# Neurobiology of Sexual Desire

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**ABSTRACT**

The aim of this paper is to elucidate the anatomical and molecular nature of sexual desire.  As such we have focused our attention to the telodiencephalic reproductive complex and the functional interactions with the cortico-limbic circuit that regulate sexual and non-sexual motivation.  Major focus of our review was on the animal studies that included hormones, peptides, neurotransmitters and the unique study paradigms that were designed to separate sexual motivation from the consumatory behavior.  We also have covered limited number of clinical trials but our primary goal was to review the animal study results.   We present rapidly evolving animal research data that we hope will contribute toward the development of new drugs that ameliorate the symptoms of hypoactive sexual desire disorders.

**Key Words:** hypoactive sexual desire disorders, sexual desire, sexual motivation, medial preoptic area, ventromedial nucleus of the hypothalamus, testosterone, estrogen

## Introduction

It took eons for Nature to create mammals as we see them today. The brain is the central organization that allows mammals to survive in a harsh environment. Two of the earliest structures that emerged were the hippocampal core for spatial memory and the orbital frontal core for object recognition.  Nature wanted to ensure that animals learn where to go to find food.  Other brain structures, such as sensory and motor cortices were created, by and large, to subserve the fundamental missions that the brain is designed to carry out.

Sexual desire is a component of procreative behavior that is essential for the sustenance of the human species.  Sexual desire is also a component of a broadly defined survival instinct.  Survival and procreation are two of the fundamental drive states of all mammals (Swanson, 2005).  Nature has laid down behavioral control columns in the brain consisting of a series of cell masses which form the medial preoptico-hypothalamic zone. These cell masses regulate motivated or goal-directed behaviors required for survival of the individual and of the species; they are ingestive, agonistic and reproductive (Nieuwenhuys *et al.*, 2008). These three behaviors require somatic, autonomic and neuroendocrine responses and all pass through initiation, appetitive, procurement

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and consummation phases. Our goal in this paper is to examine the reproductive part, especially the drive that leads to initiation.

Arts and culture mainly utilize reasoning and abstractive thinking. They originate from higher-order cognition involving symbols or inferred meaning (Burgess *et al.,* 2007; Charron and Koechlin, 2010; Gilbert *et al.,* 2006, 2007, 2010; Koechlin and Hyafil, 2007; Koechlin *et al.,* 1999, 2003; Kouneiher *et al.,* 2009; Okuda *et al.,* 2011; Ramnani and Owen, 2004).

Science, that is, "re-search" or search again infers that people are trying to ascertain what Nature has already created. Only humans pursue these goals because they enjoy a vast reservoir of episodic memories (unique to humans) (Kapur *et al.,* 1995; Nyberg *et al.,* 1996, 1995; Tulving, 2002) that allow the formation of self-identity that in turn is capable of creating the concept of future that can be bound to the drive states to pursue and achieve long-term goals (an ideal) (Conway and Pleydell-Pearce, 2000; Levine *et al.,* 1998; Thomas Antérion *et al.,* 2008). Animals do not have any of these capacities. If they do, then they are extremely limited; for example, rats have such a capacity lasting no more than several seconds (personal communication with A. David Redish, 2010).

Sexual behavior is different. Sex drive is an intrinsic, natural phenomenon, for which there is a fundamental purpose for its existence**:** to ensure that it functions optimally, Nature has created desire to engage in sexual activity and the pleasure that goes with it. For humans, Nature has been extremely generous, as humans derive pleasure from sex far more than most animals, and the duration of each episode and the frequency of sexual acts far exceed those of other animals.

Preclinical researchers have been studying sexual drive states for decades and have accomplished remarkable progress that is germane to human sexuality. In this preclinical context, the purpose of this report is to address normal and disturbed human sexual desire and sexuality, ranging from hypersexual to hyposexual desire disorders, and on how they could reflect on brain dysfunction. Brain is not an end product, but rather it is a product of evolution, i.e., a work in progress.

Through a review of the literature in this manuscript, we propose to better understand the anatomical and molecular nature of sexual desire. We will focus more on the desire than the pleasure component because in the disease process desire precedes pleasure. We refer readers to the published brain imaging study results on this topic, because they are beyond the scope of our review. We will also briefly review pharmacological attempts to modulate sexual function based on basic science research.

Desire does not exist in vacuum; desire (or motivation) is an intermediary process that propels a strategy into action. Without motivation animals would not pursue goals or engage in reward-seeking behavior. Nature has provided a rewarding experience to sexual act to ensure the sustenance of species in evolution.

## Neural basis of non-sexual desire

Although not the primary subject of this paper, there is an interface between the sexual and non-sexual motivation system; consequently, we will present a brief summary of current understanding of non-sexual motivation. A meaningful search for the brain anatomical sites and molecular mechanisms of motivation started only 30 years ago. For years, scientists had thought that the basal ganglia were designed to regulate movements as their sole function. Scientists previously had not known that there were other parts of the basal ganglia that participated in the regulation of motivation.

In the late 1970's, a neurosurgeon and limbic anatomist, Lenart Heimer, started to delineate the limbic portion of the basal ganglia that we now call the ventral striatum. The ventral striatum is made up of the nucleus accumbens and ventral pallidum. The nucleus accumbens is further divided into core and shell.

Shortly afterwards, Gordon Mogenson conceived a ground-breaking hypothesis and published a landmark paper (Kalivas and Barnes, 1993; Mogenson *et al.,* 1980) that turned the concept of basal ganglia function "upside down" in regards to motivated behavior.

Motivation emerges as part of normal development. Anatomically speaking, the region that is most critically involved in the

genesis of motivation or craving is positioned at the epicenter of the limbic circuit (Baker *et al.,* 2003; Kalivas *et al.,* 2005; McFarland *et al.,* 2003, 2004).

In humans, this region needs to be connected to the critical prefrontal regions before a full limbic circuit can be established. Research has revealed that human goal-directed behavior is mediated through this cortico-basal ganglia circuit (Alexander *et al.,* 1986). It would not be an exaggeration to state that goal-directed behavior is the raison d'être of human existence for the vast majority of the human race, a major building block of human civilization and human history.
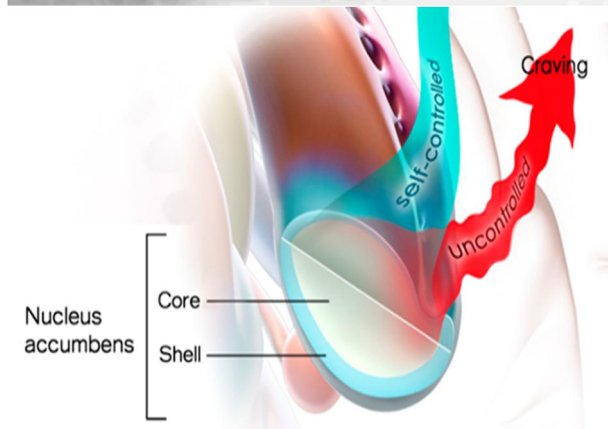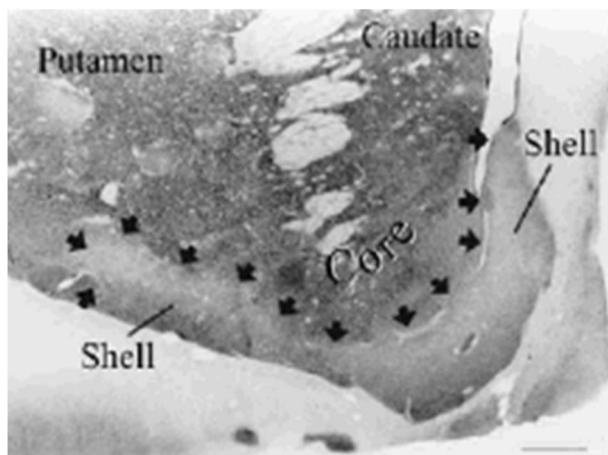


**Figure 1.** Heimer *et al.,* 2008, p. 45 (color illustration by Audra Geras)

In a series of animal studies, McFarland, Kalivas and colleagues (McFarland and Kalivas, 2001; McFarland *et al.,* 2003; 2004) presented breakthrough research findings that have led to a new insight. Their findings suggested that an increased glutamatergic signal in the nucleus accumbens is the key component of motivation and craving generation. Dopamine from the ventral tegmental area augments glutamatergic function within the core of the nucleus accumbens.

