Sex Differences in Dopamine Receptors

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Dopamine is an important neurotransmitter that plays a key role in neuropsychiatric illness.

dopamine receptors | sex differences | heteromers | neuropsychiatric disorders

1. Introduction

Dopaminergic signaling is fundamental to a number of neurobiological processes that are required for cognition [1][2][3], emotion [4], movement [5], and reward [3][6][7][8]. Dopamine signaling is mediated through G protein coupled receptors, D1, D2, D3, D4, and D5, that are categorized into two subfamilies, D1-like and D2-like, based on their structure and function [9][10][11][12]. D1-like receptors (D1 and D5) are excitatory and coupled intracellularly to canonical stimulatory Gs/olf proteins, whereas D2-like receptors (D2, D3, and D4) are inhibitory and coupled to Gi/Go proteins [11][12]. Dopamine-induced biological responses are therefore dependent on numerous factors including the subtype of dopamine receptor expressed, the receptor density, cell type, and brain region in which the receptors are located [11][13][14][15]. The type of response is further complicated as dopamine receptors can exist not only as homomeric complexes, but as heteromeric species that often exhibit pharmacological and cell signaling properties that are distinct from its constituent receptors [7][16][17][18][19][20][21].

An abundance of information exists on the role of the dopamine system in the brain. However, little is known regarding fundamental sex differences in dopamine function, despite decades old evidence from human [22][23] and animal [24][25][26][27] studies showing that sexual dimorphisms in dopamine receptor expression and function exist innately, as well as in response to various stimuli. In the years since, some additional clinical and preclinical evidence has emerged supporting the notion that the dopamine system of men and women is functionally distinct. A significant proportion of this evidence has come from studies of neuropsychiatric disorders, such as addiction or depression, disorders involving dopamine that often display sex differences in prevalence, symptomatology, and treatment responsiveness [28][29][30][31][32][33][34]. For example, clinical imaging studies have revealed brain region- and sex-specific variations in dopamine transporter (DAT) availability in depression [35], and dopamine D2-like receptor densities with nicotine addiction [36][37]. Animal studies have also been particularly useful at providing some understanding as to how the dopamine system may differ innately between males and females, with reports evaluating sex differences in dopamine release [38][39], and dopamine receptor expression, in both adult animals and during development [15][40][41][42][43]. As well, differences in functional and behavioural responses to dopamine receptor agonists and antagonists have been observed, which include sex-specific differences in decision making and learning [44][45], anxiety and depression-like behaviour [43][46], and reward [39][47][48].

2. Sex Differences in D1-Like Receptors

The D1-like class of dopamine receptors (D1 and D5) are stimulatory G protein-coupled receptors (GPCRs) that, when activated, couple to Gs/olf proteins to activate adenylate cyclase and promote the production of cyclic adenosine monophosphate (cAMP) [11][49][50]. There is high structural homology between the D1 and D5 receptor, which has made elucidating the discrete in vivo functional effects of the D1 and D5 receptor difficult, owing to a lack of subtype-specific pharmacological agonists and antagonists. In line with this, examining subtype-specific receptor expression by pharmacological or immunologic means has been historically problematic, although mRNA expression studies have played a critical role in delineating D1 or D5 receptor distribution. It is known that the D5 receptor has a higher affinity for dopamine than the D1 receptor, which shows greater constitutive activation in the absence of an agonist [51]. D1 and D5 receptors additionally have differing affinities for agonists and antagonists [52] and exhibit a widespread, but distinct, regional distribution in human, non-human primate and rodent brains [53][54][55][56].

D1 receptor mRNA shows very high expression in the striatum of non-human primates [57], a finding supported by more recent single cell RNA sequencing (scRNA-seq) studies both in non-human primates [58] and mice [58][59]. Indeed, the expression of striatal D1 receptor mRNA is localized to neurons with unique transcriptional profiles, profiles that vary depending upon the subregion in which the mRNA is expressed [58][59]. Dopamine D1 and D5 receptors both have high expression in cortical regions, although D5 receptor expression has been shown to be higher than the D1 receptor in the prefrontal cortex (PFC) of rodents [55]. D5 receptor-immunoreactivity has been shown in both interneurons, as well as in pyramidal neurons, which frequently co-express the D1 receptor [55]. However, in pyramidal neurons, there is only marginal anatomical overlap between the receptors, with the D5 receptor more commonly found in dendritic shafts and perikarya and little expression within dendritic spines [60]. As few papers have delineated the discrete functional effects of D1 and D5 receptors, for the purpose of this review, unless otherwise stated, the described findings will be inclusive of both D1 and D5 receptors (subsequently termed D1).

