REVIEW

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Dopamine and Oxytocin Interactions Underlying Behaviors: Potential Contributions to Behavioral Disorders

Tracey A. Baskerville[1] & Alison J. Douglas[2]

1 Division of Clinical Neurosciences, Garscube Estate, University of Glasgow, UK
2 Centre for Integrative Physiology, University of Edinburgh, UK

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Correspondence
Dr. Tracey Baskerville, Division of Clinical Neurosciences, University of Glasgow, Garscube Estate, Bearsden Road, Glasgow G12 8QQ
Tel.: (141) 330-7103;
Fax: (141) 943-0215;
E-mail: tab3b@clinmed.gla.ac.uk

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Dopamine is an important neuromodulator that exerts widespread effects on the central nervous system (CNS) function. Disruption in dopaminergic neurotransmission can have profound effects on mood and behavior and as such is known to be implicated in various neuropsychiatric behavioral disorders including autism and depression. The subsequent effects on other neurocircuitries due to dysregulated dopamine function have yet to be fully explored. Due to the marked social deficits observed in psychiatric patients, the neuropeptide, oxytocin is emerging as one particular neural substrate that may be influenced by the altered dopamine levels subserving neuropathologic-related behavioral diseases. Oxytocin has a substantial role in social attachment, affiliation and sexual behavior. More recently, it has emerged that disturbances in peripheral and central oxytocin levels have been detected in some patients with dopamine-dependent disorders. Thus, oxytocin is proposed to be a key neural substrate that interacts with central dopamine systems. In addition to psychosocial improvement, oxytocin has recently been implicated in mediating mesolimbic dopamine pathways during drug addiction and withdrawal. This bi-directional role of dopamine has also been implicated during some components of sexual behavior. This review will discuss evidence for the existence dopamine/oxytocin positive interaction in social behavioral paradigms and associated disorders such as sexual dysfunction, autism, addiction, anorexia/bulimia, and depression. Preliminary findings suggest that whilst further rigorous testing has to be conducted to establish a dopamine/oxytocin link in human disorders, animal models seem to indicate the existence of broad and integrated brain circuits where dopamine and oxytocin interactions at least in part mediate socio-affiliative behaviors. A profound disruption to these pathways is likely to underpin associated behavioral disorders. Central oxytocin pathways may serve as a potential therapeutic target to improve mood and socio-affiliative behaviors in patients with profound social deficits and/or drug addiction.

Introduction

The neurobiological and neurochemical mechanisms underlying the cause of prevalent psychiatric behavioral disorders such as autism in humans are not yet fully elucidated. In addition to contributing factors, including genetic predisposition and psychosocial environment, disruption to major central nervous system (CNS) neurotransmitter pathways largely influences the onset of psychiatric disorders in patients. Current therapeutic interventions are pharmacological agents, which alleviate symptoms or redress brain neurotransmitter imbalance (often coupled with psychotherapeutic approaches such as cognitive behavioral therapy). Of the many central neurotransmitters believed to be implicated in CNS behavioral disorders, the monoamine, dopamine has

received much attention due to its extensive innervation of the brain, widespread receptor distribution and subsequent role across a broad spectrum of central functions and behaviors such as cognition, emotion, perception, motivation, reward, and sleep, in addition to peripheral actions on the cardiovascular and renal systems. Disturbances in central dopaminergic pathways are known pathologic mechanisms contributing to major psychiatric illnesses such as Parkinson's disease and schizophrenia. However, such dopaminergic disruptions are also believed to underpin several behavioral disorders including social anxiety, major depressive disorders and compulsive behaviors [1–3]. Here we intend to give an overview of the role of dopamine in selected behaviors and associated disorders. Although a role for dopamine in some behaviors such as sexual dysfunction is highly likely, for others its effects and the neurocircuitries it employs remain to be fully elucidated. However, the neuropeptide oxytocin is one central mediator in particular that is garnering much research interest due to its widespread effects on CNS function.

Oxytocin has a classical role in endocrine regulation where it acts as an important mediator in parturition and the milk ejection reflex during lactation [4]. Beyond its involvement in endocrine function, oxytocin acts in the brain as a key substrate for a range of social behaviors (including social bonding, parental behavior and sexual behavior and nonsocial behaviors such as stress, anxiety and aggression) [5]. The influential role of oxytocin in mediating social behavior is due to its widespread projections and receptor distribution the patterns of which determine behavior quality. Neurologic behavioral disorders caused by profound disruptions to key dopaminergic pathways in the brain are known to adversely affect prosocial behavior in mammals [6–8]. Thus, it is not surprising that oxytocin has been potentially implicated in several dopamine-dependent behavioral disorders including anxiety and autism and as such is emerging as a potential therapeutic target in the treatment of these diseases.

While the relationship between central dopamine and oxytocin is evident in some preclinical studies investigating sexual and social behavior [9–11], evidence of neural crosstalk between these two systems under pathophysiological conditions is underresearched. This review will focus on findings from preclinical and clinical (where possible) studies which have attempted to delineate a dopaminergic–oxytocinergic link and highlight potential treatment options in the following behavioral disorders: sexual dysfunction, autism, addiction, depression, and anorexia/bulimia. First, we will outline dopamine and oxytocin sources and targets and their roles in selected behaviors. This will clarify potential brain regions involved and relevant modes of interaction. We will then explain the dopamine–oxytocin interaction in sexual function and dysfunction before analysing their interaction and role in potential dysfunction in other selected social and nonsocial contexts.

Dopamine

Dopamine Synthesis and Distribution

Dopamine is an immensely important central neurotransmitter that has widespread projections and functions throughout the CNS. Dopamine synthesis is a two-step reaction and involves the creation of L-dihydroxyphenylalanine (L-DOPA) from L-tyrosine via tyrosine hydroxylase. L-DOPA is then converted to dopamine by DOPA decarboxylase. Dopamine is then enzymatically converted to 3,4-dihydroxyphenyl acetic acid (DOPAC) and 3-methoxytyramine (3-MT) via the enzymes monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT), respectively. Finally, DOPA and 3-MT are further degraded by COMT and MAO, respectively, to yield the inactive homovanillic acid (HVA)

Dopamine Release

Dopamine has a key role in a range of neurochemical and neurohormonal functions including cognition, sexual behavior, milk production, arousal, reward, coordination and motricity. Dopaminergic neuronal cell bodies originating in the substantia nigra (SN), hypothalamus, ventral tegmental area (VTA), arcuate nucleus and the zona incerta project to various brain structures and comprise six main pathways summarized in Figure 1 and their functions in Table 2. The nigrostriatal pathway originates in the SN and projects to the striatum where it controls the initiation and movement of muscle via the prefrontal cortex. Mesolimbic pathway cell bodies are found in the VTA and terminate in various limbic regions such as the nucleus accumbens (NA) and amygdala, where they are involved in reward, desire and reinforcement behaviors. Mesocortical dopamine fibers originate in the same region but project to the cortex where they mediate emotional and motivational responses. The tuberinfundibular dopamine system has cell bodies in the arcuate nucleus and periventricular region of the hypothalamus where they project to the median eminence to regulate anterior pituitary prolactin secretion. The hypothalamic-derived incertohypothalamic dopamine pathway innervates the dorsal anterior hypothalamus, including the supraoptic nucleus (SON) and paraventricular nucleus (PVN) and the lateral septal nuclei where it is believed to have a role in endocrine regulation and sexual behavior [12,13].

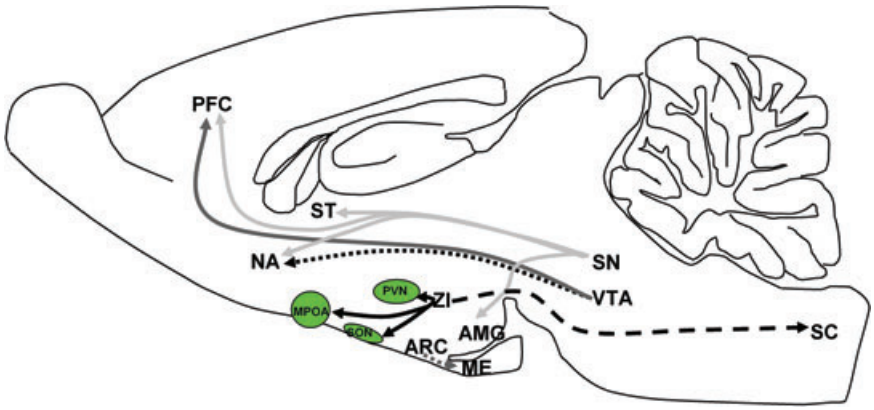

Figure 1 Major dopamine pathways in the rat brain. The nigrostriatal pathways are comprised of dopamine cell bodies in the SN, from here dopamine fibers innervate several brain regions including the ST, PFC, NA, and AMG (light graey line). Mesocortical and mesolimbic dopamine pathways originate in the VTA and project to the PFC (dark gray line), and NA (black-dotted line), respectively. The tuberoinfundibular dopamine system is comprised of dopamine fibers originating in the ARC and terminating in the ME (dark gray dotted line). Dopamine projections from the ZI to the MPOA, SON, and PVN of the hypothalamus comprise the incertohypothalamic dopamine pathway (black line). The diencephalospinal dopamine system originates in the hypothalamus and projects to the thoracolumbar spinal cord (black -hashed line). PFC, prefrontal cortex; NA, nucleus accumbens; ZI, zona incerta; MPOA, medial preoptic nucleus; PVN, paraventricular nucleus; SON, supraoptic nucleus; AMG, amygdala; ARC, arcuate nucleus; VTA, ventral tegmental area; ME, median eminence; ST, striatum; SC, spinal cord.

Finally, the diencephalospinal dopamine system originates in the hypothalamus and projects to the thoracic and lumbar spinal cord where it has a role in spinal reflex functions such as the stretch reflex [14,15] and may also contribute to spinal control of penile erection [16].

Dopamine Receptors

Five dopamine receptors exist in the CNS and comprise D1-like (D1 and D5) and D2-like (D2, D3, and D4) receptor subgroups. The receptors can be divided into two separate subgroups depending on the transduction system to which they are coupled to (1) D1-like receptors (D1 and D5) which positively activate adenylate cyclase and (2) D2-like receptors (D2, D3, and D4) which are negatively or not coupled to the enzyme. There is generally widespread expression of all dopamine receptors in the brain with abundant levels of D1 and D2 receptors and moderate expression of D3, D4, and D5 receptors [17–21]. D1 and D2 receptors are found in the striatum, cortex, hypothalamus, olfactory bulbs, and SN [19,22]. D3 receptor expression is more restricted, with the NA, olfactory tubercles and the Islands of Calleja possessing moderate to high levels of the D3 receptor [19]. In comparison to D2 receptors, D4 receptor levels appear to be less abundant in subcortical structures. The cortex, hippocampus, and striatum have all been shown to possess D4 receptors [18,19]. Finally, D5 receptor expression in the rat brain is comparatively scarce, however, D5 receptors have been shown to exist in the striatum, cortex, substantia nigra pars compacta, and NA [20].

Oxytocin

Oxytocin is a classical neuroendocrine neurohypophysial hormone, but over the last 20 years it has emerged as an influential hormone released in the brain which can initiate a wide spectrum of central effects in both males and females (see Table 1).

In the brain, the actions of oxytocin have been shown to be important in coordinating well-defined activities related to socio-sexual behaviors. Oxytocin pathways subserving maternal and social behavior are believed to be important in governing familial and nonfamilial bonds [23–26]. Another key, sometimes overlooked, role is in appetite-related behaviors where oxytocin both centrally and peripherally restrains food intake and decreases blood osmolality [27,28]. Furthermore, central oxytocin has also been shown to have anxiolytic and antistress properties whereby oxytocin-treated mice engage in more risk-taking, explorative, and investigative behaviors [29–31].

