum	Rat	6-OHDA (Parkinson's Disease Model)	HPLC	(Levandis et al. 2015)
23 pmol/g	2.3×10^{-8} M[a]	Decreased	Kidney	Rat	6-OHDA (Parkinson's Disease Model)	HPLC	(Kawamura et al. 1999)
6 pmol/g	6×10^{-9} M[a]	Decreased	Lung	Rat	6-OHDA (Parkinson's Disease Model)	HPLC	(Kawamura et al. 1999)
68 pmol/g	6.8×10^{-8} M[a]	Decreased	Pancreas	Rat	6-OHDA (Parkinson's Disease Model)	HPLC	(Kawamura et al. 1999)
27 pg/mg[b]	1.8×10^{-7} M[a]	Increased	Proximal colon	Rat	6-OHDA (Parkinson's Disease Model)	HPLC	(Garrido-Gil et al. 2018b)
43 pmol/g	4.3×10^{-8} M[a]	Decreased	Salivary gland	Rat	6-OHDA (Parkinson's Disease Model)	HPLC	(Kawamura et al. 1999)
11 pmol/g	1.1×10^{-8} M[a]	Decreased	Spleen	Rat	6-OHDA (Parkinson's Disease Model)	HPLC	(Kawamura et al. 1999)
104 pmol/g	1×10^{-7} M[a]	Decreased	Stomach	Rat	6-OHDA (Parkinson's Disease Model)	HPLC	(Kawamura et al. 1999)
3 ng/mg[b]	2×10^{-5} M[a]	Decreased	Striatum	Rat	6-OHDA (Parkinson's Disease Model)	HPLC	(Garrido-Gil et al. 2018b)
14448 pmol/g	1.4×10^{-5} M[a]	No Change	Superior cervical ganglion	Rat	6-OHDA (Parkinson's Disease Model)	HPLC	(Kawamura et al. 1999)
10 pmol/g	1×10^{-8} M[a]	No Change	Testis	Rat	6-OHDA (Parkinson's Disease Model)	HPLC	(Kawamura et al. 1999)
7 pmol/g	7×10^{-9} M[a]	Decreased	Thymus	Rat	6-OHDA (Parkinson's Disease Model)	HPLC	(Kawamura et al. 1999)
256 pmol/g	2.6×10^{-7} M[a]	Decreased	Vas deferens	Rat	6-OHDA (Parkinson's Disease Model)	HPLC	(Kawamura et al. 1999)

Original Value	Concentration of Dopamine (M)	Change From Baseline	Location	Species	Disease	Method	Reference
1 ng/mg	6.5×10^{-6} M[a]	Decreased	Spinal cord (cervical dorsal horn)	Rat	EAE (Multiple Sclerosis Model)	HPLC	(White et al. 1983)
1.09 ng/mg	7.1×10^{-6} M[a]	No Change	Spinal cord (cervical ventral horn)	Rat	EAE (Multiple Sclerosis Model)	HPLC	(White et al. 1983)
0.82 ng/mg	5.4×10^{-6} M[a]	No Change	Spinal cord (lumbar dorsal horn)	Rat	EAE (Multiple Sclerosis Model)	HPLC	(White et al. 1983)
1.06 ng/mg	6.9×10^{-6} M[a]	No Change	Spinal cord (lumbar ventral horn)	Rat	EAE (Multiple Sclerosis Model)	HPLC	(White et al. 1983)
2.34 ng/mg	1.5×10^{-5} M[a]	No Change	Spinal cord (thoracic dorsal horn)	Rat	EAE (Multiple Sclerosis Model)	HPLC	(White et al. 1983)
3.1 ng/mg	2×10^{-5} M[a]	No Change	Spinal cord (thoracic lateral horn)	Rat	EAE (Multiple Sclerosis Model)	HPLC	(White et al. 1983)
2.17 ng/mg	1.4×10^{-5} M[a]	No Change	Spinal cord (thoracic ventral horn)	Rat	EAE (Multiple Sclerosis Model)	HPLC	(White et al. 1983)
4.000 pg/mg[b]	2.6×10^{-5} M[a]	Decreased	Striatum	Mouse	EAE (Multiple Sclerosis Model)	HPLC	(Batkowiec-Iskra et al. 2007)
2.102 pg/g log10	1×10^{-9} M[a]	Decreased	Basal ganglia	Human	HIV	HPLC	(Kumar et al. 2009)
2.086 pg/g log10	1×10^{-9} M[a]	Decreased	Caudate	Human	HIV	HPLC	(Kumar et al. 2009)
2.137 pg/g log10	1×10^{-9} M[a]	No Baseline	CSF	Human	HIV	HPLC	(Kumar et al. 2009)
1.9 pg/g log10	1×10^{-9} M[a]	No Change	Frontal Cortex	Human	HIV	HPLC	(Kumar et al. 2009)
2.198 pg/g log10	1×10^{-9} M[a]	No Change	Globus pallidus	Human	HIV	HPLC	(Kumar et al. 2009)
2.163 pg/g log10	1×10^{-9} M[a]	Decreased	Putamen	Human	HIV	HPLC	(Kumar et al. 2009)
1.747 pg/g log10	1×10^{-9} M[a]	Decreased	Substantia Nigra	Human	HIV	HPLC	(Kumar et al. 2009)
32.3 pg/mL	2.1×10^{-10} M[a]	Decreased	CSF	Human	HIV (Neurologically Asymptomatic)	HPLC	(Berger et al. 1994)
18.97 pg/mL	1.2×10^{-10} M[a]	Decreased	CSF	Human	HIV (Neurologically Symptomatic)	HPLC	(Berger et al. 1994)
25 pg/mL[b]	1.6×10^{-10} M[a]	Increased	CSF	Human	HIV (Therapy Naive, Asymptomatic)	HPLC	(Scheller et al. 2010)
8.5 ng/g	5.5×10^{-8} M[a]	Decreased	Heart	Mouse	MPTP (Parkinson's Disease Model)	HPLC	(Amino et al. 2008)
0.46 pg/g	3×10^{-6} M[a]	Decreased	Putamen	Primate	MPTP (Parkinson's Disease Model)	HPLC	(Pifl et al. 2014)
5.2 pmol/mg	5.2×10^{-6} M[a]	Decreased	Spleen	Mouse	MPTP (Parkinson's Disease Model)	HPLC	(Tsao et al. 1997)
48 ng/mg	3.1×10^{-4} M[a]	Decreased	Striatum	Mouse	MPTP (Parkinson's Disease Model)	HPLC	(Petzinger et al. 2007)
6.9 pmol/mg	6.9×10^{-6} M[a]	Decreased	Thymus	Mouse	MPTP (Parkinson's Disease Model)	HPLC	(Tsao et al. 1997)
16.5 pmol/mg	1.7×10^{-5} M[a]	Decreased	Whole Brain	Mouse	MPTP (Parkinson's Disease Model)	HPLC	(Tsao et al. 1997)