When primed with cocaine, McFarland, Kalivas and colleagues found increased extracellular glutamate and dopamine within the nucleus accumbens but only among the extinguished rats, not among the yoked rats (that is, if rats were trained to receive cocaine by pressing a lever, yoked rats continued to receive cocaine as long as they kept pressing the lever but the extinguished rats did not, so in this case lever pressing behavior had stopped hence extinction). Among the yoked rats they found increased dopamine levels only, not glutamate (Baker *et al.,* 2003; Kalivas and McFarland, 2003; Kalivas *et al.,* 2003; 2005; 2006; McFarland and Kalivas, 2001; McFarland *et al.,* 2003; 2004)

From these findings, the authors concluded that elevated extracellular glutamate levels in the core of the nucleus accumbens were responsible for the increased craving and they found that glutamatergic inputs came from the prelimbic area. In humans, plausible counterparts of the rat prelimbic area are Brodmann areas 10, 9, 46, 24 and 32ac (personal communication with Joseph Price, 2009).

The central concept in this finding is that craving is primarily driven by glutamate and that it is mediated through the core of the nucleus accumbens. The core circuit is linked to the motor circuit and the shell circuit is linked to the limbic circuit (Zahm, 1999). For this reason researchers thought that motor circuit cannot harbor feelings like craving. Within the basal ganglia system, however, there is a spiraling, ventral to dorsal, anatomical system that gradually turns motivation into action (Haber and Knutson, 2010). Only in the environment of increased glutamate in the core of the nucleus accumbens, rats would show increased urgency to seek out cocaine. Rats with increased dopamine levels alone in the core did not show such urgency (desire).

Although dopamine fails to trigger motivation on its own, dopamine bound to the D1 receptor neurons within the core of the nucleus accumbens augment glutamatergic signal transduction leading to the induction of more intense motivation or craving.

Once a cognitive plan is formed within the prelimbic area, the signal is carried to the core of nucleus accumbens where glutamate molecules generate motivation (Baker *et al.,* 2003; Kalivas *et al.,* 2005; McFarland *et al.,* 2003; 2004). The homeostasis of the glutamate activity within the core of nucleus accumbens is the root mediator for the genesis of motivation or craving (Kalivas, 2009).

Sesaek and Grace, in a masterful paper, detailed how the hippocampal and amygdala inputs interact with the prefrontal cortical inputs to the nucleus accumbens, further strengthening the signal to generate motivation (Humphries and Prescott, 2010; Sesack and Grace, 2010, see pages 31-33).
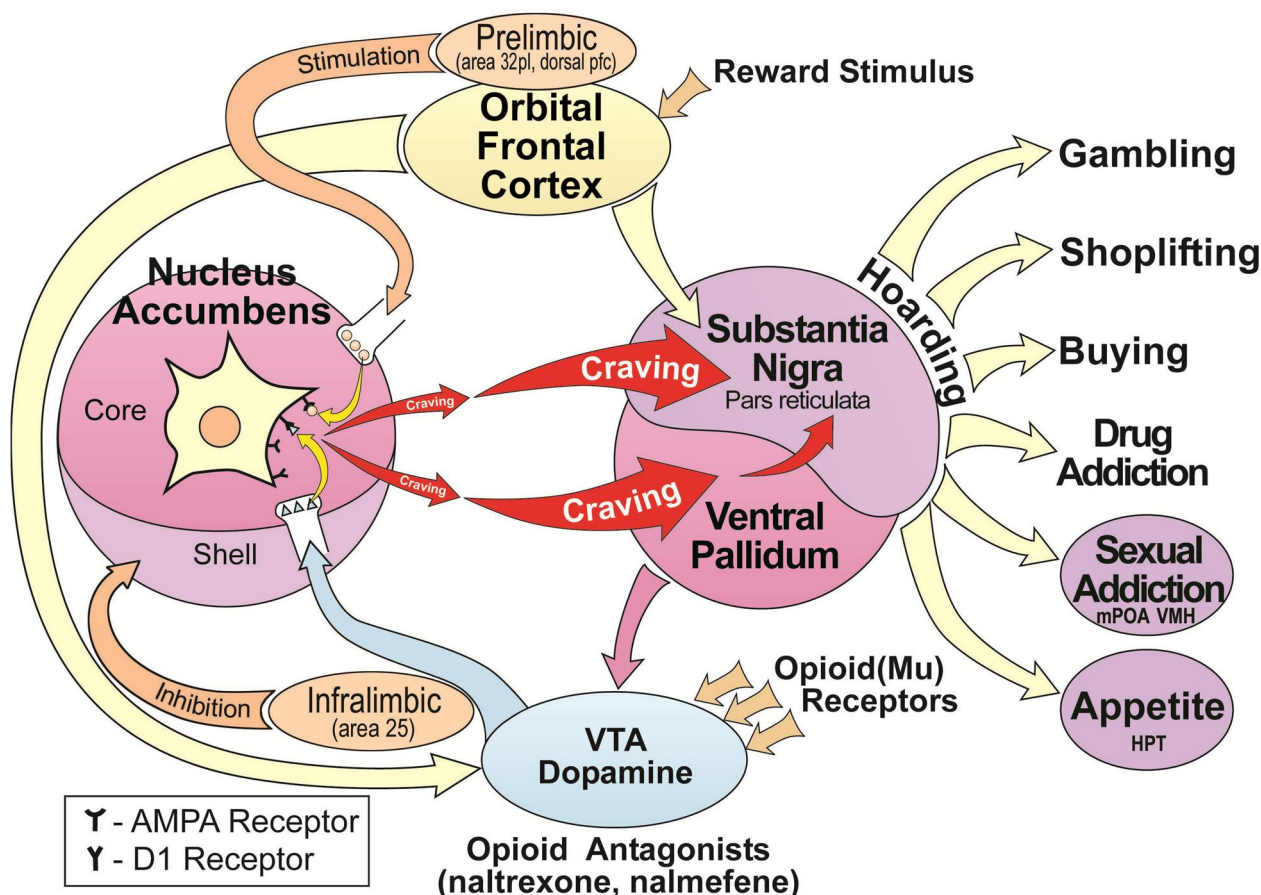


**Figure 2.** Higher brain structures such as the orbital frontal cortex, selected prefrontal areas (prelimbic area in animals) receive and interpret incoming sensory information. When a rewarding sensory input or thought is detected, pyramidal cells in the prelimbic area send signals to the core of the nucleus accumbens where motivation, urge and craving are generated so that the person has sufficient motivation (desire) to engage in a behavior to secure the targeted object. The molecule that mediates this signal is glutamate. The prefrontal brain simultaneously sends signals to the ventral tegmental area to activate dopamine neurons in that area. When these dopamine neurons are activated, dopamine is released in the core of the nucleus accumbens and augments glutamate function. Together they generate a powerful motivation to engage in foraging and other reward-seeking behavior. Once the rewards have been fulfilled, animals and humans feel satisfaction, pleasure and/or excitement. When these circuits are over-heated, mammals feel uncontrollable urges to engage in a behavior even if the behavior might bring about unbearable negative consequences subsequently (e.g. loss of money from gambling, divorce, etc.). These comprise behavioral or drug addictions. Key: Pfc – prefrontal cortex; mPOA - medial preoptic area; HPT - hypothalamus; VMH - ventromedial nucleus of the hypothalamus (illustration by David Mottet).

## Neural basis of sexual desire

Sex researchers have traced the neural basis of sexual excitement and sexual motivation. First, the process of evoking sexual desire will be described briefly. The three branches of the trigeminal nerve cover touch sensation for the

entire face. The facial touch signals reach the trigeminal ganglion, pass through the pons and arrive at the ventral posteromedial nucleus of the thalamus, then they continue to course to the primary sensory cortex in the postcentral gyrus of the parietal lobe before

they reach the touch sensation association cortex which is located posterior to the post central gyrus. Touch sensation signals in the association cortex project to the hippocampal formation and amygdaloid complex and finally reach the medial preoptic area and ventromedial hypothalamic nucleus within the hypothalamus, in other words, the telodiencephalic reproductive complex (Nieuwenhuys *et al.,* 2008). As mentioned before, these regions of the hypothalamus contain cells with highly concentrated androgen (Barley *et al.,* 1975; Naess, 1976; Naess *et al.,* 1975) and estrogen (Pfaff, 1980; Pfaff and Keiner, 1973).