Oxytocin Synthesis and Distribution

Oxytocin is primarily synthesized in hypothalamic magnocellular neurosecretory cells in the SON and PVN, where it is transported to the neurohypophysis and released into the blood. From here oxytocin has a

Table 1 Oxytocin systems

Oxytocin systems	Origin	Projections	Function
Magnocellular (axonal)	SON/PVN	Posterior pituitary	Parturition, uterine contractions, milk ejection reflex
Magnocellular (dendritic)	SON/PVN	SON/PVN, extrahypothalamic regions	Autoregulation, endocannabinoid stimulation
Parvocellular	PVN	Ventral tegmental area, hippocampus, brainstem, spinal cord	Penile erection, ejaculation, gastric reflexes, respiration

Central oxytocin pathways. Within the CNS, two major oxytocin pathways exist; (1) the magnocellular oxytocin system originating in the SON and PVN can be further subdivided by its release characteristics in to axonal release (into the posterior pituitary) which regulates reproductive behavior and dendritic release (within the SON and PVN and may diffuse to other distant sites) to mediate oxytocin autoregulation (2) the parvocellular oxytocin system originates in the parvocellular PVN and projects to numerous CNS sites to regulate autonomic functions such as respiration and gastric reflexes.

vital role in reproduction, mediating smooth muscle contraction at precisely defined times to facilitate delivery of uterine contents at birth and milk (nutrition) to offspring during suckling [27,32–34]. Similarly, oxytocin is also generated in parvocellular neurons in the PVN, which project to extrahypothalamic regions within the CNS where they have a role in mediating various autonomic functions [35–38]. Oxytocinergic fibers are not restricted to the hypothalamus but also lie in various other brain regions including the hippocampus, cortex, SN, brain stem, and the spinal cord [4,39,40]. With its diffuse potential targets, oxytocin is able to influence a range of neuroendocrine-mediated functions governing social and affiliative behaviors such as maternal and socio-sexual behavior [9,26,32,41–44].

Oxytocin Release

As previously mentioned, magnocellular and parvocellular oxytocin release into systemic circulation and the CNS occurs via projections to the posterior pituitary and extrahypothalamic brain regions, respectively (see Table 2). Oxytocin release from axon terminals occurs in the classical manner where axonal terminal release is preceded by an influx of calcium into axonal terminals in response to an invading action potential. However, as first demonstrated by Moos et al. [45], oxytocin can also be released somatodendritically from magnocellular oxytocin neurons in the PVN and SON to regulate its own release. This finding was further substantiated in numerous *in vivo* studies using microdialysis to quantitatively measure oxytocin release in the plasma and the brain of parturient and lactating rats [46–48]. Unlike axonal release of oxytocin, dendritic release of oxytocin is triggered by release of calcium from intracellular stores and is generally electrically independent [49,50]. Central (axon terminal) and peripheral (via hypophyseal secretion into circulation) oxytocin release from magnocellular cells can act synergistically to influence behavioral consequences. During various paradigms like suckling, there is a concomitant release of oxytocin into the bloodstream, SON, and PVN [46,51]. Such synergy between the central and peripheral oxytocin systems does not always exist and there can be an apparent disassociation between the two as seen during a psychosocial stressor such as social defeat [52,53]. Engelmann et al. [54] demonstrated that whilst intra-SON oxytocin release increased in response to social defeat, peripheral oxytocin release remained unaffected.

Table 2 Dopamine systems

Dopamine systems	Origin	Projections	Function
Nigrostriatal	SN (A9)	Striatum	Motricity
Mesocortical	VTA(A10)	Cortex	Emotionality
Mesolimbic	VTA(A10)	NAc	Reward and desire
Tuberoinfundibular	Arcuate Nucleus (A12)	Median Eminence	Regulation of prolactin release
Incertohypothalamic	Zona Incerta (A13) Periventricular region (A14)	Various hypothalamic nuclei, thalamus	Sexual arousal and copulation
Diencephalospinal	Hypothalamus (A11)	Spinal cord	Afferent stretch reflex, contraction of penile striated muscles

Central dopamine pathways. Within the CNS, three major dopamine pathways exist; the nigrostriatal, mesocortical/mesolimbic and tuberoinfundibular systems which influence motor function, mood, reward and neuropeptide release. There are two additional minor dopamine pathways; the incertohypothalamic and diencephalospinal systems which are believed to modulate elements of sexual behavior. SN = substantia nigra; VTA = ventral tegmental area; Nac = nucleus accumbens).

Thus, it can be seen that during certain neuroendocrine-mediated behaviors, centrally acting and peripherally acting oxytocin may act in unison or independently to exert their behaviorally specific effects.

Oxytocin Receptors

The encoded oxytocin receptor is a 389-amino acid polypeptide with seven transmembrane domains and is thus part of the G protein-coupled receptor family. When oxytocin binds to its receptor it initiates a cascade of intracellular events that culminate in a range of cellular responses including an increase in neuronal firing, neurotransmitter release, smooth muscle contraction and protein phosphorylation. In rats, peripheral expression of oxytocin receptors is concentrated (but not exclusively) in the male and female reproductive tract and in myoepithelial cells in mammary tissue [4,55]. In addition, oxytocin receptors are also abundantly expressed throughout the CNS and often exist in the same regions containing oxytocin fibers. In addition to their expression in the SON and PVN, oxytocin receptors are also found in the regions of the cortex, hippocampus, limbic system, basal ganglia, medial preoptic area (MPOA), olfactory bulbs, amygdala, and the brain stem [56,57]. There is widespread distribution of oxytocin receptors in the thoracic and lumbosacral segments of the spinal cord, with the dorsal horn, dorsal gray commissure, intermediolateral cell column all possessing oxytocin receptors [58]. However, some brain areas show a distinct mismatch between oxytocin fiber distribution and oxytocin receptor expression, such as seen in the amygdala and olfactory bulbs where there is a significantly greater proportion of oxytocin receptors compared to oxytocin fibers that innervate these nuclei [59–61]. Such an anatomical mismatch gives rise to the possibility that centrally released oxytocin can diffuse to distant sites within the brain to exert its effects. Therefore, oxytocin in the brain is described as a neuromodulator and appears to have broad permissive actions.

Dopamine and Oxytocin Interactions

Stimulation of central dopamine and oxytocin pathways are known to have similar effects on certain social and affiliative behaviors such as sexual behavior and pair bonding [62,63]. In addition to producing similar prosocial behavioral responses, anatomical, and immunocytochemical studies have revealed that the receptor binding sites and neuronal fibers of these two neuroregulators exist in the same CNS regions, often in close apposition to each other [58,64–69]. Furthermore, we have recently shown that hypothalamic oxytocin cells express dopamine receptors [70] suggesting direct regulation and in the context of sexual behavior, both dopamine and oxytocin activity are known to increase in the same brain region of male rats [71,72]. These observations have led some researchers to believe that central dopamine and oxytocin systems interact with each other to regulate socio-affiliative behavior. As associated behavioral disorders and more profound social deficits are often seen in patients with psychiatric disorders such as autism and depression, it seems logical to assume that disruptions to the integration between dopamine and oxytocin pathways may partly underlie social impairments found in these patients.

Based on this evidence above we will now aim to describe a basic framework of "interaction" between dopamine and oxytocin pathways in a socio-sexual context based on rodent studies, for referring to later in the review (see Figure 2). We provide a general but not exhaustive summary of brain nuclei known to regulate two well-understood social behavior contexts (sexual behavior and pair bonding) and the existence of an overlap of dopamine/oxytocin receptors and projections in these regions. More in-depth neuropharmacological evidence relating to each particular behavioral paradigm will be discussed later in each subsection.

Framework of Proposed Interactions between Dopamine and Oxytocin

Common central brain regions believed to be involved in mediating socio-sexual behaviors include the MPOA, SON, PVN, amygdala, NA, and the VTA. The hypothalamus and limbic system appear to be crucial components for the execution of socio-affiliative behaviors in rodents and for mediating reward pathways as a consequence of social interaction [70,73–76].

Sexual Behavior

The MPOA, SON, and PVN are understood to have roles in regulating penile erection and copulation in male rodents [70,77,78]. These oxytocin-rich nuclei are innervated by dopaminergic fibers from the incertohypothalamic system (located in the zona incerta) (see Figure 2) [64,65] and are known to express dopamine D2-like receptors [70] suggesting a direct regulation of hypothalamic oxytocin by dopamine. In addition to local dendritic oxytocin release from magnocellular neurons [50] the PVN exerts its widespread effects via oxytocin release in other key brain regions notably the hippocampus, amygdala, VTA, and spinal cord to mediate sexual behavior components [73,74].

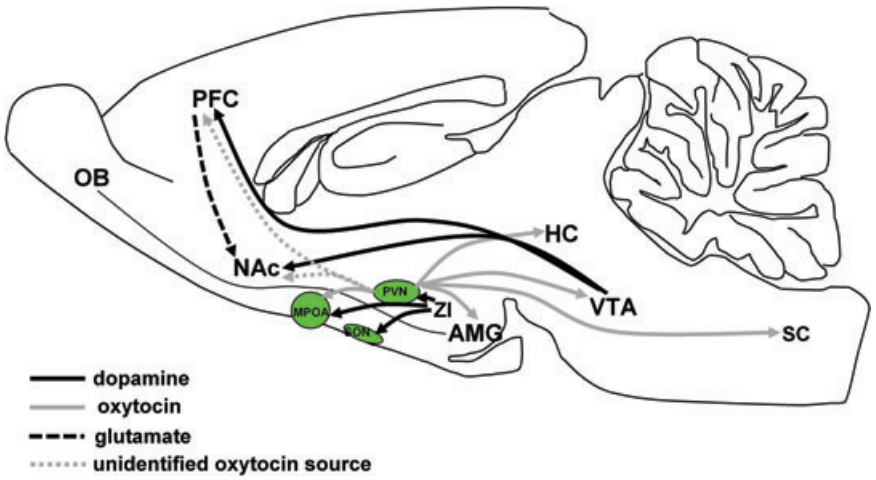

Figure 2 Major dopamine pathways and their relationship to oxytocin neuron populations. Basic framework of proposed interactions between dopamine and oxytocin in the rodent social brain. Sagittal view of a rat brain illustrating potential neural pathways involving dopamine and oxytocin during sociosexual behavior (proposed pathways underlying pair bonding were taken from prairie vole literature as rats do not form pair bonds). Sociosexual behavior is governed by oxytocin release from the hypothalamic nuclei, namely, MPOA, SON, and PVN which receive dopaminergic innervation originating in the ZI. The hypothalamus exerts its pro-social effects using oxytocin via (1) magnocellular oxytocin dendritic release which inturn diffuses throughtout the hypothalamus and to other sites and (2) via PVN extra-hypothalamic oxytocin projections to the hippocampus, amygdala, VTA, and spinal cord where they have a role in sexual behavior, reward and pair bonding. During mating oxytocin release in the AMG, HC, and VTA facilitates social learning and memory and stimulates mesolimbic dopaminergic reward pathways projecting to the NA and PFC. Mating encourages pair bonding possibly via oxytocin release (likely to be supplied by the PVN) in the PFC and the NA, (or in the case of males, vasopressin release in the ventral pallidium, not shown). PFC dopamine levels may increase upon oxytocinergic stimulation leading to further dopamine release in the NA via glutamatergic projections. Concurrently, NA dopamine may also be directly activated by oxytocin to modulate pair bonding. NA, nucleus accumbens; ZI, zona incerta; MPOA, medial preoptic nucleus; PVN, paraventricular nucleus; SON, supraoptic nucleus; AMG, amygdala; VTA, ventral tegmental area; HC, hippocampus; PFC, prefrontal cortex; OB, olfatory bulbs; SC, spinal cord.