Overall, studies evaluating sex differences in D1 receptor expression are sparse, and those that do exist are preclinical, using rodent models. For example, in comparison to female rats, evidence indicates that male rats show a transient overproduction of dorsal striatal D1 receptors during puberty, a sex difference that does not persist into adulthood due to the subsequent pruning of the receptors [42]. In contrast, the overproduction of dopamine D1 receptors in the male rat nucleus accumbens (NAc) does persist into adulthood [42], with adult male rats showing significantly higher D1 receptor expression than that of their adult female counterparts [42][43]. Another study showed that 30-day-old juvenile female rats exhibited greater concentrations of D1 receptors in the cortex and the striatum compared to males [61]. Furthermore, rodent females appear to exhibit a greater D1:D2 receptor expression ratio in the infralimbic cortex throughout development compared to their male counterparts [41]. Yet, in the insular cortex, males exhibited a drastic increase in D1:D2 expression ratio throughout development [41]. Male rats also exhibit a more prominent increase in striatal D1 receptors early in development followed by a rapid decrease in dopamine D1 receptors in adulthood compared to females [40]. This increase in striatal D1 receptors in males during such a critical time is proposed to have a role in the expression of hyperactivity in attention deficit

hyperactivity disorder (ADHD) [40], which is further explored in the ADHD section of this review. Environmental factors may also influence dopamine function, with preclinical research showing that early stress exposure induces sex-specific outcomes in D1 receptor mRNA expression and binding [62][63]. Specifically, early stress induced by maternal separation upregulated D1 receptor gene expression in the brain stem of male, but not female, rats [62]. In addition, prenatal alcohol exposure of rhesus monkeys increased D1 receptor binding in the PFC of male monkeys only [63].

Functional differences in dopamine D1 receptors also exist between males and females, with sex differences in responsivity to D1 receptor agonists reported [64][65]. For example, when exposed to a single systemic injection of D1 agonist SKF 81297 or SKF 82958, female rats exhibited an initial increase in locomotor activity, within the first 5 min, while this effect was not observed in males [65]. Although, both males and females exhibited an overall equal increase in agonist-induced locomotor responses across the entire testing period [65][66]. This agonist-induced increase in locomotion was attenuated in both sexes by the D1 antagonist SCH 23390, albeit with greater sensitivity in females [66]. Further, administration of a D1 receptor partial agonist, SKF 38393, infused directly into the NAc, reduced social interaction behaviour in female mice, with no effect in males [64]. Social learning was also impaired in both male and female mice when the D1 antagonist SCH 23390 was infused into the hippocampus, although males showed increased sensitivity to the drug [45][67]. Together, these findings indicate that sex differences exist in innate D1 receptor functional responses, which in turn influence behavioural outcomes.

3. Sex Differences in D2-Like Receptors

D2-like dopamine receptors (D2, D3, and D4) mediate inhibitory neurotransmission as they are coupled to Gi/Go proteins to reduce cAMP concentrations [68]. D2-like receptors demonstrate a greater affinity for dopamine compared to D1 receptors that supports differential roles for D1 and D2 receptor subgroups [12]. Of the dopamine D2-like receptors, the D2 receptor shows the greatest distribution and highest overall availability, particularly in cortical and subcortical regions [69][70][71][72], and therefore, has received greater attention in the literature compared to D3 and D4 receptors. As with striatal D1 receptors, D2 receptors also are localized to neurons that have a distinct subregion-dependent transcriptional profile [58][59]. Whereas D2-like receptors have been identified in the temporal cortex, frontal cortex, hippocampus, caudate, putamen, ventral striatum, and pallidum of humans [69], non-human primate and rodent studies have shown D3 receptors in the NAc, olfactory tubercle, dorsal subiculum, and amygdala in rodents [72], and D4 receptor localization in the cerebral cortex, hippocampus, substantia nigra, among other regions [73][74]. With D2-like receptors dispersed throughout various brain regions, they are involved in many critical functions and pathways, including memory and locomotion [75][76]. As with D1-like receptors, the majority of studies group dopamine D2-like receptors together (subsequently termed D2 receptors).

Similar to D1 receptors, studies examining sex differences in D2 receptor expression are somewhat limited. PET studies in human subjects have revealed that women have higher D2 receptor expression than men in the frontal and temporal cortices as well as the thalamus [23]. D2 receptor density in the striatum has also shown to decline with age in a sex-specific manner, with men experiencing a greater exponential decline compared to women [77]. Preclinical work in animals further supports sex differences in D2 receptor expression, with male rats expressing a

higher density in the cortex, and female rats exhibiting higher density in the striatum [43][61]. Moreover, male rats expressed a greater increase in striatal D2 receptors throughout early development compared to females [40]. Aside from receptor densities, males demonstrate a higher basal activation of D2 receptors in the medial PFC compared to females, as measured by autoradiography using the D2/D3 receptor agonist quinpirole [78]. From a functional perspective, using the rat version of the Iowa gambling task, one study showed that administration of the D2 receptor antagonist eticlopride decreased advantageous responding in male, but not female rats, whereas administration of quinpirole decreased advantageous responding selectively in females [44]. Genetic knockout of the *Drd2* gene, selectively in neurons expressing the serotonergic transcription factor gene *Pet1*, also resulted in sex-specific alterations in behaviour in mice, with males showing increased sociability and females decreased acoustic startle responses [79].