By the time signals reach the association cortex, the person understands the meaning of the sensation. This happens because within the association cortex sensory information undergoes extensive associative elaboration as it becomes incorporated into the texture of cognition, that is, sensation is transformed to awareness (Mesulam, 1998). The association cortex interacts with the higher association areas in the prefrontal, temporal and parietal cortices. Higher order association areas integrate various sensory modalities to form the basis of the highest mental processes and also integrate past experiences to come up with planning and decision making (executive function).
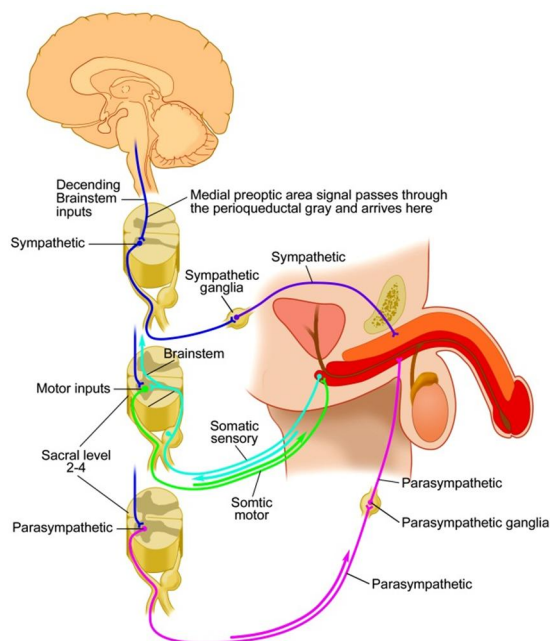


**Figure 3.** A diagrammatic representation of the sympathetic and parasympathetic circuits that regulate sexual function, a major corridor that interconnects to the central telodiencephalic reproductive complex (illustration by David Mottet).

Memory networks are vital parts of the survival and reproductive complex. Without memory networks, animals cannot fulfill two of their fundamental missions, i.e., food seeking and procreation. Anatomically speaking, sleep networks exist alongside the food-seeking and procreation networks, indicating that these triumvirate networks help animals adapt to and exploit the environment, and also avoid dangers to help them navigate successfully through perilous environments.

The signals transfer from the CNS to the periphery as follows: the medial preoptic area and ventromedial hypothalamic nucleus project the signals to the periaqueductal gray; pass through retroambiguus nucleus to reach the lumbosacral motor neurons that lead to perineal striated muscles that then augment penile erection (Nieuwenhuys, 2008). Sacral (level 2-4) components of parasympathetic outflow reach parasympathetic ganglia in the pelvis and innervate the penis, which is proerectile. Outflow from sympathetic ganglia in the pelvis, on the other hand, innervate the penis, which is antierectile (Giuliano and Rampin, 2000) (see Fig 3).

In addition to the above system, most recently, Sakamoto and his colleagues proposed the role of gastrin-releasing peptide in the upper lumbar spinal cord (L3, L4; ejaculation center) to drive lower spinal autonomic and somatic centers that coordinate male reproductive functions such as erection and ejaculation (see Fig 4).

Afferent signals are mediated through the sensory impulses from the genitals through the lower lumbar and upper sacral segments and reach the periaqueductal gray defined as the anterolateral system. Afferent fibers terminate in the basal telencephalon, thalamus, hypothalamus and brain stem that are directly connected to the reproductive network (Nieuwenhuys, 2008).

Thus, the three systems, sympathetic, parasympathetic and somatic nuclei are capable of integrating information from the genital organs and eliciting reflexive erections. This same spinal network receives supraspinal information leading to harmonious integration of sensory/motor inputs/outputs to optimize sexual performance.

Thus, sexual desire and behavior is regulated through complex central and

peripheral neural networks that are hard-wired through the entire body but principally through the telodiencephalic reproductive complex and genital organs. Androgen and estrogen receptors are most highly concentrated in these areas.
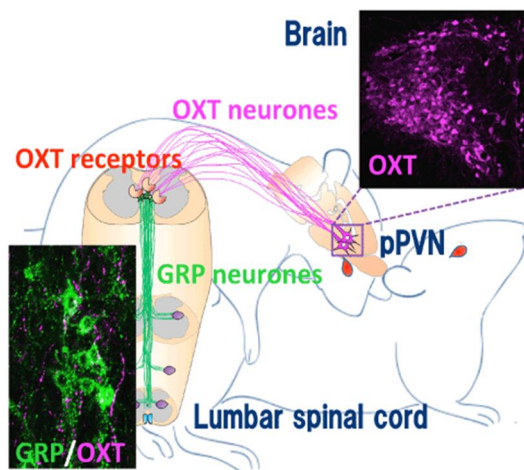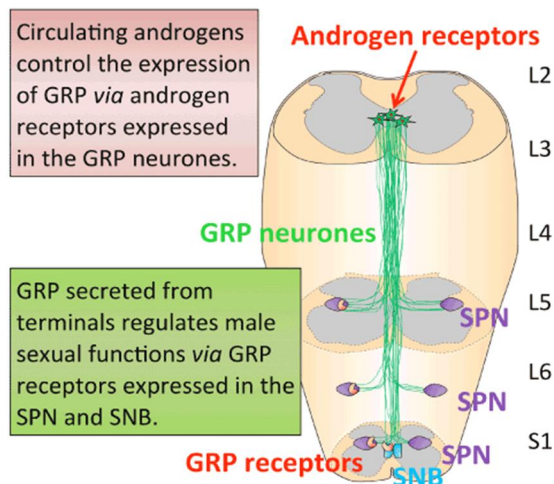




**Figure 4.** A schematic presentation of the gastrin-releasing peptide system (Upper image), which controls male sexual functions in the lumbar spinal cord. A sexually dimorphic spinal cord system of gastrin releasing peptide-containing neurons in the lumbar spinal cord (at the L3–L4 level) – 'the ejaculation center' – projects axons to the autonomic center (sacral parasympathetic nucleus) and to the somatic center (spinal nucleus of the bulbocavernosus) in the lower lumbar spinal cord. These centers regulate penile reflexes and trigger ejaculation via gastrin releasing peptide receptor-mediated mechanisms. Oxytocin – gastrin releasing peptide system (below image), which controls male sexual functions in the lumbar spinal cord. Hypothalamic oxytocinergic efferents trigger ejaculation via an oxytocin receptor-mediated mechanism in the spinal gastrin releasing peptide system during male sexual behavior. Key: GRP – gastrin-releasing peptide; OXT – oxytocin; pPVN, parvocellular part of the hypothalamic paraventricular nucleus; SNB - spinal nucleus of the bulbocavernosus; SPN - sacral parasympathetic nucleus (illustration used with permission from Sakamoto *et al.,* 2012).

Female rodents adopt a sexually receptive posture, referred to as lordosis, which allows the male to mount and intromit. The ventromedial nucleus of the hypothalamus is an essential brain region for executing this behavior. If the ventromedial nucleus of the hypothalamus is damaged or destroyed, the female will not exhibit sexual receptivity. The estrogen receptor expressing neurons of the ventromedial nucleus of the hypothalamus then project to the estrogen sensitive neurons of the midbrain central gray, and those neurons project down to the spinal cord, thus activating the motor neurons which innervate the critical spinal muscle groups. Thus the behavioral flexibility and cognitive solicitations that female rats engage in, involve the interplay between the medial preoptic area and the ventral medial nucleus of the hypothalamus, mesolimbic systems, and cortical activation.

Pfaff and colleagues elucidated the cellular targets for steroid hormones in the hypothalamus and limbic forebrain neurons. Knocking out the gene for the estrogen receptor in animals prevents female reproductive behavior. Progesterone can turn on genes, through estrogen, in the forebrain that in turn modulates reproductive behavior (Pfaff *et al.,* 1994).