The hippocampus and amygdala, which are important in processing social emotions and memory comprise part of the limbic system which also includes the NA, a key site involved in arousal, motivation and reward. The VTA, hippocampus, and amygdala all receive oxytocin input from the PVN [79–81], contain oxytocin receptor mRNA [82,83] and are highly responsive to the pro-erectile effects of oxytocin [73,74]. Furthermore, recent immunocytochemical studies revealed that oxytocin fibers originating in the PVN, lie in close apposition to mesolimbic dopamine cell bodies in the VTA that terminate in the NA [73], thus providing some neuroanatomical basis of a potential paraventricular oxytocin input to mesolimbic dopamine fibers. In addition to the NA [84], the VTA also supplies dopaminergic fibers to the hippocampus and amygdala [85] suggesting that dopamine–oxytocin interactions within these nuclei may also have a bi-directional role.

Taken together this provides some preclinical evidence for an oxytocin–dopamine (and/or dopamine–oxytocin) circuit operating between the PVN, VTA, hippocampus, and amygdala during penile erection. In summary, it has been proposed that during sexual arousal, stimulation of the mesolimbic dopamine system via oxytocin (released in the VTA, hippocampus, and amygdala) activates inturn incertohypothalamic dopamine fibers innervating the MPOA, SON, and PVN of the hypothalamus. From here oxytocin is believed to act within the hypothalamus, in limbic brain regions and the spinal cord, culminating in the activation of mesolimbic dopamine reward pathways and expression of penile erection (see Figures 2 and 3 for summary).

Pair Bonding

Most studies examining the neural correlates of pair bonding use prairie voles as unlike rats, they form long-lasting bonds after mating and can display high social functioning in certain behavioral paradigms [76,86]. Similar to sexual behavior, the limbic system has a highly integrated role in social attachment behaviors such as pair bonding [66] via its dense projections to the prefrontal cortex, a region known to mediate complex cognitive behaviors. The prefrontal cortex and NA receive dense dopaminergic input largely from the VTA and an oxytocinergic innervation, the source of which is not known, although it is likely to originate in the PVN. In addition, both dopamine and oxytocin receptors are known to be

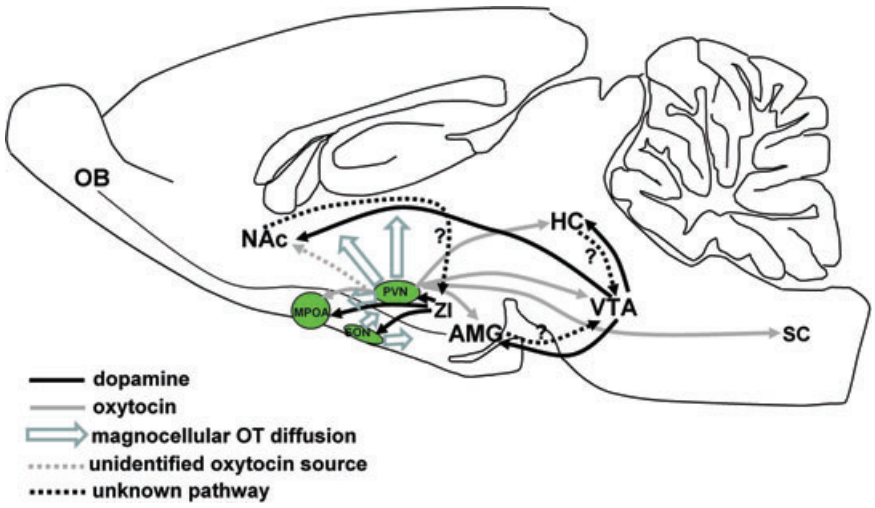

Figure 3 Dopamine and oxytocin interactions during penile erection. Sagittal view of a rat brain illustrating proposed interactions between dopamine and oxytocin in the rodent brain during penile erection. During sexual arousal oxytocin acts in the AMG, HC, and VTA via parvocellular oxytocin projections and magnocellular oxytocin diffusion to stimulate the mesolimbic dopamine pathways originating in the VTA and projecting to the NA, which mediate sexual motivation and reward. Concurrently, meslimbic dopamine activates (via an unkown pathway) the incertohypothalamic doapmine system to stimulate oxytocinergic neurons in the PVN which then project to the SC and facilitate penile erection. The role of oxytocin action in the MPOA and SON during penile erection remains unknown, however, they may be involved in mediating those sexual events occurring after erection such as pelvic thrusting and/or ejaculation. OT, oxytocin; NA, nucleus accumbens; ZI, zona incerta; MPOA, medial preoptic nucleus; PVN, paraventricular nucleus; SON, supraoptic nucleus; AMG, amygdala; VTA, ventral tegmental area; HC, hippocampus; OB, olfatory bulbs; SC, spinal cord.

abundantly expressed in the prefrontal cortex and the NA [66,87,88]; however, the phenotype of these neurons has yet to be identified. Thus, it may be that, in addition to mesocortical and mesolimbic stimulation during pair bonding, dopamine and oxytocin (via hypothalamic input) may also interact in the prefrontal cortex to modulate dopamine activity in the NA (behavioral neuropharmacological studies are required to confirm this). Concurrently, there may also be coactivation of dopamine and oxyocin in the NA as revealed in a recent study where stimulation of D2-like receptors and oxytocin receptors in the NA facilitated pair bond formation in female prairie voles [89]. Thus, the prefrontal cortex and NA may serve as other potential integrative sites for dopamine and oxytocin pathways underlying natural reward circuits and social attachment behaviors governing for example, maternal, and pair bonding (see Figure 2 for summary).

Sexual Behavior Dysfunction

Male Sexual Behavior

The Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Assocation) (DSM-IV) classification for men with sexual dysfunction disorder is the inability to achieve or maintain penile erection until completion of sexual activity. Erectile dysfunction can be separated into two main categories where the causes are either psychologic (where underlying emotional or mental health processes such as depression and anxiety affect the ability to achieve erection) or organic (where there is a central and/or peripheral disorder in the erectile pathway) in origin. Psyhcologic, organic causes and a mixture of both comprise approximately 12%, 68%, and 20% of those reporting erectile dysfunction [90]. In our opinion, the most convincing evidence to suggest a central dopamine/oxytocin link in CNS function has originated from preclinical studies investigating male sexual function. The aim of such studies has been to explore a dopamine/oxytocin basis in penile erection in healthy rodents in the hope of better understanding the erectile process in humans which inturn may aid in the development of potential therapies for treating erectile dysfunction. A model of erectile dysfunction has been identified in rats [91]; however to our knowledge, there are no reports in the literature examining or manipulating dopamine/oxytocin pathways in this model. So for this section of the review we will mainly focus on (unless stated otherwise) studies using healthy rodents. In addition, whilst there has been a recent suggestion that dopamine and oxytocin may partly mediate the ejaculatory component of sexual behavior in rats [92], it is the serotonergic system that is generally believed to influence central oxytocin neurotransmission at ejaculation

[93]. Thus, this section of the review will focus on penile erection in rodents and potential therapeutic implications for humans with psychogenic erectile dysfunction.

Mechanisms of Penile Erection

Whilst peripheral processes control contractant and relaxant capacities of corpus cavernosum smooth muscle, penile erection, a spinal reflex, is centrally mediated and involves both spinal and supraspinal pathways [94]. It is a complex response influenced by neural, steroidal, hormonal and vascular inputs [95–97]. Upon appropriate stimulation (e.g., tactile, visual, and auditory) supraspinal (those originating in the PVN) and peripheral pathways converge on spinal pro-erectile centers to activate autonomic fibers running in cavernosal nerves, which provide the neuronal efferents to the penis. This integrated and coordinated input into the spinal cord culminates in engorgement of the penis with blood and penile rigidity (enhanced by contraction of the perineal striated muscles).

In healthy human males, circulating oxytocin levels in the blood are known to rise during sexual arousal, penile erection and ejaculation [98,99]. Similarly in male rats, peripheral and either intracerebroventricular (i.c.v.) or microinjection in various brain regions (including the amygdala, hippocampus, VTA, PVN, and lumbar spinal cord) of oxytocin facilitates penile erection and copulation [10,73,74,100,101]. Both rodent and human studies suggest that oxytocin acts as an important mediator for both appetitive and consummatory phases in male sexual behavior. In addition to oxytocin, dopamine is also known to partly comprise those excitation pathways governing the expression of sexual behavior. Dopaminergic agonists have been shown to exert erectogenic effects in clinical studies [102]. Similarly, when administered locally into the MPOA or PVN in the male rat, dopamine receptor agonists exert a facilitatory effect on almost all aspects of male sexual behavior, particularly penile erection [77,103–105]. Such findings have led researchers to believe that central dopaminergic and oxytocinergic pathways may interact with each other to mediate erectile function; however, the nature of interactions and brain circuits employed by dopamine/oxytocin are only beginning to be probed.

Morphological and Electrophysiological Evidence

As mentioned previously in the rat, the oxytocin-rich MPOA, SON, and PVN of the hypothalamus receive dopaminergic input [64,65] and are believed to be critical integrative sites for male sexual behavior [77,78,106] (see Figures 2 and 3). We have recently shown that oxytocin cells in the MPOA, SON, and PVN possess dopamine D2, D3, and D4 receptors [70] which suggest that dopamine may be able to directly influence hypothalamic oxytocin neurotransmission via D2-like receptors. The ability of dopamine to positively influence hypothalamic oxytocin release was first demonstrated in early *in vitro* studies [107]. Since then, there have been several *in vivo* studies demonstrating a marked increase in oxytocin concentration in the blood, hippocampus and PVN in response to dopaminergic stimulation [41,108–111]. Electrophysiology has also shown that specific targeting of D1, and D3 receptors can influence the depolarization of oxytocin cells in the hypothalamus [112,113] which further confirms the dopamine receptor(s) involved in central oxytocin release.

Behavioral Pharmacological Evidence

Behavioral pharmacological studies in rats have been extremely informative and insightful by revealing a strong link between central dopamine and oxytocin neurotransmission in the context of sexual behavior. The relationship between dopamine and oxytocin neurons in the PVN during penile erection was substantiated by the attenuation of apomorphine-induced penile erection after bilateral lesioning of the PVN [114] thus depleting extra-hypothalamic oxytocin stores [115]. Stimulation of penile erection by apomorphine or the selective D4 receptor agonist, PD 168077 is also prevented by i.c.v., but not intra-PVN delivery of an oxytocin receptor antagonist [104,105,116] suggesting that oxytocin receptors located outwith the PVN are involved in mediating apomorphine-induced penile erection. Dopamine agonist-induced penile erection can be inhibited by oxytocin receptor blockade [114]; however, penile erection elicited by oxytocin is not inhibited by dopamine receptor blockade [117] suggesting that dopamine may lie upstream to oxytocin pathways. More recently, this finding was contradicted after Martino et al. [101] revealed the pro-erectile effect of oxytocin was inhibited by the dopamine receptor antagonist, clozapine, which suggests that oxytocin may be able to modulate central dopamine neurotransmission in regulating erectile function. To add to the neurochemical complexities subserving penile erection, we have recently shown that dopamine may differentially stimulate oxytocin subpopulations to produce erectile events. This dissociation appears to be dependent on whether intromission (physiological marker of penile erection where male rat positions himself behind and mounts receptive female leading to a train of pelvic thrusts, termed *in copula* penile erection) is achieved. In our study, we found naive rats

administered with the D2/D3 agonist, Quinelorane but not the D4 agonist, PD168077 (i.c.v.) displayed multiple erectile episodes associated with the activation of parvocellular oxytocin neurons but had no apparent effect on magnocellular oxytocin cells. In a separate study, we aimed to block endogenous dopamine release in sexually experienced males allowed full access to receptive females by i.c.v. injection of a D2, D3, or D4 dopamine antagonist. We found that blockade of central D4 receptors was the most effective at inhibiting intromission and this was correlated with attenuation of magnocellular oxytocin neuron activation [70] suggesting that *in copula* erection in rats may be D4 receptor-mediated.