With regard to the dopamine D3 receptor specifically, functional studies employing transgenic lines or selective pharmacological agents have been beneficial in delineating not only the functional importance of the D3 receptor, but in the identification of sex differences. In a transgenic reporter mouse model of dopamine D3 receptors, males and females were shown to differ in D3 receptor mRNA expression and its co-expression with either D1 or D2 receptor mRNA [72]. Specifically, in the NAc, male mice had greater co-expression of D3 and D1 receptor mRNA at both postnatal day 35 and 70, as well as greater co-expression of D3 and D2 receptor mRNA, whereas on postnatal day 35, females had a higher co-expression of D3 and D2 receptor mRNA compared to males [72]. When dopamine D3 receptor knockout (D3-/-) mice were evaluated, they exhibited hyperactivity [75]. However, female D3-/- mice showed higher activity in a running wheel compared to their male counterparts [75]. Further, both male and female D3-/- mice exhibited hyperalgesia, although females expressed significantly less nociceptive behaviours compared to their sex-matched wildtype litter mates [80]. Pharmacological studies have also been utilized, as the administration of the D2/D3 receptor agonist quinpirole to non-human primates elicited yawning in males to a greater degree compared to females [81]. It was established that yawning correlated with dopamine D3 receptor densities in various regions, including the globus pallidus, caudate nucleus, putamen, ventral pallidum, and hippocampus [81]. There is little information that exists on innate sex differences in dopamine D4 receptor expression and function; although, the antagonist clozapine, which has a high affinity for the D4 receptor, was found to increase hypothalamic D4 receptor expression to a greater extent in females compared to males [82].

4. Sex Differences in the Dopamine D1–D2 Receptor Heteromer

Although, traditionally, GPCRs, such as the dopamine receptors, have been previously depicted as monomeric entities, it is now widely accepted that GPCRs exist as oligomeric complexes [7][83][84][85]. In addition to homomeric receptor complexes, numerous reports have demonstrated that dopamine receptors can form heteromeric complexes with other subtypes of dopamine receptors as well as with other GPCRs or ion channels [7][16][17][18][86][87][88][89][90][91][92][93][94][95] that may exhibit discrete distributions in the brain with distinct pharmacological and functional properties from their constituent receptors. Co-expression of D1 and D2 receptor mRNA or protein has been previously shown in the PFC [96][97], striatum [59][97][98][99][100][101], and in various regions of the basal ganglia

[99] of rodents. In the striatum, D1 and D2 receptors are predominantly segregated to discrete populations of medium spiny neurons, although it has been hypothesized that the subset of neurons that co-express both receptors may represent a third distinct neuronal pathway [14]. This idea is supported by a recent sc-RNA-seq study that showed striatal *Drd1a* and *Drd2* transcripts were co-expressed selectively in an MSN subtype that also expresses protocadherin 8 (Pcdh8) [59]. At a subregional level, striatal dopamine D1 and D2 receptors more commonly colocalize within the NAc, with highest co-expression in the shell subregion and lowest in the dorsal striatum [97][98][99][100][101].

A physical interaction between endogenously expressed striatal D1 and D2 receptors was first identified using quantitative confocal FRET in brain sections *in situ* [102][103][104]. Several studies have since demonstrated the formation of D1–D2 heteromers in the mesolimbic and basal ganglia circuitry of humans, non-human primates and rodents [97][99][100][105][106], although there has been some controversy as to the existence of the receptor complex under physiological conditions [107]. Unlike its constituent receptors, the D1–D2 heteromer couples to the Gq protein to increase intracellular calcium both in vitro in cells and neurons [43][95], as well as in vivo in the striatum [108], and to increase brain-derived neurotrophic factor (BDNF) expression and signaling [102][109]. Unfortunately, there is an almost total lack of research on sex differences in dopamine receptor heteromer expression and function, with only a single paper highlighting sex differences in dopamine D1–D2 receptor heteromer expression and function [43]. Hasbi et al. [43] demonstrated that in the caudate nucleus of non-human primate and in rat striatum, female animals expressed a higher density of D1–D2 heteromer complexes and a greater number of D1–D2 co-expressing neurons compared to males [43]. Interestingly, this sex difference in D1–D2 heteromer expression occurred despite the lower overall D1 receptor densities in females in these regions [43]. At a functional level, the sex difference in D1–D2 heteromer expression further led to corresponding differences in basal and heteromer-stimulated activities of two signaling pathways—BDNF/tropomyosin receptor kinase B (TrkB) and Akt/glycogen synthase kinase-3 (GSK-3)/β-catenin [43].

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