Pfaff and colleagues recently proposed that sexual arousal precedes sexual motivation and understanding neuroanatomical, neurophysiological and molecular properties of the reticular neurons within the nucleus gigantocellularis of the mammalian medulla is critical. Generalized arousal is central to understanding how motivated behaviors such as satisfying the hunger urge, quenching thirst and sexual behaviors arise (Pfaff *et al.,* 2012; Schober *et al.,* 2011). A portion of what has been described above is schematically presented below. Table 1 below summarizes anatomical sites and neurotransmitters coordinating sensory input and subsequent changes in sexual desire.
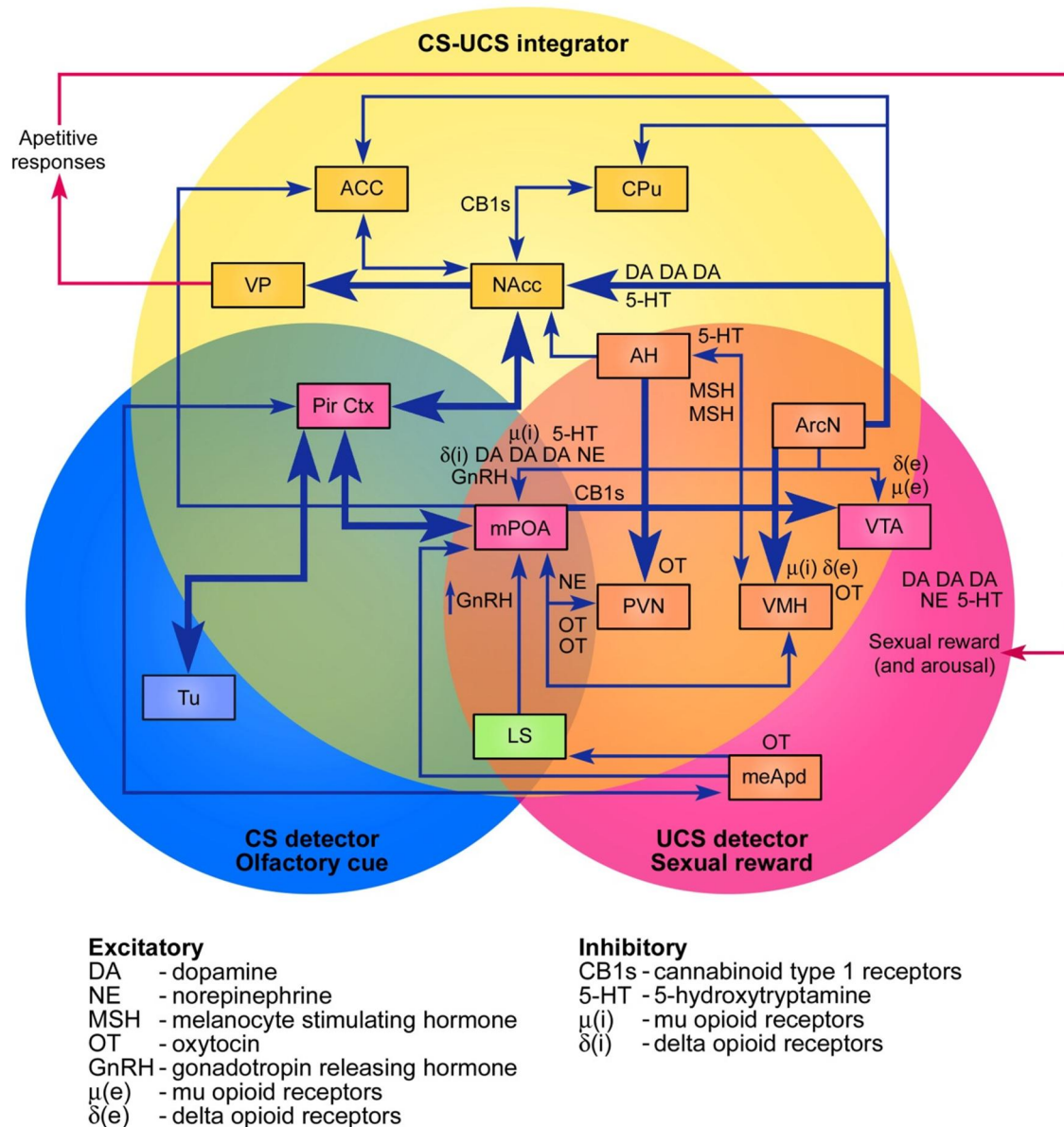
**Figure 5.** The neural correlates for the sensory inputs and learned behavior affecting sexual desire. The brain learns to reinforce behavior that brings about reward. Notice how well the brain is organized to maximally exploit available sensory information, namely, tactile, olfactory, visual, vestibular and auditory. Three common regions, the piriform cortex, medial preoptic area, and ventral tegmental area, are activated in male and female rats by conditioned olfactory stimuli. Opioid actions in the ventral tegmental area potentiate mesolimbic dopamine activation, whereas opioid action in the medial preoptic area inhibits sexual arousal and desire. Red are excitatory for sexual motivation whereas blue are inhibitory. Opioids can be excitatory in the ventral tegmental area, inhibitory in the medial preoptic area, or either in the ventromedial nucleus of the hypothalamus. Dopamine, gonadotropin releasing hormone, melanocyte stimulating hormone, noradrenaline, and oxytocin are excitatory whereas serotonin, opioids, and the endocannabinoids are inhibitory. Key: CS - conditioned stimulus; UCS - unconditioned stimulus; ACC - anterior cingulate cortex; AH – anterior hypothalamus; ArcN - arcuate nucleus of the hypothalamus; CPu - caudate putamen (striatum); LS - lateral septum; MeApd - posterior-dorsal nucleus of the medial amygdala; mPOA - medial preoptic area; NAcc - nucleus accumbens; Pir Ctx - piriform cortex; PVN - paraventricular nucleus of the hypothalamus; Tu - olfactory tubercle; VMH - ventromedial nucleus of the hypothalamus; VP - ventral pallidum; VTA - ventral tegmental area; Modified from Georgiadis *et al.,* 2012; also see Pfaus *et al.,* 2012, page 49; Pfaus *et al.,* 2010 (illustration modified by David Mottet).

**Table 1.** Anatomical sites and neurotransmitters coordinating sensory input and subsequent changes in sexual desire. Key: AH – anterior hypothalamus; CB1s – cannabinoid type 1 receptors; δ (e) – delta excitatory opioid receptors; δ (i) – delta inhibitory opioid receptors; DA – dopamine; 5-HT – 5-hydroxytryptamine; GnRH – gonadotropin releasing hormone; MeApd - posterior-dorsal nucleus of the medial amygdala; mPOA - medial preoptic area; MSH – melanocyte stimulating hormone; μ(e) – mu excitatory opioid receptor; μ(i) – mu inhibitory opioid receptor; NAcc - nucleus accumbens; NE – norepinephrine; OT – oxytocin; PVN - paraventricular nucleus of the hypothalamus; VMH - ventromedial nucleus of the hypothalamus; VTA - ventral tegmental area; NT-Neurotransmitter.

| NT | AH | MeApd | mPOA | NAcc | PVN | VMH | VTA |
|------|----|-------|------|------|-----|-----|-----|
| DA   |    |       | E    | E    |     |     | E   |
| NE   |    |       | E    |      | E   |     | E   |
| MSH  | E  |       |      |      |     |     |     |
| OT   |    | E     |      |      | E   | E   |     |
| GnRH |    |       | E    |      |     |     |     |
| μ(e) |    |       |      |      |     |     | E   |
| δ (e)|    |       |      |      | E   | E   |     |
| CB1s |    |       |      | I    |     |     | I   |
| 5-HT | I  |       | I    | I    |     |     | I   |
| μ(i) |    |       | I    |      | I   |     |     |
| δ (i)|    |       | I    |      |     |     |     |

## Where in the brain and how is sexual motivation processed?

The genesis of sexual motivation begins with the arrival of sexually stimulating sensory signals at the hub of the telodiencephalic reproductive complex, called the medial preoptic area. Signals can also be generated internally through volitional imagery or recall of past events in the case of humans. In humans, the medial preoptic area receives highly processed somatosensory information from cortical association areas via the hippocampal formation and amygdaloid complex. This is, in part, accomplished through the cingulate neurons that receive afferents from the association cortices and form neocortico-temporo-hippocampal projections. From the hippocampus, the hippocampo-hypothalamic projections reach the lateral septum and the amygdalo-hypothalamic projections reach the Bed nucleus of the stria terminalis where they pass through synaptic relays. The signals then reach their final destination, the medial preoptic area. The medial preoptic area also integrates information from the ventromedial nucleus of the hypothalamus, suprachiasmatic nucleus, infundibular nucleus, ventral

premammillary nucleus and projects information to the nucleus of the diagonal band of Broca. Collectively, this neural network is called the telodiencephalic reproductive complex.