It is not clear as to whether during penile erection dopamine increases oxytocin levels in the PVN (via magnocellular cells) and/or at sites outwith the PVN (via parvocellular cells) such as in the spinal cord where proerectile centers exist [58] or the hippocampus [108]. There is increasing evidence to suggest that parvocellular oxytocin neurons are part of the neural network controlling penile erection [108,118,119]. Apomorphine-induced penile erection involves, at least in part, release of oxytocin at extrahypothalamic areas via these parvocellular fibers; however, intrahypothalamic oxytocin release and action cannot be ruled out. In agreement with this we have recently demonstrated in anesthetized rats, that blockade of oxytocin receptors in the lumbosacral spinal cord significantly reduces the facilitatory effect of intravenous (i.v.) injection of apomorphine on intracavernous pressure rises (ICP, physiological index of penile erection) leading us to believe that dopamine may activate a paraventriculospinal pathway in the generation of erection [70]. Contrary to these findings, we were unable to show that apomorphine (i.v.) markedly affected spinal oxytocin release in the lumbosacral spinal cord (unpublished observations), which leads us to conclude that spinal oxytocin may have only a minor modulatory role in apomorphine-induced penile erection and there is involvement of other neuromediators. Indeed, central oxytocin receptors are highly homologous to another key neuropeptide, vasopressin [4]. Such similarities in receptor structure will undoubtedly influence ligand receptor recognition/activation. In the spinal cord for example, conflicting data has revealed that oxytocin may exert its effects via vasopressin [120] or oxytocin receptor activation [121], suggesting a role for central vasopressin in regulating male sexual behavior cannot be ruled out.

Potential Brain Circuits

Some recently published animal data has implicated involvement of other brain nuclei in the complex communication network which uses central dopamine and oxytocin systems to mediate rodent sexual behavior (see Figure 3). Oxytocin stimulation of the ventral subiculum in the hippocampus, medial amygdale or VTA, and apomorphine microinjection in the PVN all induce penile erection preceded with a marked increase in mesolimbic dopamine activity suggesting an oxytocin–dopamine driven pathway. Both responses were inhibited after blockade of central oxytocin receptors and hypothalamic and mesolimbic dopamine receptors [73,74,110,122]. Thus, such findings suggest that not only dopamine–oxytocin but oxytocin–dopamine pathways may subserve penile erection but also implicates a role for dopamine and oxytocin in the activation of pathways governing sexual motivation and sexual reward. Taken together, these findings suggest dopamine/oxytocin interactions underpinning erectile function involve dopamine and oxytocin-containing nuclei within and outwith the PVN that form a much larger and highly integrated network subserving appetitive and consummatory components of sexual behavior (see Figure 3 for summary).

So referring to our framework for interaction, a substantial amount of evidence of dopamine and oxytocin projections, targets and receptor localization, and sophisticated pharmacological studies, allow us to conclude that dopamine–oxytocin (and oxytocin–dopamine) interaction is important for the normal display of penile erection.

Treatment of Erectile Dysfunction

In humans erectile dysfunction is characterized by the inability to achieve and maintain penile erection sufficient to engage in sexual intimacy and affects around 2 million men in the United Kingdom. Despite other contributing factors such as age, prevailing underlying vascular diseases and psychogenic factors, the causes of erectile dysfunction are in most cases due to a disruption in either or both peripheral and central pathways controlling penile erection. Whilst the use of nonpharmacologic therapies such as vacuum erection devices, penile implants and psychotherapy have reported some success in patients unable to achieve erection [123]; pharmacotherapy targeting peripheral (and in some cases central) sites currently remains first-line treatment. Currently, the intracellular messenger nitric oxide (NO) has been receiving some attention due to its ability to act on postganglionic parasympathetic fibers innervating penile smooth muscle and so aid in initiating and maintaining erection. Indeed, pharmacological agents acting to replenish NO have shown some success in preclinical and clinical studies of erectile dysfunction; however, research is still at an early stage [124]. The dopamine agonist, apomorphine

did show some clinical success due to its ability to activate pro-erectile sites in the CNS and induce erectile responses [125,126]. However, there was limited patient tolerance due to adverse side effects [127]; some too severe to provide any long-term treatment. Intranasal delivery of apomorphine may be a potentially effective alternate route of administration since it facilitates preferential delivery to the brain [128], was shown to be a powerful sexual stimulant in male rats and was also well tolerated by patients without adversely affecting cardiovascular function or inducing nausea [129,130]. However, the effectiveness of intransal apomorphine as a powerful erectogenic without substantial adverse side effects warrants further investigation.

Oxytocin has become a key clinical target due to its potent erectogenic effects in preclinical studies [9,101] and seemingly lack of severe side effects when given in low doses, e.g., to pregnant patients to induce labour [131]. However, to date there are no oxytocin agonists clinically available for the treatment of erectile dysfunction. According to the literature, at present, there do not appear to be any clinical studies exploring the effects of oxytocics in patients with erectile dysfunction and this is presumably due to the greater clinical outcome of other pharmacotherapies such as those targeting the melanocortin system. Bremelanotide, a melanocortin agonist, is one of the first centrally acting agents shown to have greater clinical efficacy and patient satisfaction than currently available treatments [132,133]. Interestingly, bremelanotide is likely to act via oxytocin as oxytocin neurons express melanocortin receptors and the endogenous melanocortin, alpha melanocyte stimulating hormone activates oxytocin neurons and facilitates sexual behavior in rats [106]. Phosphodiesterase-5 inhibitors (PDE-5) (such as Viagra) are currently the safest treatment for patients with erectile dysfunction with fewer contraindications [102,126,134] and provide overall greater patient satisfaction [135]. However, they act peripherally and are effective in maintaining penile erection in patients capable of initiating sexual arousal; however, they are not able to induce penile erection. Thus, those patients where psychogenic factors are a contributing factor would benefit from treatments aimed at targeting the CNS. Patients suffering psychological disorders such as depression and anxiety or neurologic conditions such as Parkinson's disease, where there is profound disruption to central dopamine pathways (and presumably oxytocin neurotransmission), frequently report bouts of erectile dysfunction [136,137]. Thus, development of specific dopaminergic ligands (specific for D2-like receptors) or oxytocics which would act to redress central dopamine and oxytocin levels in the CNS may aid in the treatment of patients reporting decreased libido. However, administering dopaminergic agents aimed at selectively targeting for example, central D2-like receptors does not appear to be more advantageous since the unwanted peripheral side effects still persist. The lack of biological receptor specificity to delineate central and peripheral (located in the area postrema in the brain) receptors remains a huge hurdle for pharmacotherpeutic development.

Development of novel pharmacotherapies targeting the central oxytocin system is at a preliminary stage [138]; however, issues with regard to accessing CNS sites has proved problematic since oxytocin does not readily pass the blood–brain barrier. Delivery into the CNS via intranasal administration of other neuropeptides such as vasopressin has been reported in humans [139], furthermore, intranasal delivery of oxytocin was shown to exert antidepressant effects in humans [140], suggesting this could be one route of administration whereby oxytocin can act centrally. It is too premature to speculate on the potential therapeutic value of oxytocinergic stimulants; however, activation of the central oxytocin system may offer some promise and potential benefits over viagra, especially in those patients who experience difficulties in arousal/initiating penile erection. Thus, there is a need for more explorative research to aid in the development of safe and effective treatment for erectile dysfunction.

Female Sexual Behavior

The DMS-IV classification of female sexual dysfunction is defined as a "disturbance in sexual desire and in the psychophysiological changes that characterize the sexual response cycle and cause marked distress and interpersonal difficulty." In women, there are four main categories, which are used to define female sexual disorders: sexual desire, sexual arousal, sexual orgasmic, and sexual pain disorders [141]. However, the criteria used to diagnose female sexual dysfunction remains a contentious subject, as unlike men, there is not a quantifiable physiological index that can be measured in women. In addition, the female sexual response is highly sensitive to emotional and psychosocial states, both of which can influence sexual desire, arousal, and gratification. Thus, attempting to understand the neurobiology underlying the different facets of female sexual function using rodent models remains very difficult, however, they are now beginning to be explored [142]. Unlike penile erection, identifying a potential link between central dopamine and oxytocin pathways during female sexual behavior has yet to be investigated in preclinical studies and to our knowledge animals model of female sexual dysfunction have yet to be established. Sexually receptive female rats display proceptive behaviors which are comprised of "ear wiggling,"

"hopping," and "darting" (analogous to sexual arousal in women) to generate male attention and facilitate sexual activity. Female rats then display receptive behaviors, which include lordosis, a supraspinal reflex (believed to be analogous to orgasm in women), which is expressed in response to tactile , e.g., mounting male rat. Here the female displays a characteristic posture by arching the back moving the tail to allow penetration by the male rat) [77,143]. The involvement of dopamine and activation of central brain regions containing oxytocin cells during sexual behavior paradigms in female rats [142] suggests similar neurochemical processes involved in male sexual behavior may also be operative in females. Similar to those key regions comprising the basic framework for sexual behavior in males (see Figure 3), the MPOA, PVN, and amygdala are activated upon sexual stimulation; however, the ventromedial hypothalamus, bed nucleus of stria terminalis and lateral septum have also been implicated in the expression of female sexual behavior (not included in basic framework in Figure 3) [144–146].

Clinical studies have reported that plasma oxytocin levels in healthy women are markedly elevated during sexual arousal, orgasm, and remain high during the refractory period immediately after orgasm suggesting a role for oxytocin in female appetitive, consummative and postcoital behavior [98,147]. In female rats, sexual behavior culminating in lordosis coincides with activation of oxytocin cells in the ventromedial hypothalamus believed to be supplied by neurons in the PVN [144]. In gonadal steroid primed females, microinjection of oxytocin into the MPOA, VMH, or lateral ventricle facilitated the expression of female sexual behavior which was subsequently inhibited after central administration of an oxytocin antagonist [148–150]. As in humans, understanding the neural basis of female sexual behavior in rodents is further complicated by the basal levels of circulating oestrogen and progesterone (depending upon stage of oestrus cycle) and may help explain some discrepancies in the literature regarding the prosexual effects of oxytocin in females [150].

The role of dopamine in female sexual function is more ambiguous than in males. Some findings have shown dopamine to participate in the activation of those pathways controlling sexual motivation, sexual arousal and sexual reward in females [77,142]. However, its involvement in female sexual reflexes is less well defined. Early studies suggested that dopamine may have an inhibitory role in females as inferred by studies using dopamine agonists such as quinelorane and analyzing their effect on lordosis. The authors found that stimulation of central dopaminergic systems (although which pathways is unknown) reduced the expression and duration of lordosis [151,152] whilst others reported the opposite [153,154]. Lesioning of dopamine-rich regions such as the MPOA and microinjection of dopamine antagonists into the MPOA markedly disrupts appetitive behaviors in female rats. Selective blockade of MPOA D1 receptors in particular attenuates vaginocervical stimulation-induced neuronal activation [155,156]. These findings suggests dopamine action in the MPOA is important in the sexually active female rat. Furthermore, microdialysis has revealed an increase in dopamine levels in the NA in female hamsters and rats in the presence of a sexual stimulus (exposure to unaccessible male) and during mating [157,158] which is similar to those observations in males. As with oxytocin, dopamine's role in female sexual behavior is dependent on the hormonal treatments administered to female rats, which can clearly influence the effect of dopamine agonists on sexual behavior. Lordotic responses in nonreceptive and receptive rats appear to differ after dopaminergic stimulation [153,159]. Thus, our understanding of dopamine's involvement in component behaviors of female sexual activity is more complex and requires more thorough investigation.