Original Value	Concentration of Dopamine (M)	Change From Baseline	Location	Species	Disease	Method	Reference
0.3 ug/g [b]	2×10^{-6} M [a]	No Change	Olfactory Bulb	Primate	MPTP (Parkinson's Disease Model)	HPLC	(Pifl et al. 2017)
1.24 ng/mg	8×10^{-6} M [a]	Decreased	Caudate	Human	Parkinson's Disease	HPLC	(Wilson et al. 1996b)
2969 fmol/mg	3×10^{-9} M [a]	Decreased	Caudate	Human	Parkinson's Disease	HPLC	(Goldstein et al. 2011)
513 ng/g	3.3×10^{-6} M [a]	Decreased	Caudate nucleus	Human	Parkinson's Disease	HPLC	(Rajput et al. 2008)
83 fmol/mg	8.3×10^{-8} M [a]	No Change	Cortex	Human	Parkinson's Disease	HPLC	(Goldstein et al. 2011)
0.01 ng/ml	6.5×10^{-11} M [a]	No Change	CSF	Human	Parkinson's Disease	HPLC	(Eldrup et al. 1995)
1.22 ng/ml	8×10^{-9} M [a]	No Change	CSF	Human	Parkinson's Disease	HPLC	(Engelborghs et al. 2003)
0.01 nM	1×10^{-11} M	No Change	CSF	Human	Parkinson's Disease (No L-dopa Treatment)	HPLC	(Andersen et al. 2017)
0.15 nM	1.5×10^{-10} M	No Change	CSF	Human	Parkinson's Disease (No L-dopa Treatment, Nondyskinetic)	HPLC	(Andersen et al. 2017)
0.25 nM	2.5×10^{-10} M	No Change	CSF	Human	Parkinson's Disease (No L-dopa Treatment, Dyskinetic)	HPLC	(Andersen et al. 2017)
89 ng/g	5.8×10^{-7} M [a]	Decreased	Globus pallidus (external)	Human	Parkinson's Disease	HPLC	(Rajput et al. 2008)
37 ng/g	2.4×10^{-7} M [a]	Decreased	Globus pallidus (Internal)	Human	Parkinson's Disease	HPLC	(Rajput et al. 2008)
0.02 ng/ml	1.3×10^{-10} M [a]	No Change	Plasma	Human	Parkinson's Disease	HPLC	(Eldrup et al. 1995)
1130 fmol/mg	1.1×10^{-6} M [a]	Decreased	Putamen	Human	Parkinson's Disease	HPLC	(Goldstein et al. 2011)
0.14 pg/g	9×10^{-7} M [a]	Decreased	Putamen	Human	Parkinson's Disease	HPLC	(Pifl et al. 2014)
0.21 ng/mg	1.4×10^{-6} M [a]	Decreased	Putamen	Human	Parkinson's Disease	HPLC	(Wilson et al. 1996b)
25 pg/ml	1.6×10^{-10} M [a]	No Baseline	Synovial fluid	Human	Rheumatoid Arthritis	HPLC	(Nakano et al. 2011)
0.5 nM [b]	5×10^{-10} M	No Baseline	TH+ Synovial Cells	Human	Rheumatoid Arthritis	HPLC	(Capellino et al. 2010)
17 pmol/g	1.7×10^{-8} M [a]	Decreased	Colon	Rat	TNBS (Colitis Model)	HPLC	(Magro et al. 2004)
28 pmol/g	2.8×10^{-8} M [a]	No Change	Ileum	Rat	TNBS (Colitis Model)	HPLC	(Magro et al. 2004)
50 nmol/g	5×10^{-8} M [a]	Decreased	Colon	Human	Ulcerative Colitis and Crohn's Disease	HPLC	(Magro et al. 2002)

[a] Concentrations calculated by dividing values by the molecular weight of dopamine (153.18 g/mol) if not already in a molar value, and multiplying the density of tissues or fluids (kg/L or kg/m^3)

[b] Estimate obtained from graph because no values given in text, or averaged values if multiple control values were given

[c] Value obtained from one or an average of treatment groups other than control because no absolute control given

[d] Averaged male and female control groups