The amygdaloid complex also carries olfactory information derived from the main and accessory olfactory systems. The accessory olfactory or vomeronasal system comprises the vomeronasal organ, vomeronasal nerve and the accessory olfactory bulb. Signals from the vomeronasal system are carried through the medial amygdaloid nucleus. The vomeronasal system is specialized in the transduction of perhormonal information (Luo *et al.,* 2003). Perhormone is thought to mediate the detection of most gender and species-specific cues involved in the control of mating behavior (Dulac and Torello, 2003).

The Bed nucleus of the stria terminalis together with the medial amygdaloid nucleus transduces steroid signals from the gonads and transmits chemosensory signals to the medial preoptic area to control the expression of copulatory behavior (Wood and Swann, 1999, p. 423-444; 2005). These regions are also activated conditionally by main olfactory and somatosensory cues associated with sexual reward in male and female rats.

Lesions of the Bed nucleus of the stria terminalis reduce chemo-investigation (Powers *et al.,* 1987), while exposure to female hamster vaginal secretions stimulates Fos expression in the Bed nucleus of stria terminalis (Fiber *et al.,* 1993). The Bed nucleus of the stria terminalis contains receptors for the gonadal steroids, androgen and estrogen (Wood and Newman, 1995a; Wood *et al.,* 1992) and steroids placed in the Bed nucleus of stria terminalis enhance mating behavior in castrated males (Wood and Newman, 1995b).

In mammals, perhormonal communication plays an important role in reproductive behavior but in humans, this system is vestigial (Bjarnadóttir *et al.,* 2005). Although perhormonal products are thriving in the market place, science is yet to prove the commercial value of these products.

Gonadotropin releasing hormone is released within this reproductive complex (median eminence), and gonadotropins are carried through the hypothalamo-hypophyseal portal system to the anterior pituitary, where they stimulate the synthesis and secretion of

luteinizing hormone and follicle stimulating hormone. Gonadotropin-producing cells are widely scattered throughout the hypothalamus and nearby basal telencephalic regions, about half of these neurons in the preoptic and basal telencephalic regions project to the median eminence. The telodiencephalic reproductive complex is where gonadotropin producing cells are widely scattered and this is also where receptors for androgen and estrogen are highly concentrated. Gonadal steroid hormones and gonadotropin releasing hormone regulate each other through a feedback regulation.

Steroid hormone actions are divided between the classic intracellular receptor-mediated genomic actions which involve interaction with DNA and induction or inhibition of gene transcription that transform downstream neurotransmitter and receptor up-or-down regulations, and the nonclassical membrane mediated effects that are rapid and involve second messenger systems and/or changes in ion flux (Boulware and Mermelstein, 2005; 2009; Gronemeyer, 1991; Mermelstein, 2009; Mermelstein and Micevych, 2008; Mermelstein *et al.,* 1996, Micevych and Mermelstein, 2008). It is now understood that within the telodiencephalic system steroids can act through the classic slow genomic effects as well as via membrane mediated fast actions (McCarthy, 1995; Micevych and Mermelstein, 2008). During the reproductive period, cells within the telodiencephalic reproductive complex show increased number of steroid receptors and matched gonadal steroid hormone concentration. The highly concentrated gonadal steroid hormones are essential in this part of the brain because so many biological functions depend on the presence of these hormones.

The magnocellular nucleus of the medial preoptic area is separated from the traditional medial preoptic nucleus and surrounded by the medial preoptic area; the cells in this nucleus express estrogen receptor α. The majority of the afferents come from the hypothalamus and the amygdala but it also receives input from the rest of the telodiencephalic reproductive complex (Wang and Swann, 2006). Once afferent chemosensory signals reach this nucleus, the signals are reinforced by gonadal hormonal cues as well as the somatosensory signals coming from the genitalia (Ju *et al.,* 1987). This afferent network is critical for male mating behavior. The genesis of sexual desire begins here in both male (Hull, 2011) and female (Graham and Pfaus, 2012) rodents.

Through a series of published papers Sakuma and colleagues also presented evidence that neurons in the preoptic area are activated during precopulatory motivational behavior. An increase in locomotion in females in estrus, which apparently depends on estrogen-sensitive preoptic area projections to the midbrain locomotor region, has been considered to embody enhanced sexual motivation (Kato and Sakuma, 2000; Sakuma, 1995, 2008). Sakuma further demonstrated evidence of differential control of proceptive and receptive components of female rat sexual behavior by the preoptic area (Sakuma, 1995, this is printed in Japanese but English version can be found through Google search).

Microdialysis experiments have shown that elevated dopamine levels in the medial preoptic area at the time sexual receptivity is initiated by hormonal priming in females. In addition, there is a further increase in dopamine release when the male and female rats are allowed to copulate, but not when they are physically separated. This is an argument for a physiological role of dopamine in the appetitive phase of sexual behavior in female rats (Matuszewich *et al.,* 2000).

Specific tests have been developed to discriminate the appetitive from the consumatory component of sexual behavior, such as the bilevel chambers. In this test, the male rat chases the female from one level to another after each intromission. The number of level changes in a fixed time before the introduction of the female is considered a measure of the anticipatory phase (or motivation) of sexual activity. Such tests evidenced that dopamine plays a role in the anticipatory or appetitive phase of the sexual behavior in male rats (Giuliano and Allard, 2001; Pfaus and Everitt, 1995).

Instrumental measures of sexual motivation were achieved by training males to work for an estrus female, presented in an operant chamber under a second-order schedule of reinforcement. The medial preoptic area lesions abolished mounts, intromissions and ejaculation, but did not disrupt instrumental responses. Castration abolished attempts to copulate and also caused a marked decrease in instrumental responses. Testosterone resulted in the prompt

reinstatement of instrumental responses and more gradual recovery of unconditioned sexual behavior. The early assumption that the medial preoptic area lesioned animals are sexually uninterested or unaroused by a female in heat has been questioned by a series of observations of the sexual and associated behaviors that survive medial preoptic area lesions (Everitt and Stacey, 1987; Hansen and af Hagelsrum, 1984; Hansen *et al.,* 1982; Hart, 1986; Ryan and Frankel, 1978; Slimp *et al.,* 1978).

Measurement of instrumental behavior under the second order schedule of sexual reinforcement, behavior that is an expression of sexual interest that does not depend on consummatory competence, has provided further evidence that medial preoptic area lesioned male rats are not sexually unarousable or disinterested. Rather, with their having worked to gain access to a female and investigated and pursued her, it is the capacity to display the consummatory responses of mounting and intromission on proximal contact with a female that is impaired.

Thus, instrumental and consummatory responses are dissociated by the lesion and focus attention more clearly on the nature of the deficit induced by it (Everitt and Stacey, 1987). This deficit appears, therefore, to be of a performance rather than a motivational/arousal nature (Beach, 1956), and indicates that an important function of the preoptic area in regulating the expression of sexual behavior in the male rat may be to engage the neural mechanisms that subserve thrusting and other genitopelvic copulatory reflexes that are believed to be located in the brain stem and spinal cord (Everitt and Stacey, 1987; Hansen, 1982; Hansen and af Hagelsrum, 1984; Hansen *et al.,* 1982).

There have been attempts to assess the motivational effects of sex steroids by using various forms of instrumental techniques. Warner (1927) reported that willingness of male rats to cross an electrified grid to gain access to a female was reduced by castration, whereas females tolerated more intense levels of shock at estrus than at diestrus to gain access to a male.

Replacement of testosterone to the long-term castrate produced results that more clearly support an effect on a motivational process. In the first session following replacement, males showed a marked increase in their willingness to work for a female so that their response rates did not differ from those of controls or from their own precastration performance recorded 14 weeks earlier. Here then is direct evidence to suggest that testosterone exerts effects on the male's behavior that are independent from an improvement in consummatory competence – effects, therefore, on incentive motivation that govern appetitive responses, such as those measured under the second-order schedule (Everitt, 1990; Everitt and Stacey, 1987).

The hypothesis that brain areas mediating copulation are independent of those mediating sexual motivation has been supported in recent studies of appetitive sexual behavior. For example, castration of male rats abolishes an acquired preference for an environment previously paired with receptive female rats, whereas lesions of the medial preoptic area do not (Alexander *et al.,* 1994; Hughes *et al.,* 1990). In contrast, 6-hydroxydopamine lesions of the mesolimbic brain dopamine system have produced deficits in appetitive sexual behavior but not in copulatory behavior (Alexander *et al.,* 1994; Everitt, 1990).