To our knowledge, there are no data available examining an interaction between dopamine and oxytocin during female behavior studies in rodents. It is tempting to suggest that similar cross-talk between dopaminergic and oxytocinergic processes may subserve components of female sexual behavior as seen in males since disruption to the MPOA, known to be highly responsive to the prosexual effects of both dopamine and oxytocin in male rats, attenuates expression of sexual behavior in females. It may be that as indicated in males, the MPOA may form part of larger circuit involving oxytocin/dopamine interactions extending to key nuclei in the limbic system such as the VTA and NA to mediate the expression and reinforcement properties of lordosis. Therefore, there is not enough evidence to say yet that female proceptive or receptive behavior relies on a dopamine–oxytocin interaction according to our framework, although some elements clearly depend upon one or other factor. More explorative studies have to be carried out to confirm the role of oxytocin in dopamine-mediated processes governing female sexual behavior.

Female Sexual Dysfunction and Treatment

There are currently no therapeutic interventions available for women suffering sexual desire/arousal disorders. Similar to males, some clinical success has been reported with the CNS-acting agent, bremelanocortin where females reported enhanced sexual desire, arousal and significantly greater satisfaction during intercourse [160,161]. This suggests the melanocortin system may be a promising candidate and of potential therapeutic value.

Augmentation of the serotonergic system appears to be another area of sexual pharmacology that is of interest. The serotonin agonist, flibanserin (targets 5-HTA1A and 2A receptors) has reached clinical trials and acts to dampen the serotonergic system and redress dopaminergic and noradrenergic brain levels in a dual manner by decreasing serotonin levels and inhibiting cortical serotonergic neurotransmission [142 and references therein]. Because preclinical studies are at such a preliminary stage investigating the role of dopamine and oxytocin pathways in female sexual behavior, it is difficult to draw conclusions regarding any potential treatment options targeting these two systems. However, it could be postulated that since oxytocin release in women has been positively correlated to romantically linked affiliation cues, sexual arousal, and orgasm [98,162], similar parallels may be drawn in females from clinical trials in males, because similar dopamine and oxytocin systems appear to underlie female and male sexual components; however, currently it is too early to say.

Social and Parental Behavior and Related Disorders

Socially related behaviors other than sexual behavior include social bonding and maternal behavior, each of which comprise recognition, memory, seeking close proximity to conspecifics, and other behavioral components. There are some well-described functions for both oxytocin and dopamine in the control of these social parameters. The fundamental evidence for oxytocin's role is that oxytocin- or oxytocin receptor-null mice exhibit deficits in social recognition and social memory [25,163–165] indicating the necessity of oxytocin in facilitating interaction between individuals. Oxytocin in the brain also has antistress and antianxiety roles [166], further showing its pleiotropic nature in handling social situations. Similarly, disruption of dopamine signalling in transgenic mice also leads to social abnormalities [167,168], e.g., dopamine transporter null mice, that have increased extracellular dopamine and decreased dopamine receptor expression, exhibit increased social reactivity. We will analyze the reciprocal role that oxytocin and dopamine play in such behaviors in rodents and humans and then discuss whether disorders of social behavior, such as autism, can be explained by oxytocin and/or dopamine dysfunction.

Social Bonding

Social bonding includes elements such as time spent together in close proximity, choice of the known individual over another unknown individual (social preference), and social recognition. Social recognition is experimentally tested in the lab by measuring the time spent investigating a known individual compared to an unknown one and relies on olfactory and visual cues. Olfactory learning is a major component of recognition, involving noradrenaline-mediated disinhibition of mitral cells [169]. However, olfactory and visual cues also both use oxytocin [170,171]. Unlike wild-type mice oxytocin null mice cannot remember conspecific mice that they have recently been exposed to. Oxytocin receptor is expressed in the olfactory bulb, and although the PVN is considered a major source of oxytocin mediating social behaviors, oxytocinergic fibers have not been observed to appose either mitral or glomerular cells so the origin of oxytocin must be from other release sites, e.g., magnocellular dendrites. Other centers for oxytocin action in social recognition include the lateral septum, medial amygdala and MPOA, which also express oxytocin receptor. Since oxytocin can act via noradrenaline or other classical neurotransmitters (glutamate, GABA) in some areas, it is thought to modulate olfactory learning rather than directly stimulate the olfactory substrate [26], so as dopamine also plays a role in the olfactory bulb in social recognition oxytocin may also modulate dopamine release in order to mediate its effects.

Dopamine modulates odour detection and discrimination, which is part of olfactory memory formation [170,172,173], although others argue that dopamine (D2) plays a more prominent role in consolidation of memory rather than recognition *per se* [174]. So both oxytocin and dopamine play a role within the olfactory bulb in social recognition/memory. The Bruce Effect is an example of the consequences of lack of social recognition; in mated female mice, implantation failure occurs in response to pheromones from a stranger male; both oxytocin and dopamine action in the olfactory bulb are implicated in this phenomenon [175]. However, due to lack of evidence for their interaction within the olfactory bulb, attempts to fit our proposed interaction framework to this behavior is difficult. The precise phenotypes of neurones expressing dopamine or oxytocin receptors are not reported and the source of dopamine or oxytocin in the olfactory bulbs is unclear, while pharmacological approaches have not yet targeted the olfactory bulb selectively. The evidence suggests that there is a local synergistic, if not interactive, effect of oxytocin and dopamine within the olfactory bulbs, but there may also be interaction upstream, in other dopamine or oxytocin source or target sites.

Associated with social recognition, bonding develops under certain circumstances. Animals can develop a close association that is measurable by the social preference

test. Bonding behavior between adults has been closely studied over the past decade using prairie voles as a model species since they develop a well-defined partner preference. When male and female prairie voles spend time together partner preference increases. However, after copulation partner preference is strongly elicited, and the paired voles attain a monogamous-like affiliation. There is even an associated induction of parental behavior in male prairie voles which will be discussed later. This remarkable postcopulatory bonding between adults is attributed in part to both dopamine and oxytocin in both females and males [176], and the NA has been identified as the main forebrain center for the effect. As discussed below, this phenomenon represents another example of dopamine–oxytocin interaction in a behavioral context.

Importantly, the partner preference induction is dependent upon oxytocin receptor distribution in the brain. The NA and the caudate putamen have high densities of oxytocin receptors in animals where partner preference is induced but not in other species, such as the montane or meadow vole or mouse [176]. Oxytocin release increases in the NA in female voles during pairing [68], although the source of oxytocin is unclear. Increased social contact is inducible by intra-cerebral oxytocin infusion and can be induced not only in voles but also in rats and squirrel monkeys; and partner preference is blocked by oxytocin antagonist infusion into the NA. After mating oxytocin release also increases in the PVN and extrahypothalamic regions such as the amygdala in male and female rats [72] (and see above), so conceivably these regions could also play a role in partner bonding. Interestingly mating-induced oxytocin release in rats has been shown to underlie postcopulation anxiolysis so if also true for other rodents this may be a component of the bonding behavior. Whether this occurs in the prairie vole model is unknown and pair bonding in rats is not typically induced by copulation.

The NA is also an important center for dopamine action during pair bond formation in prairie voles [176]. Mating increases dopamine turnover in the NA in males and females- NA neurones are known to express dopamine receptors and dopamine acts via D2 receptors to facilitate partner preference. The phenotype of dopamine target neurones is not described but dopamine presumably acts by regulating the predominant NA GABA neurones, although some evidence indicates that it also modulates incoming glutamatergic afferents [177]. As for oxytocin, dopamine D2 agonists facilitate and antagonists attenuate partner preference behavior.

There is a reasonable body of evidence revealing an oxytocin–dopamine interaction in partner preference. The NA is rich in both oxytocin and dopamine receptors; if coexpressed pre- or postsynaptically it would provide a clear basis for coregulation of the same target neurones, but this is unknown. As well as acting in the NA it appears that mating-dependent release of oxytocin activates a mesolimbic (VTA) dopamine circuit and induces dopamine release in the NA, indicating upstream regulation of a dopamine circuit. Therefore, in association with copulation oxytocin and dopamine link the state of sexual arousal with that of bonding [74]. However, it has not been shown that oxytocin release increases in the VTA where it might stimulate dopaminergic projections at copulation or with pair bonding, although, neuroanatomical evidence has proved indicative (Melis et al., 2007. On the other hand, recent reports propose dopamine acts via oxytocin since concurrent reciprocal activation of dopamine and oxytocin receptors in the NA occurs [89,176]. Pharmacological studies are needed to tease out the precise roles of oxytocin and dopamine in the NA and VTA. One might also ask whether dopamine action on PVN (or SON) oxytocin neurones is necessary for induction of partner preference. Evidence in the prairie vole is lacking but we would speculate that it is part of the complex cascade leading to arousal and social interaction that precedes copulation and bonding.

It should, however, be noted that another hypothalamic peptide related to oxytocin, vasopressin, has also important interactions with dopamine in the NA in social recognition and the formation of pair bonding [176]. There is substantial evidence of prominent vasopressin V1a receptor expression in the NA and ventral pallidum that facilitates the formation of pair bonds and this dependent upon a specific sequence in the 5′ flanking region of the gene that determines its brain expression pattern. Vasopressin neurones lie adjacent to oxytocin neurones in the PVN and SON, and also express D2-like receptors [70], so dopamine may control vasopressin release and action in parallel with oxytocin. Whether vasopressin also controls dopamine neurone activity or release (as oxytocin does, see above) is unclear at present. Interestingly though, viral vector insertion of the prairie vole V1A receptor into the mouse brain induces susceptibility to the formation of pair bonds similar to that seen in prairie voles [178].

So, it appears that robust oxytocin–dopamine and/or dopamine–oxytocin connections are involved in social interactions. In mating it may be that dopamine–oxytocin connections are initially involved in penile erection [70], (see above; Figure 3) but then oxytocin-driven dopamine effects mediate subsequent related behaviors such as bonding and reward. However, it is apparent that their interaction at multiple brain locations matches with our framework, and occurs in a social context with more than one potential outcome: copulation and bonding.

Studies of the roles of oxytocin and dopamine in social behaviors in humans are appearing more now with the application of functional magnetic resonance imaging (fMRI) and gene expression studies on post mortem tissue. For example, it can be observed that high intensity fMRI signals are observed in the VTA and SN upon viewing a loved partner [179], and these correlate with the distribution of human oxytocin receptor expression and an interaction with the dopamine system [180]. Other strategies include analysis of peripheral oxytocin concentration [98,181]. Although these do not necessarily correlate with the release or action of brain oxytocin, some importance is attached to increasing levels that correlate to positive mood and prosocial behaviors and, along with studies investigating the effects of intra-nasal administration of oxytocin, have gained some credibility in recent years [182].

Lack of social recognition and inability to form social bonds are characteristics of a host of psychiatric disturbances, the most profound perhaps being autism. Autism and autism-spectrum-disorders represent a profound disturbance in the ability to form social bonds in humans and are most commonly found in males. Although underlying causes are multiple, and include a variety of potential genetic mechanisms, naturally associations between oxytocin and dopamine in autism have been sought to explain the condition.

Autism

The DSM-IV definition of autism is the inability to socially interact due to a deficit in verbal and nonverbal communication, social awareness and interactions and imaginative play. Autism-spectrum-disorders are complex neurodevelopmental disorders characterized by social withdrawal [183] and no adequate animal models have yet been reported. A role for oxytocin has been implied since plasma oxytocin concentrations (which can be a marker for social behaviors in humans) [98,181] are low in autistic boys [184,185] and oxytocin infusions or intranasal administration improve emotion recognition and facilitate trust analyzed using fMRI studies in humans, particularly revealing the amygdala as a target [186–188]. Additionally there is a proposed link between oxytocin receptor polymorphisms and autism in some families [182,189–191], which might adversely alter expression patterns and densities in a way that contributes to the altered social behavior. However, like bonding, autism is also associated with polymorphisms in the vasopressin receptor 1A gene, particularly in the amygdale [192]. Overall the evidence for oxytocin is contradictory, as discussed in more detail in an excellent review by Hammock and Young (2008) [176]. For example, in one study autistic children with circulating oxytocin levels in the normal range were the most profoundly asocial, so peripheral hormone levels may not reflect central oxytocin release or action in this condition. In contrast to oxytocin, stronger evidence links dopamine dysfunction with autism-like disorders. Reports are mixed but variations in the dopamine system such as dopamine transporter and D4 receptor genes and activity are implicated. Attention deficit/hyperactivity disorder, one of the range of autism-spectrum-disorders, also appears to exhibit similar dysfunction of dopamine systems [193–197]. Whether there are parallel changes in oxytocin release and dopamine activity in relevant brain regions, such as the NA, VTA or ventral pallidum in people with autism-related disorders is uninvestigated, but a joint role for oxytocin and dopamine seems possible.