## Role of neurotransmitters and modulators in the regulation of sexual motivation
### Dopamine

Dopamine within the medial preoptic area and ventromedial nucleus of the hypothalamus plays an important role in rodent sexual behavior. Dopamine in these areas originates from the diverse dopamine cell groups located in the midbrain. These include periventricular A14 group. Traditionally, incertohypothalamic dopamine cell group (A 13) was believed to be the source of dopamine in the hypothalamic nuclei (Moore and Looklingland, 1995) but recent study suggested that only a few dopamine cells in the A 13 reach these nuclei. No single cell group seems to be providing majority of axonal afferents to these nuclei. More than half come from outside the A 8-15 dopamine cell group (Miller and Lonstein, 2009).

Medial preoptic area lesions disrupt male sexual behavior in all vertebrate species that have been studied (Hull and Rodriguez-Manzo, 2009). There is a close correlation between male rat sexual behavior and

extracellular dopamine levels in the medial preoptic area (Hull, 2011). Dopamine is released in the medial preoptic area of male rats in response to an estrous female and during copulation (Hull *et al.,* 1995).

In Japanese quails, higher pre-copulatory levels of dopamine in the medial preoptic area predict higher frequency of the consummatory response (Kleitz-Nelson *et al.,* 2010a). Kleitz-Nelson and colleagues also found an increase in dopamine levels in the medial preoptic area in the presence of a female quail, which returned to baseline after removal of the female. However, there was only a rise in dopamine in quail who copulated, suggesting that dopamine action in the medial preoptic area is directly related to sexual motivation as well as copulatory behavior (Kleitz-Nelson *et al.,* 2010b).

The recent presence of testosterone was necessary for both dopamine release and copulation. Intact males, testosterone-treated castrates, and oil-treated castrates that copulated showed a pre-copulatory dopamine increase, which was maintained or increased further during mating (Hull *et al.,* 1995; Sato and Hull, 2006). Oil-treated castrates that did not copulate did not show the increase. There was both behavioral and anatomical specificity for the dopamine response. Furthermore, the fact that dopamine increased before mating began suggests that the increase was not caused by copulation, but was probably associated with sexual motivation (Hull, 2011). Testosterone treatment for two days did not restore mating or the dopamine response; most of the five-day testosterone-treated castrates were able to copulate and showed a dopamine response, with half of them able to ejaculate**,** but all of the castrates treated with testosterone for 10 days copulated to ejaculation, and all showed the dopamine response (Putnam *et al.,* 2001). There were again numerous correlations between copulatory measures and dopamine levels. Therefore, both the loss of copulation following castration and its restoration by testosterone are closely associated with the medial preoptic area dopamine response to an estrous female (Hull, 2011).

Although extracellular levels of medial preoptic area dopamine are lower in castrates than in gonadally intact males, intracellular levels are actually higher than in intact males (Du *et al.,* 1998). Indeed, there was a negative correlation between tissue (stored) dopamine levels and the ability to copulate (Putnam *et al.,* 2005). Therefore, synthesis and storage of dopamine in the medial preoptic area is at least as great in castrates as in intact males; the deficiency in castrates is not in their ability to synthesize and store dopamine, but rather in their ability to release their abundant stores.

Studies have shown that dopamine release patterns in the medial preoptic area and nucleus accumbens of male rats during copulation are virtually identical (Blackburn *et al.,* 1992; Pfaus, 2009)**,** suggesting functional relationships between the two regions as described below.

Lesions of the medial preoptic area disrupt certain appetitive behaviors, such as solicitation in female rats or sexually rewarded maze learning in male rats, and abolish the initiation of copulation in male rats and the timing of pacing and lordosis in female rats (Hoshina *et al.,* 1994; Paredes and Baum, 1997). Lesions of the nucleus accumbens disrupt the ability of distal sexual cues to elicit sexual arousal in male rats (Kippin *et al.,* 2004; Liu *et al.,* 1998) and disrupt approach behavior in female rats (Guarraci *et al.,* 2002). These study results suggest that sexual motivation is significantly linked to the nucleus accumbens but consummatory behavior is closely associated with medial preoptic area for males and ventral medial nucleus of hypothalamus for females (lordosis) (Pfaus, 2009). Furthermore, the medial preoptic area is critical for female solicitations and hops and darts, not the ventromedial nucleus of the hypothalamus. So the same neurochemical systems in the medial preoptic area that give rise to erection and ejaculation in male rats, give rise to solicitations in females.

Estradiol facilitates dopamine release, and testosterone potentiates the synthesis of nitric oxide that controls dopamine release in rats (Becker, 1990; Sanderson *et al.,* 2008; Sato *et al.,* 2005). Thus, steroid hormones appear to set the stage for increased dopamine synthesis and release during periods in which sexual responding might be enhanced. Like humans, male and female rats display increased motor output in anticipation of sexual rewards. These measures of anticipatory excitement can be increased by treatments that increase the incentive salience of the sex partner and by dopamine agonist

drugs or other psychomotor stimulant drugs (Pfaus, 2009).

These measures can be reduced by systemic treatment with dopamine antagonists or by direct microinjection of a dopamine antagonist into the medial preoptic area or nucleus accumbens. All animals will work to obtain sexual rewards, and such behavior can be viewed as analogous to desire. Sexual rewards may come in the form of primary reinforcers (e.g., orgasm in humans, ejaculation in male rats, or the ability to regulate or "pace" copulation in female rats) or secondary reinforcers, such as stimuli associated with sexual gratification (Pfaus, 2009).

Hull and colleagues have stated that the desire/ejaculation (D1/D2) receptor ratio in the medial preoptic area of male rats is critical for the stimulation of sexual arousal and D1 and D2 through integrated control of behavior and autonomic processes (Hull *et al.,* 1989). This makes the coordinated activation of medial preoptic area and nucleus accumbens critical in the stimulation of sexual excitement. Interestingly, ejaculation decreases dopamine release precipitously in the medial preoptic area and nucleus accumbens, but not in striatum, of male rats (Blackburn *et al.,* 1992). This decline lasts through the absolute refractory period and is followed by a progressive increase during the relative refractory period, when arousing stimuli can activate copulation in male rats (Meisel and Sachs, 1994). Interestingly, in males that copulate to sexual exhaustion, dopamine in the nucleus accumbens reduces to precopulatory baseline levels (Fiorino *et al.,* 1997). Removal and reintroduction of the familiar female do not increase dopamine release, but placement of a new receptive female with a male results in a small increase. However, this increase is not of sufficient magnitude to induce a full copulatory response (Pfaus, 2009).

The stimuli from a receptive female or copulation itself leads to the release of dopamine in at least three integrative hubs. The nigrostriatal system promotes somatomotor activity; the mesolimbic system subserves numerous types of motivation; and the medial preoptic area focuses the motivation onto specific sexual targets, increases copulatory rate and efficiency, and coordinates genital reflexes. The previous

presence of testosterone is permissive for dopamine release in the medial preoptic area, both during basal conditions and in response to a female (Pfaus, 2009).

Behavioral sensitization induced by D-amphetamine administration cross-sensitized and facilitated sexual behavior in rats. D-amphetamine sensitized rats had a greater increase in dopamine efflux in the nucleus accumbens during copulation compared to nonsensitized control rats, suggesting the role of mesolimbic dopamine in motivated behaviors including sex (Fiorino and Phillips, 1999 a&b).

Some of the glutamatergic inputs to the medial preoptic area are from the medial amygdala and Bed nucleus of the stria terminalis, which mediate the female-stimulated increase in dopamine, which in turn enhances copulatory ability. Extracellular glutamate in the medial preoptic area increases during copulation, especially during ejaculation, and increased glutamate facilitates copulation and genital reflexes. Previous sexual experience also facilitates copulation. Experience enhances processing of sexual stimuli, and its effects require activation of glutamate NMDA receptors and nitric oxide in the medial preoptic area (Hull and Dominguez, 2006).

Testosterone, glutamate, nitric oxide and previous sexual experience promote medial preoptic area dopamine release and mating. Dopamine in the nucleus accumbens augments motivation but dopamine in the lateral hypothalamus dampens motivated behaviors.

*Norepinephrine*
Central noradrenergic systems play a vital role in general arousal and in the control of autonomic outflow. Cell bodies arise in the locus coeruleus at the border of the midbrain and brain stem and project to virtually all forebrain regions, including the hypothalamus, limbic and motor systems, and cortex (Moore and Bloom, 1979). Norepinephrine binds to two classes of receptors, classically termed "α" and "β," respectively, and differentiated according to whether the receptor stimulates (β) or inhibits (α) the stimulation of the second messenger adenylate cyclase (Cooper *et al.,* 1991). The receptors are further classified into $a_1$ and $a_2$ subtypes, which are found either

postsynaptically or presynaptically, respectively. Thus, actions of norepinephrine at $a_1$ receptors result in a postsynaptic effect, whereas actions at presynaptic $α_2$ receptors serve as a short-loop inhibitory feedback mechanism that reduces norepinephrine release. Drugs such as clonidine that act as $α_2$ agonists reduce norepinephrine release and lead to less sympathetic tone and sedation, whereas drugs such as yohimbine that act as $α_2$ antagonists block the ability of endogenous norepinephrine to induce inhibitory feedback and thus result in sustained noradrenergic tone.

Estradiol increases norepinephrine synthesis in the brains of female rats (Ramírez and Carrer, 1982), and norepinephrine transmission in the ventromedial hypothalamus potentiates lordosis in female rats (Fernández-Guasti et al., 1985; Kow and Pfaff, 1988). Estradiol also suppresses $α_1$ noradrenergic receptor densities in the medial preoptic area of female rats (Weiland and Wise, 1987). Although systemic administration of the $α_2$ agonist clonidine to sexually inactive, castrated male rats does not stimulate copulation (Malmnäs, 1973), it decreases the proportion of gonadally intact, sexually active male rats that achieve ejaculation (Clark and Smith, 1990).

In women, clonidine reduces the vaginal response to erotic stimuli (Meston et al., 1997). Administration of the $α_2$ antagonist yohimbine stimulates penile erection in male rats and in men via autonomic activation (Allard and Giuliano, 2001) and can reverse the sexual inhibition that follows sexual exhaustion in male rats (Rodríguez-Manzo and Fernández-Guasti, 1994).

Yohimbine increases the rate of mounting in male rats (Clark, 1995) except at high doses where it inhibited mounting altogether. Conversely, lesions of noradrenergic cells in the locus ceruleus increase the postejaculatory refractory period of male rats, and administration of norepinephrine synthesis inhibitors like sodium diethyldithiocarbamate increases the mount and intromission latencies, suggesting a decrement in sexual desire (McIntosh and Barfield, 1984). It is likely that decreased noradrenergic tone could easily account for decreases in sexual desire owing to insufficient general arousal. This may play a role in the manifestation of decreased sexual desire in

generally hypoarousable individuals (Pfaus, 2009; Pfaff et al., 2012; Schober et al., 2011).

*Serotonin*

Serotonin release within the medial preoptic area does not seem to alter sexual behavior significantly. However, serotonin release in the lateral hypothalamus at the time of ejaculation seems to impair male copulation (Lorrain et al., 1997). This has clinical relevance because SSRIs often inhibit sexual performance (Delgado et al., 2005; Montejo et al., 2001). Earlier, Zemlan and his colleagues (1977) reported that systemic increases in serotonin were associated with female sexual dysfunction. Lorraine and colleagues reported that serotonin levels in the anterior lateral hypothalamus were increased after ejaculation (Lorrain et al., 1997) and increased release of serotonin in the lateral hypothalamus decreased dopamine release in the nucleus accumbens (Lorrain et al., 1999). Serotonin in the perifornical lateral hypothalamus inhibits sexual behavior by inhibiting orexin neurons, which normally stimulates neurons in the mesocorticolimbic dopamine tract (Hull, 2011). This finding may explain postejaculatory quiescence or lack of energy reported by patients taking SSRIs.

Serotonin is associated with the inhibitory feedback of sexual satiety during the postejaculatory interval after ejaculation (Bitran et al., 1987; Mas et al., 1987; McIntosh et al., 1984). The relationship between serotonin and lordosis behavior in female rats is well documented (Frankfurt et al., 1994), indicating an inhibitory role of serotonin in female sexual behavior such as lordosis response (Allen et al., 1993; Uphouse, 2000).

In female rats, SSRI-treated females had sexual dysfunction such as increased escape behavior and decreased active investigation of the male (Adams et al., 2012). In male rats, subchronic administration of SSRI significantly reduced sexual motivation and increased ejaculatory latency (Vega Matuszcyk et al., 1998). Even maternal exposure to SSRI during pregnancy and lactation decreased sexual motivation of male pups (Gouvêa et al., 2008).

In human studies, 41% of patients on SSRIs reported sexual dysfunction such as decreased desire, orgasmic dysfunction, or ejaculatory dysfunction (Landen et al., 2005). In another study, SSRI paroxetine and

sertraline significantly increased intravaginal ejaculation latency time (Waldinger *et al.,* 2001).

### Melanocortins

Neuropeptides derived from proopiomelanocortin include β-endorphin, adrenocorticotrophic hormone, and α-melanocyte stimulating hormone. The latter two bind to different melanocortin receptors of which at least five types exist (Voisey *et al.,* 2003). Of those, the melanocortin receptor 3 and 4 subtypes exist in hypothalamic and limbic regions of the mammalian brain (Oosterom *et al.,* 1999). Cell bodies of this system arise in the arcuate and periarcuate nuclei near the base of the third ventricle in the hypothalamus and project axons diffusely to the hypothalamus, limbic system, midbrain, and brain stem (Heisler *et al.,* 2003; O'Donohue and Dorsa, 1982). Estradiol increases α-melanocyte stimulating hormone levels in the mediobasal hypothalamus of female rats (Medina *et al.,* 1998; Wilson *et al.,* 1991), suggesting that α-melanocyte stimulating hormone release may be one of several intermediaries of estrogen action (Pfaus, 2009).

Recently, two melanocortin receptor agonists, melanotan-II and its metabolite bremelanotide (formerly PT-141), have been reported to stimulate both sexual arousal and desire in humans and rats following intranasal, intravenous, and subcutaneous administration (currently under clinical trial). Both melanotan-II and bremelanotide stimulate erection in sexually functional men and rats, and in men with erectile dysfunction (Diamond *et al.,* 2004; Hadley, 2005; Rosen *et al.,* 2004).

Melanocortin-II and bremelanotide increase measures of sexual desire, including solicitations and hops and darts in rats (Pfaus *et al.,* 2004; Rössler *et al.,* 2006) and subjective measures of desire in women (Diamond *et al.,* 2006; Hadley, 2005). The effectiveness of systemic melanocortin-II and bremelanotide to stimulate sexual desire in female rats has been replicated following infusions to the lateral ventricles of the brain and following infusions directly to the medial preoptic area (Pfaus *et al.,* 2007). Interestingly, systemic administration of bremelanotide stimulates dopamine release selectively in the medial preoptic area, and its effect on solicitations is blocked by coadministration of a selective melanocotin receptor 4 antagonist or $D_1$ antagonist (Pfaus *et al.,* 2007). This suggests that melanocortins act presynaptically to increase dopamine release in the medial preoptic area and that such release acts on $D_1$ receptors there to facilitate sexual desire. It is not yet known whether this mechanism also controls the induction of penile erection.

### Oxytocin

Oxytocin is a neuropeptide that has been identified as a "bonding hormone" in both sexual and parental behavior (Carter *et al.,* 1992; Young and Wang, 2004). Oxytocin cell bodies are found in the paraventricular and supraoptic nuclei of the hypothalamus. Large, magnocellular neurons in those regions project to the posterior pituitary whereas small, parvocellular neurons project diffusely throughout the hypothalamus and limbic system. Infusions of oxytocin to the medial preoptic area or ventromedial hypothalamus facilitate lordosis behavior in female rats (Caldwell *et al.,* 1989; Schulze and Gorzalka, 1991), whereas infusions to the paraventricular nucleus of the hypothalamus of male rats stimulate penile erection (Kita *et al.,* 2006).

Systemic administration of oxytocin facilitates ejaculation in male rats treated chronically with fluoxetine (Cantor *et al.,* 1999; de Jong *et al.,* 2007). Conversely, infusion of an oxytocin receptor antagonist blocks bonding.