Treatments for Autism-Spectrum Disorders

Despite the relatively weak evidence for a role for oxytocin in autism, oxytocin treatment has been reported to successfully reduce some characteristic behaviors in autistic patients [198]. Since it is likely that intranasal oxytocin may pass the blood brain barrier [139], there have been some reports of humans showing improvement in communicating behavior and secure relationship attachment [182,199]. Therefore such an approach can potentially be developed into therapies that abrogate some of the more overt social behavioral deficits in autism. On the other hand, drugs targeting the dopamine system such as risperidone and olanzapine seem relatively effective [200]. It may be that combined therapy targeting oxytocin and dopamine systems together would be synergistic, resulting in more effective therapy.

Maternal behavior also creates a bond between mother and offspring akin to that of the social adult-adult bond so we will now outline the parallels between social and maternal behavior and the relative contributions of oxytocin and dopamine.

Parental Behavior

Oxytocin and dopamine are also key neuromodulators of maternal and paternal behavior. It has been recognized for many decades that oxytocin in the brain plays a key role in maternal behaviors [201], and is mainly facilitatory rather than essential, unlike for other social behaviors as discussed above [163,165,202]. More recently, reports of its role in paternal behaviors are emerging, including in prairie voles where mating not only induces social bonding but also paternal care behaviors in males [203–206]. Similarities between mechanisms in mothers and fathers include enhanced oxytocin expression in the

PVN in paternal compared to nonpaternal males and increased vasopressin V1a receptors in the prefrontal cortex in the male marmoset [207]. However, maternal behavior is much better investigated and understood, especially the role of oxytocin in sheep and rodents, so this section will concentrate on evidence from females.

Initially oxytocin was considered to be important for onset of maternal care perinatally but is now recognized to also maintain the suite of behaviors involved. Thus, central oxytocin facilitates care behaviors (pup licking, grooming and nesting behavior), delivery of nutrition to offspring (particularly the milk provision via the ejection reflex for which oxytocin is essential [163], and arched back nursing [kyphosis]), offspring protection (against predators but also including maternal aggression against conspecifics) and, importantly, bonding [26,201,208,209]. Some of these social-like behaviors are comparable to the adult-adult bonding as discussed above, and involve recognition mechanisms.

Mother-infant recognition may be similar to adult-adult recognition in that oxytocin mediates olfactory memory for offspring. This is very well investigated in sheep, where olfactory memory is a crucial, postbirth link between ewe and lamb and is necessary before any further behaviors, including allowing lamb suckling, are performed [26,170]. Such olfactory memory is part of mother-infant bonding in sheep that occurs at birth and can be induced by vagino-cervical stimulation under appropriate steroid conditions. Bonding between ewe and lamb does not occur in the absence of vagino-cervical stimulation, and even in women it has been reported that after caesarean birth, bonding with the baby takes significantly longer than after vaginal delivery [210]. Bonding combined with olfactory memory of the young initiates the other maternal caring and nurturing behaviors [26]. Initially, birth and vagino-cervical stimulation increase oxytocin release in various brain regions, including the PVN, SON, MPOA, SN, septum and olfactory bulb in both rats and sheep [26,170], which are known to be key regions mediating maternal interaction from a variety of activity and lesioning studies. Mimicking this endogenous release pattern with central administration of oxytocin induces, and oxytocin antagonist inhibits, maternal behaviors in rodents and sheep. However, as for prairie vole bonding, oxytocin receptor distribution is most important in quality of behavior performed. Not only does oxytocin receptor expression increase perinatally and into lactation [201], but 'good' maternal behavior, commonly defined as high licking, grooming and arched back nursing, correlates with wider and higher density of distribution of oxytocin receptor in a rat model [211]. Furthermore, such good behavior can be epi-genetically inherited by daughters, as care received neonatally determines their brain oxytocin receptor distribution and maternal behavior quality in adulthood [212]. Therefore receptor patterns rather than strictly quantity of neuropeptide release may be particularly important in determining quality across the range of social behaviors. Maternal experience is important too: stress exposure perinatally alters oxytocin receptor expression patterns correlated with poorer behavior [213], and this may also extend to stress emanating from prolonged conditions relating to a difficult (e.g., psychological disturbances) or ill child. The best evidence links oxytocin to maternal behavior in women in a correlative way, e.g., fMRI imaging of the maternal brain while viewing photos of their baby reveals activation of oxytocin target regions (e.g., SN) [214], and increased CSF or plasma oxytocin levels [26,215] are evident compared to women who are not mothers. Further indication of a role for oxytocin in primates comes from central administration of oxytocin to rhesus monkeys which increases maternal behaviors [216], and oxytocin is widely believed to be evolutionarily important in maternal care across a range of species.

Proof of the importance of dopamine activity in mothers' brains was shown in dopamine transporter knockout mice which exhibited impaired maternal behavior [217,218]. Like oxytocin, dopamine release is also elevated in the PVN, SON, MPOA, SN, septum and olfactory bulb in rats and sheep [26,170]. Unlike oxytocin, where receptor distribution is primarily important, levels of dopamine in the NA equate with quality of maternal behavior [219]. Lesioning the VTA, using 6-hydroxydopamine to selectively destroy monoamine cells, also blocks maternal behavior [26] indicating that as a potentially important source of dopamine in mothers' performance. Evidence indicates that extensive interaction between oxytocin and dopamine plays a role.

Oxytocin modifies targets directly and/or presynaptically, at least partly via monoamines, including dopamine, and GABA [26], so could potentially gate dopamine effects. At birth oxytocin receptor increases in many classical dopamine target regions, including NA, olfactory bulb, and prefrontal cortex, increasing the potential for oxytocin regulation of the dopamine release at onset of maternal behavior [26]. However, oxytocin receptor expression evidently decreases in the SN, showing that control of the nigrostriatal dopamine neurones and their emanating pathway(s) is differentially altered from other dopamine sources. Oxytocin released after birth or vagino-cervical stimulation modulates dopamine activity in the NA, VTA and SN, and dopamine reciprocates with action within the PVN [26]. It has been proposed that oxytocin action on dopamine neurone activity in the SN promotes immobility to facilitate offspring suckling, but the coregulation is also associated with behavioral drive

as well as feelings of reward associated with the neonate [208]. How this equates with decreased oxytocin receptor in the SN is unknown, but may indicate a shift in oxytocin control from one mediator to another within the SN. Interestingly, mothers showing better maternal behavior (high licking and grooming) have increased oxytocinergic projections to the VTA and more dopamine release within the NA, powerfully revealing the importance of the oxytocin–dopamine interaction located in the mesolimbic pathway [220]. So there are similarities between maternal bonding and adult bonding in the neurochemical oxytocin–dopamine interaction but corresponding experiments have not all been performed to clearly compare them or to match to our framework. Interestingly, recognition of the mother by the offspring (rat pups) also involves monoamines [221], and others have speculated that oxytocin action in the offspring brain might parallel that of the mother [176].

Disorders of parental behavior are not yet well described, let alone understood physiologically, but have profound consequences on offspring. One topical and emerging field is that of offspring adverse programming arising from parental and/or postnatal stress. Adverse neonatal programming can also be produced by poor parental care, whether or not stress is manifest. Such adverse long term consequences on offspring psychological and physical development arising from parental stress or poor parental care in the neonatal period include susceptibility to anxiety and depression disorders, obesity, and cardiovascular disease [222]. In fact, perinatal stress and level of maternal attachment also has an impact on dopamine systems in the offspring, detrimentally altering its release and activity parameters and reproductive development [223,224].

So, abnormal or inappropriate parental behavior in humans has far-reaching consequences for children and, for offspring, perinatal experience received has a huge impact on their later development. As indicated earlier, there is also a reciprocal effect, where disruptive or socially compromised children inflict stress and long-term consequences on the parents and their behaviors. This is only just being recognized as a problem for families, and will have costs for the health and social services in the future. Understanding of the causes of poor parental behavior is only just emerging, but includes parents receiving poor parental care when they were young and peri-natal stress exposure, setting up a vicious cycle that is difficult to investigate in humans and challenging to treat. However, some progress is being made to enlighten the underlying maternal brain dysfunction, and recent evidence indicates that mothers' low responsiveness to their toddler correlates with less efficient oxytocin receptor gene variants [225]. Breaking the repeated cycle of transgenerational poor parental care would have long lasting desirable emotional and economical benefits for individuals, families and governments. Simply targeting the dopamine/oxytocin systems is not a viable option. Since problems occur at multiple cellular, organismal and social levels, addressing each parameter on its own is not likely to impact on the problem in any meaningful way, and a multidimensional approach will be required.

A dysregulation of oxytocin and/or dopamine activity coupled with an impairment of social interactions has also been observed in a variety of diseases and disorders ranging from anorexia to Parkinson's disease [182]. Furthermore there has been an expansion in the research of an oxytocin or dopamine basis (and those neural circuitries upstream/downstream) in multiple behavioral syndromes. This review does not aim to cover the all diseases and disorders exhibiting inherent abnormalities in behavior but will now consider the role of these neuromodulators in selected behavioral disorders such as drug addiction and anorexia.

Addiction

The DSM-IV recently classified drug addiction as an individual who persists in the using of alcohol or other drugs despite problems related to use of the substance, resulting in a significant impairment in functioning. Due to the devastating impact on addicts' lives and the socioeconomic burden associated with addiction, the neural basis of drug use disorders is being increasingly explored. Hurdles such as the heterogeneous nature of biological and genetic determinants add to the complexities of understanding drug seeking behavior. Additionally, drug addiction models used in experimental studies do not consider social environment and so do not closely mirror drug-seeking behavior in humans. Some elegant preclinical studies however, have revealed interesting information regarding social consequences of drug use [226,227] and those neural correlates, such as oxytocin, subserving addiction [228,229].

The role of the mesolimbic dopamine system in the rewarding effects of drugs of abuse has been well documented [230–233], with MDMA, cocaine and opiates known to influence dopaminergic neurotransmission in these motivational pathways [229,234] and produce marked impairment in prosocial behavior [235,236]. The mesolimbic system has been established as a key component of rewarding properties of natural rewards such as sex and food and maladaptive rewards such as drugs of abuse and is believed to drive chronic drug use. As mentioned previously, dopaminergic projections originating in the VTA and extending to the NA, amygdala,

olfactory tubercle and prefrontal cortex (see basic framework diagram in Figure 2, not all nuclei shown) comprise the mesolimbic pathway. In humans, fMRI studies revealed distinct brain activation in the VTA during cocaine self-administration in cocaine addicts which is indicative of mesolimbic dopamine activation [237]. Animal studies using *in vivo* microdialysis, where small changes in neurotransmitter concentrations can be detected, have shown that psychostimulants such as alcohol and cocaine activate mesolimbic reward circuits and increase dopamine levels in the NA [238,239]. Specific dopamine receptors mediating drug reinforcement pathways have yet to be elucidated; however, dopamine D1-like and D2-like receptors appear to be implicated in regulating the acute reinforcing properties of cocaine as evidenced from rodent studies where dopamine agonists and antagonists acting on all dopamine receptors reinstated or inhibited drug-seeking behavior, respectively [240,241]. Furthermore, disruption to the mesolimbic dopamine via selective ablation of the NA results in decreased self-administration of cocaine without affecting feeding behavior in rats [242]. Taken together, these findings emphasize the importance of the mesolimbic dopamine reward pathway in the processing of maladaptive rewards in particular, which drives continued drug administration leading to chronic drug abuse.

Because drug addiction has such a profound effect on a wide spectrum of social behaviors including social bonding, maternal and sexual behavior, it is not surprising that oxytocin has also become a key area of focus in addiction research. A role for oxytocin in drug addiction is not altogether surprising since oxytocin fibers innervate and receptors are expressed in known dopamine-containing nuclei important in reward assessment including the VTA and amygdala [79,80,82,243].

Dopamine/Oxytocin Interactions

Drugs of abuse known to target the mesolimbic system, such as cocaine markedly reduce the levels of oxytocin in the hippocampus, hypothalamus, NA and plasma when taken repeatedly over time [244]. These long-term disruptions to central oxytocin systems due to chronic abuse of psychostimulants, presumably contributes to the impaired social and emotional capabilities often observed in drug addicts. Whilst it is apparent that dopamine can influence oxytocin release in a chronic drug use context, these two neuromodulators may also function in a bidirectional manner during the development of tolerance and dependence to drugs of abuse.

It has been suggested that oxytocin may possess antipsychotic properties due to its ability to block cocaine-induced dopamine release in the NA [245] and to attenuate characteristic locomotor activities associated with cocaine addiction [229,246–248]. Furthermore, microinjection of physiological doses of oxytocin into the NA, amygdala and the hippocampus attenuate morphine tolerance and dependence and cocaine-induced hyperactive locomotor activity [249]. So, the data suggest a potential role for oxytocin in the regulation of chronic drug abuse by influencing dopaminergic activity in key limbic brain sites and altering behavioral responses associated with addiction.

In addition to having a neuromodulatory role influencing neuroadaptive processes responsible for tolerance and dependence [229], recent findings have also alluded to a role for oxytocin in drug withdrawal [234,250]. Opiate drugs strongly inhibit oxytocin neurones since they coexpress opioid receptors. Endogenous opioid systems control oxytocin during physiological conditions, e.g., pregnancy and birth [27]. However, oxytocin neurones develop tolerance and dependence for opiates, which means that they are able to maintain their physiological roles even under pathologic conditions which may include drug addiction [251]. On the flip side, it also means that upon withdrawal and similar to dopamine systems [252,253], the whole oxytocin system is dysfunctional (temporarily or could be permanently) and this has long term physiological and social implications for those trying to withdraw and avoid drug taking situations or triggers.

The data suggest oxytocin action in key limbic brain regions has a regulatory role in attenuating drug tolerance and dependence and promoting drug withdrawal, presumably via its actions on mesolimbic dopamine reward pathways. So, referring to our original framework (Figure 2), there appears to be a growing body of evidence to suggest dopamine and oxytocin pathways may be two potential neural correlates mediating drug addiction. Central oxytocin sites are one area of addiction neurobiology that has yet to be fully explored and may serve as a potential neural substrate that could be potentially exploited for pharmacotherapeutic benefit in the treatment of drug use disorders and withdrawal.

Treatments for Addiction

Treatment for nicotine addiction has has shown some success with the use of dugs such as buproprion (inhibits the depletion of central dopamine and noradrenaline stores and antagonizes nicotinic receptors) [254] and varenicline (mimics the actions of nicotine) which were both shown to promote smoking abstinence [255,256]. However, currently there are no available

pharmacotherapies, which specifically target other forms of psychostimulant addiction. Approved treatment options merely treat the symptoms associated with the addiction. Medication alone is not remotely sufficient to effectively tackle drug addiction. Psychotherapy, self-help/support groups and community-based projects such as substance abuse programs all play extremely important roles in trying to achieve and maintain abstinence in drug use disorders. In cocaine addiction there have been numerous clinical studies conducted and designed to target various neurotransmitter pathways in the brain with central GABA and dopamine systems proving to be potential therapeutic endpoints [257]. Potentiation of GABAergic neurotransmission via $GABA_A$ and $GABA_B$ receptor activation or inhibiting the degradation of GABA have reported some success in reducing cocaine use in dependent subjects [258–260]. In addition, drugs acting to enhance central dopaminergic activity (presumably in the mesolimbic system) have shown some success in humans as evidenced by an increase in urine screening protocols testing negative for addictive drugs [261]. The current medical therapy for opioid dependence is oral administration of the opioid analgesic, methadone. Methadone treatment remains the most effective treatment for opioid dependent patients, proving to be a more effective deterrent of heroin use than other nonpharmacological methods such as detoxification programs and prescribing placebo medication [262]. Whilst findings from controlled clinical trials using pharmacological agents to, for example, interfere with the metabolic degradation of alcohol or potentiate GABAergic function, have shown some promise in regard to amelioration of withdrawal symptoms and reducing drug seeking behavior [263,264]. The limited data available and pharmacologically induced adverse side effects emphasize the need for more exploratory work to be conducted in preclinical and clinical addiction studies. Preliminary work investigating the role of oxytocin in acute and long term repetitive drug use has implicated effectiveness of this neuropeptide in influencing neuro-adaptive processes and ultimately drug craving behavior [234]. Intranasal oxytocin administration would presumably help to redress hypothalamic oxytocin levels that are found to be diminished in alcohol dependent subjects [265]. Other therapies to restrain wildly high central oxytocin during opiate withdrawal are envisaged as potentially useful. Presumably oxytocin-induced stimulation of mesolimbic dopamine pathways to improve mood and behavioral symptoms associated with drug seeking behavior and withdrawal to stabilize social behaviors would be beneficial treatment strategies. Ultimately oxytocin's facilitatory role on psychosocial recovery may help to improve recovery and enhance receptivity to social support in dependent drug users.

Anorexia/Bulimia

The DSM-IV classification for eating disorders such as anorexia nervosa includes the refusal to maintain normal body weight, having an intense fear of gaining weight and a disturbance in the perception of body weight or shape. Anorexia nervosa and bulimia nervosa are complex psychological disorders associated with dysfunctional control of appetite for food and body weight. Anorexia involves fear-like and obsession-like behaviors, and affects about 0.3% of the population, mostly teenage girls. It is a DSM-IV classified mental disorder with serious comorbid consequences, including clinical depression, drug abuse and obsessive-compulsive disorder, as well as other related conditions like lack of reproductive ability. Bulimia is similar, though more common than anorexia, but also involves binge eating [266] and sufferers are particularly susceptible to addictive behaviors. Control of appetite is multidimensional, involving many interacting hypothalamic neuropeptides, peripheral energy signaling peptides and other neurotransmitters mediating hunger, satiety and reward, and evidently several of these elements are disturbed in anorexia and bulimia. The arcuate nucleus is a major integrating center for the control of appetite receiving input from higher centers and the gut as well as being able to sense circulating factors due to its leaky blood brain barrier. Major arcuate neuropeptides primarily include the orexigenic factors neuropeptide Y (NPY) and agouti-related protein (AgRP), and anorexigenic peptides such as alpha melanocyte stimulating hormone (αMSH), and cocaine-and-amphetamine-related-transcript (CART). The arcuate communicates with the PVN and lateral hypothalamus in particular to control appetite, but also with other nuclei such as the SON, ventromedial nucleus and brainstem.

In fact the SON and PVN are emerging as regions that respond particularly to eating, neurones becoming activated strongly at the start of a meal [267]. Oxytocin is one of the nonarcuate anorexigenic peptides involved in signaling satiety, and so administration of oxytocin intracerebrally inhibits appetite, and oxytocin antagonist prolongs meal duration. Oxytocin is thought to be recruited downstream of the major appetite peptides from the arcuate nucleus [268]. For example, αMSH stimulates SON oxytocin neurones via melanocortin receptor 4 (MCR4). Interestingly, MCR4 agonists developed by the pharmaceutical industry to treat obesity also precipitated side effects such as prolonged penile erection in clinical trials, and we now know that is due to activation of central oxytocin systems [269], so there is a potential neuropeptide link between eating and sex. As well as the arcuate-oxytocin drive there is a bi-directional link

between the gut and oxytocin neurones, where eating (gastric distension) stimulates oxytocin activity in the SON and PVN [267] and oxytocin projections from the PVN to the brainstem regulate gastric reflexes [270]. However, apart from the brainstem, how and where oxytocin acts to mediate satiety is unclear.

A role for oxytocin in anorexia or bulimia is not well investigated. One might expect that if oxytocin dysregulation is involved in the low appetite element of anorexia that its expression and or activity would be enhanced, but the evidence available tends to suggest that oxytocin is not an underlying cause [271]. Another anorexigenic peptide, nesfatin-1, is associated with anorexia. Intriguingly, nesfatin-1 is coexpressed in PVN oxytocin neurones [272] and stimulates intra-PVN oxytocin release. Since oxytocin mediates nesfatin-induced inhibition of appetite [273], this perhaps indicates a previously unrecognized role of oxytocin in anorexia, though further detailed studies are required. Evidence also seems to point towards mis-control of the orexigenic peptide AgRP in anorexia [274], and this might act at least partly via oxytocin too- AgRP acts as a MCR4 antagonist and inhibits oxytocin neurone responses to ingestive behavior [275]. On the other hand, lack of oxytocin may underlie decreased satiety in the Prader Willi syndrome [274], which is a rare genetic condition characterized by hyperphagia, obesity, reproduction failure and mental retardation. Clearly further research is needed to clarify a role for oxytocin in eating disorders.

Dopamine's function in signalling both food-seeking behavior and reward plays an important role in appetite and satiety [266,276]. First, dopamine deficient mice become completely aphagic and need dopamine replacement for any feeding to occur [277]. Secondly, mesocortical dopamine (from the VTA acting in the striatum and prefrontal cortex), but not mesolimbic dopamine (from VTA projecting to NA) pathways have a propensity to mediate food reward and anticipation of food [242,278]. Dopamine activity responds to olfactory and visual food-related stimuli and so in parallel with social recognition and sexual arousal responds to valid external cues. Dopamine is reported to be recruited by many appetite neuropeptides, including NPY, αMSH and AGRP, especially modulating NA dopamine release and activity [277]. The relevant dopaminergic regions, the VTA and NA, respond to gut signals such as ghrelin, which acts partly directly in the NA and VTA and partly indirectly via the arcuate, particularly AgRP [279] or αMSH, both of which also regulate oxytocin responses to appetite signals as indicated above. In addition, catecholamine lesion of the PVN disrupts AgRP expression and signalling, so upstream dopamine modulation of neuroendocrine systems may also be recruited in control of the arcuate peptides [280].

Much evidence links dopamine with anorexia: there is altered dopamine function in the striatum and caudate putamen, along with other monoamines, particularly serotonin [266,281]. There is thought to be decreased dopamine turnover, as indicated from measuring CSF levels of dopamine metabolites in anorectic patients. This seems to reflect dysfunction of the dopaminergic system, which is associated with symptoms such as the inability to experience motivation and reward. Low dopamine is also associated with motor hyperactivity, a core symptom of anorexia nervosa that increases with the level of starvation [281]. PET imaging implicates altered dopamine activity in anorexic patients [266], while binge eating is associated with a polymorphism in the dopamine transporter gene in women [282], also indicating that altered dopamine concentrations at relevant target regions play an important role. Dysregulation of other monoamines is also apparent, with serotonin inhibiting food intake. However, dieting reduces tryptophan, the precursor for serotonin, perhaps explaining why patients have unexpectedly low serotonin in their CSF [281]. Serotonin and noradrenaline transmitter systems are both dysfunctional in bulimic patients [281], again based on CSF analysis so precision in changes at monoamine sources or targets are unknown.

With the lack of a relevant animal model for anorexia or bulimia, it is hard to find evidence in the literature for whether dopamine or oxytocin play a primary role in these eating disorders, let alone whether their interaction explains part of the phenotype. There have been limited opportunities to experimentally study any potential interaction between dopamine and oxytocin in this context, perhaps because the study of oxytocin in anorexia or obesity has been relatively limited up to now. However, if as indicated above there is a robust coregulation of reward by oxytocin and dopamine it might be expected that disturbances in food reward that are associated with anorexia/bulimia could be explained by disruption in oxytocin–dopamine pathways.

Treatment of Anorexia/Bulimia

In the past antidopaminergic drugs such as fluoxetine and phentermine proved effective for binge-eating disorders along with simultaneous cognitive behavioral therapy, but have not typically been used for treating anorexia despite the evidence for dopamine malfunction [281], probably due to poor tolerance of side effects. Anorexics seem to respond better to antidepressants and selective serotonin reuptake inhibitors than binge-eating patients [266]. SSRI are also effective—because anorexia is often

associated with depression-like symptoms, perhaps they effectively dissociate emotional elements such as anxiety from appetitive elements of the disorder. Given the role of central oxytocin in fear, anxiety and appetite control, as well as its known interactions with dopamine in other CNS disorders, oxytocin should be addressed more in the future as a potential component of treatment for these conditions. As indicated above, it is well recognized that anorexia/bulimia and other various behavioral disorders are associated with coexpression of anxiety- or depression-like symptoms so we will now address the roles of dopamine and oxytocin in major depression.

Major Depression

The DSM-IV definition of depression is the persistence of depressed mood and/or loss of of interest or pleasure in daily activities consistently for at least a 2-week period. Depression is reported to affect up to 10% of people in the United Kingdom at some time during their lives, and one in fifty experience severe depression. Causes are multiple and varied and include acute and chronic conditions, as well as neonatal programming, which confers susceptibility to psychological disorders in later life, including depression. Furthermore, major depression can be experienced by mothers perinatally (postpartum psychosis), also with consequences for the child. In other disorders such as Parkinson's Disease, schizophrenia and anorexia, depression is comorbid due to the neurochemical nature of the condition. In addition, many CNS disorders elicit depression due to lack of support, and lack of recovery or appropriate treatment. Symptoms of chronic or major depression include feelings of sadness, low self-worth, withdrawal from social situations, high anxiety and poor stress coping.

A major cause of depression is chronic stress. A core hypothalamic center mediating stress responses is the hypothalamo–pituitary–adrenal (HPA) axis, where the expression, release and responsivity of corticotrophin-releasing hormone (CRH) and vasopressin from the PVN are altered, leading to prolonged misregulation of pituitary adrenocorticotrophic hormone (ACTH) and adrenal cortex glucocorticoids (cortisol in humans and corticosterone in rodents). Chronic stress leads to sustained characteristic changes in physiology and behavior that are typical of depression. The typical hypercortisolemia and elevated sympathetic hormone tone are due to stress-induced adaptations in the limbic and hypothalamic control centers, including altered glucocorticoid feedback control [283]. Although there are many brain and body adaptations with depression, and multiple interacting mechanisms have been proposed to either underlie or arise as a consequence of depression, for brevity this review aims to focus only on potential mechanisms involving dopamine and oxytocin.

Stress, or other mechanisms arising from trauma or disease, causes dysregulation of central monoamines (serotonin, noradrenaline, and dopamine), which are major players mediating the adverse symptoms of depression [284]. Noradrenaline and serotonin act in a variety of relevant brain regions, including primarily in the PVN, but dopamine activity in the prefrontal cortex, NA, amygdala, and BNST, rather than the hypothalamus, is associated with stress response [285]. The main dopamine neurones that are stress sensitive are in the VTA and they project to cortical regions, so dopamine release increases in the prefrontal cortex in response to a variety of stressors [286]. Therefore stress effects on dopamine release and action in hypothalamic nuclei such as the PVN and SON are weak and dopamine's role in stress is mostly limited to hedonic and reward aspects of stress [286]. Analysis of human brain regions using microarray particularly reveals abnormal dopamine regulation in the prefrontal cortex in psychiatric disorders such as depression and bi-polar disorder [287]. Glutamate and GABA systems are also evidently dysregulated there, so there is a disintegration of the major excitatory and inhibitory neurotransmitters as well as the monoamines, and these modifications may be linked.

There are a variety of rodent models of depression and a suite of physiological and behavioral tests to analyse perceptible components of depressive symptoms. One such test is the dexamethasone-suppression test, which reveals alterations in glucocorticoid feedback. It has been shown using this approach that decreased dopamine in the prefrontal cortex accompanies prolonged stress-induced behavioral depression revealed [288], so the dopaminergic system is a potentially important target for therapies for human depression. Although it has been recognized for some time that low brain serotonin activity underlies HPA axis adaptations in depression, recent evidence further indicates that linked dysfunction of dopamine and serotonin systems is associated with depressive disorders [289–291].

As mentioned above (in the "Social Behavior" section), oxytocin has a strong antistress role, inhibiting HPA axis secretory and behavioral responses to stress, primarily by acting within the PVN to inhibit corticotrophin-releasing hormone neurones, although is also secreted and may inhibit pituitary corticotrophs [166]. Oxytocin also plays an important role in mediating anxiety and oxytocin-null mice exhibit increased anxiety behavior [166] by acting in the PVN, SON, and amygdala. Glucocorticoids such as corticosterone inhibit magnocellular oxytocin neurones [292], so during chronic stress and depression the

anxiolytic and antistress effects of oxytocin are attenuated, preventing action of this important controller, and so lack of central oxytocin is associated with depression.

In humans there is some evidence that low oxytocin correlates with depression in women, since plasma concentrations are reduced, but this was not observed in men [293]. If reduced oxytocin secretion reflects reduced central oxytocin release in women it may indicate that the oxytocin system is susceptible to stress in women particularly and therefore could have selective consequences for reproduction and offspring care and development. In rat models of high anxiety oxytocin mediates enhanced maternal behavioral and hormonal responses to stress [294], perhaps in an effort to overcome the inherent anxiety phenotype. Because glucocorticoid secretion increases prior to birth in both rodents and women, and oxytocin neurone responses to stress are inhibited in late gestation [295], oxytocin dysfunction in the maternal rat brain is a candidate for explaining postnatal depression [294]. Oxytocin neurones are also sensitive to the rapidly changing sex steroid environment perinatally, further reinforcing the concept that oxytocin neurones participate in the onset of depressive symptoms. Furthermore, central oxytocin control of stress responsiveness may also be partly inherited since the important brain oxytocin receptor expression levels and patterns are susceptible to epigenetic inheritance [211,296], (see above).

Despite the multiple studies showing separate roles for dopamine and oxytocin, reports of a joint role for dopamine and oxytocin in depression are limited and tend to be negative, e.g., the dopamine agonist apomorphine has no effect on peripheral oxytocin secretion in depressed patients [297]. This may be since the main regions where dopamine responds to stress (i.e., prefrontal cortex) overlap little with oxytocin sources or targets, although oxytocin can act in the VTA, possibly on dopamine somata. With chronic stress or hypercortisolemia any drive to oxytocin neurones would be limited, preventing any protective effect of oxytocin or dopamine against depression. Therefore, referring to our framework, a lack of dopamine–oxytocin interaction in depression under typical conditions is suspected. On the other hand, it might be speculated that in physiological states where the oxytocin system is highly activated, such as at birth, that increased oxytocin action in the PVN, SON, amygdala, and BNST would impact more on dopamine signalling and/or rise above a threshold that activates VTA dopamine neurones. Unlike dopamine, strong evidence points towards an anxiolytic effect of oxytocin via serotonin in a mouse model of depression [291]. Thus oxytocin could still be a relevant target for therapeutic intervention in anxiety and depression disorders.

Treatments for Depression

Current drugs for treating depression include the tricyclic antidepressants, the selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, and noradrenaline reuptake inhibitors. However more recent developments have shown the potential for dopamine reuptake inhibitor drugs, either alone or in combination with serotonin and/or noradrenaline uptake inhibitors, in treating depression and major depressive disorders [298,299]. Rat models and current clinical trials (clinicaltrials.gov) indicate that dopamine agonists are also effective antidepressants, acting partly via serotonin mechanisms [300]. However, oxytocin is not a pharmacological target as yet, although intranasal oxytocin treatment has the potential for reducing depression-related symptoms in men [140]. Since the current main drug treatment for depression, selective serotonin reuptake inhibitors, is not effective in a large majority of patients or has only a delayed effect in ameliorating symptoms [301], perhaps the interaction between oxytocin-serotonin, or oxytocin–dopamine-serotonin could be exploited further in developing new treatments for major depression.

Conclusion

Dopamine and oxytocin are two key centrally acting agents with widespread functions in the brain. Many behavioral disorders discussed are associated with oxytocin and/or dopamine dysregulation (Table 3). Whilst they are both involved in mediating organic functions such as penile erection, disruptions to either one of these pathways can have a marked effect on downstream neural processes, which can lead to profound social behavior deficits and establishment of altered behavioral states (e.g., social withdrawal and chronic drug use). We find dopamine and oxytocin may operate in a bidirectional manner driving organic functions such as penile erection (dopamine–oxytocin) and reinforcing/rewarding properties of social and addictive behaviors (oxytocin–dopamine) (see Figure 4). These two neuromodulators serve as potential neural correlates, which form a much larger neural network comprised of multiple neurochemical pathways and intricate circuitries. Trying to delineate a link between dopamine and oxytocin in normal and pathologic contexts remains a huge undertaking; however, progress is being made and warrants further and more thorough investigation.

Conflict of Interest

There were no conflicts of interest in preparation of this manuscript.

Table 3 Overview of the involvement of oxytocin and dopamine in CNS disorders and whether they are drug targets currently used in clinical therapy

Disorders	Oxytocin role	Dopamine role	Treatment targets? (dopamine/oxytocin?)
Sexual dysfunction			
erectile dysfunction- male	Decrease	Decrease	Dopamine or oxytocin
sexual desire disorders- female	Unknown	Unknown	Neither
Social dysfunction			
parental behavior	Decrease?	Unknown	Neither
autism	Decrease?	Decrease?	Dopamine
Drug addiction	Decrease	Increases[a]	Dopamine[b] or oxytocin[b]
Depression	Decrease	Decrease	Dopamine[b]
Eating disorders			
anorexia and bulimia	No change?	Increase	Dopamine[c]

[a]And/or mimic effects.
[b]Preliminary work/trials.
[c]In the past but superseded by newer treatments.

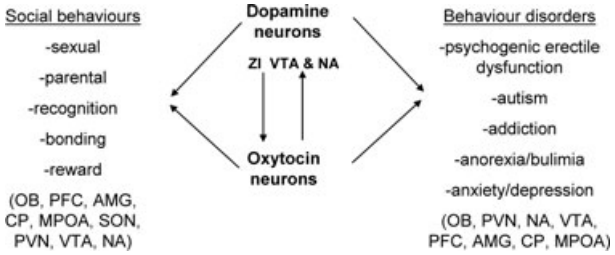

Figure 4 Summary of dopamine and oxytocin involvement in social behavior and behavioral disorders. Summary of potential dopamine and oxytocin interactions underlying socio-affiliative behaviors and subsequent behavioral disorders. Central oxytocin neurons activated by incertohypothalamic (ZI) dopamine input and mesolimbic dopamine pathways driven by hypothalamic and limbic oxytocin release comprise part of the neural circuitry governing social behaviors. Disruptions or changes in these neurochemical pathways may partly underpin pathophysiologic mechanisms contributing to organic functions such as erectile dysfunction, but also adversely affect an array of social parameters, which can lead to the development of profound behavioral disorders. NA, nucleus accumbens; ZI, MPOA, medial preoptic nucleus; PVN, paraventricular nucleus; SON, supraoptic nucleus; AMG, amygdala; VTA, ventral tegmental area; HC, hippocampus; OB, olfatory bulbs; CP, caudate putamen; PFC, prefrontal cortex.

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