Sexual incentives activate oxytocin release in the brain of male rats (Hillegaart *et al.,* 1998), and neutral odors associated with sexual rewards activate parvocellular oxytocin neurons selectively in the paraventricular nucleus of the hypothalamus of male rats (Ménard *et al.,* 2005). Interestingly, stimulation of $D_2$ receptors in the paraventricular nucleus of the hypothalamus stimulates oxytocin release and increases extracellular dopamine levels in the nucleus accumbens (Succu *et al.,* 2007), suggesting another mechanism by which hypothalamic dopamine can integrate with mesolimbic dopamine through an oxytocin intermediary. It is also notable that the paraventricular nucleus of the hypothalamus receives a substantial neural projection from the medial preoptic area (Saphier and Feldman, 1986),

raising the possibility that the activation of the medial preoptic area can lead in sequence to the activation of the paraventricular nucleus of the hypothalamus.

Oxytocin induces penile erection and increases dopamine concentration in the nucleus accumbens. This oxytocin-induced penile erection is mediated by an activation of glutamatergic neurons projecting to the ventral tegmental area (Succu *et al.,* 2011). Oxytocin induces penile erection when injected into diverse areas such as the paraventricular nucleus of the hypothalamus, region $CA_1$ of the hippocampus, ventral tegmental area, ventral subiculum, and posteromedial cortical nucleus of the amygdale (Melis *et al.,* 2011). These complex neural pathways control penile erection, sexual motivation, and sexual rewards by modulating the activity of oxytocinergic neurons and mesolimbic dopaminergic neurons.

### Orexin

A group of neurons in the lateral hypothalamus produces the peptide orexin. Serotonin was previously reported to inhibit orexin neurons (Li *et al.,* 2002). Orexin is primarily known for its stimulation of feeding behavior (Kotz, 2006; Thorpe *et al.,* 2005) and control of sleep-wake cycles (Saper *et al.,* 2005; Sutcliffe and de Lecea, 2002). Orexin-containing neurons had previously been reported to project to the ventral tegmental area (Fadel and Deutch, 2002) the source of the mesocorticolimbic dopamine tract.

Furthermore, intra-ventral tegmental area administration of orexin was reported to increase dopamine release in the nucleus accumbens (Korotkova *et al.,* 2003; Narita *et al.,* 2006). Lateral hypothalamic neurons that were inhibited by post-ejaculatory serotonin might be those orexigen containing cells. Muschamp and colleagues showed that mating increased c-Fos-immunoreactivity in orexigen containing cells (Muschamp *et al.,* 2007). In addition, castration decreased the number of orexigen immunoreactive neurons, which were mostly restored by systemic injections of estradiol. Orexin is behaviorally relevant, as systemic administration of an orexin antagonist impaired copulation (Muschamp *et al.,* 2007). In addition, microinjection of orexin into the ventral tegmental area produced dose-dependent effects on dopaminergic cell firing.

Triple-label immunohistochemistry revealed that mating increased c-Fos immunoreactivity in dopaminergic neurons in the ventral tegmental area that were opposed to orexigen fibers. Therefore, orexin neurons appear to act in a steroid-dependent manner to activate the mesocorticolimbic dopamine pathway, thereby promoting sexual behavior and other natural and drug-induced rewards (Hull, 2011).

Conversely, other studies showed that orexin antagonist did not affect sexual motivation (Bai *et al.,* 2009) and orexin cell-specific lesions did not affect sexual performance or motivation (Di Sebastiano *et al.,* 2010, 2011). In this study, however, Di Sebastiano and colleagues showed that orexin lesion prevented formation of mating-induced conditioned place preference, suggesting that orexin may not be essential for sexual performance, but is critical for processing of sexual reward and conditioned cue-induced responses associated with sexual reward.

### Glutamate

Hull and colleagues have conducted a series of studies examining the role of glutamate within the medial preoptic area and its influence on copulation (Dominguez and Hull, 2010; Dominguez *et al.,* 2004; 2006; Hull, 2011; Hull and Dominguez, 2006; Muschamp *et al.,* 2004; Powell *et al.,* 2003; Vigdorchik *et al.,* 2012). These studies demonstrated evidence that glutamate augments dopamine action in the medial preoptic area and facilitates copulation.

In a series of studies, Pfaus and colleagues examined the role of glutamate in the ventromedial nucleus of the hypothalamus and found the inhibitory role of the glutamate receptors, both appetitive and consumatory, at the ventromedial nucleus of the hypothalamus (Georgescu and Pfaus, 2006 a&b; Georgescu *et al.,* 2009, 2012). Kow and colleagues also reported inhibitory effects of glutamate in the ventromedial nucleus of the hypothalamus but noted that inhibitory neural mechanisms were different from the facilitatory mechanisms (Kow *et al.,* 1985).

Kia and colleagues also reported colocalization of estrogen receptor α and NMDA-2D receptors, suggesting interactions between NMDA receptors and estrogen in amygdaloid and hypothalamic nuclei (Kia *et al.,* 2002). Blutstein and colleagues reported

evidence of increased glutamate mediated signal transduction within hypothalamus and hippocampus (Blutstein *et al.,* 2006). Orexin facilitates glutamate-mediated responses, and is necessary for glutamate-dependent long-term potentiation in ventral tegmental area dopamine neurons (Aston-Jones *et al.,* 2010).

### Androgen and estrogen

Instead of modulating individual signal transduction modes, androgen and estrogen enter into the intracellular nucleus and modify gene expression that leads to a vast array of structural and functional changes in preparation for satisfactory sexual performance. Receptor and neurotransmitter numbers, sensitivity, and ion channel conductance change dramatically under hormonal influence (Pfaff, 1999). Recent findings that estrogen binds to cell surface estrogen receptors have expanded the scope of knowledge in this area (Boulware and Mermelstein, 2005, 2009; Mermelstein and Micevych, 2008; Mermelstein *et al.,* 1996, 2009; Micevych and Mermelstein, 2008).

## Role of mesolimbic-mesocortical pathways in the regulation of sexual motivation

There are certain motivational actions that require the nucleus accumbens, especially in situations where reward is unpredictable, that is, when animals have to chase the rewarding object or have to move from distal to proximal. Lesions of the nucleus accumbens disrupt the ability of distal sexual cues to elicit sexual arousal in male rats (Kippin *et al.,* 2004; Liu *et al.,* 1998) and disrupt approach behavior in female rats (Guarraci *et al.,* 2002). These study results suggest that sexual motivation is significantly linked to the nucleus accumbens, but consummatory behavior is closely associated with the medial preoptic area for males and the ventral medial nucleus of hypothalamus for females (lordosis). The medial preoptic area is more of a center that coordinates the internal state with external contingencies. In general, dopamine within the medial preoptic area is critical for solicitations in females (Graham and Pfaus, 2010; Pfaus *et al.,* 2012). As summarized below, many studies have reported involvement of the nucleus accumbens in the regulation of sexual motivation.

Results from classical copulatory experiments support a positive involvement of dopamine in the nucleus accumbens in the anticipatory phase of sexual behavior (Giuliano and Allard, 2001).

Estrogen activation within the nucleus accumbens modulates motivational components of pacing behavior in rats (Xiao and Becker, 1997). Nucleus accumbens lesions increased the number of rejection responses to male mount attempts without modifying either receptivity estimated by lordosis reflex or soliciting behaviors (Rivas and Mir, 1990).

Copulation of sexually naive rats to one ejaculation results in sensitized dopamine release and greater induction of Fos (a marker of neuronal activation) in the nucleus accumbens in response to a female behind a screen, relative to males allowed to intromit only during their first experience or that remain sexually naive (Bialy and Kaczmarek, 1996; Bradley and Meisel, 2001; López and Ettenberg, 2002).

Males allowed repeated ejaculatory experiences with sexually receptive females have increased numbers of dendritic spines in the nucleus accumbens relative to males allowed one multiejaculatory experience. Males allowed 16 multiejaculatory experiences have increased glucose metabolism in limbic structures relative to sexually naive males or those allowed three multi ejaculatory experiences (Sakata *et al.,* 2002 a&b). Those data suggest that experience with ejaculation in males activates endogenous opioid reward systems and sensitizes mesolimbic systems associated with incentive motivation in male rats (Robinson and Berridge, 1993).

In contrast, 6-hydroxydopamine lesions of the mesolimbic brain dopamine system have produced deficits in appetitive sexual behavior but not in copulatory behavior (Alexander *et al.,* 1994; Everitt, 1990). Wood has reviewed involvement of complex a complex network of limbic nuclei (Wood, 1997).

Through a series of published studies Pfaus and colleagues examined neurotransmitter regulation within the nucleus accumbens. Sexual activity increases dopamine transmission in the nucleus accumbens and striatum of female rats (Pfaus *et al.,* 1995). Dopamine transmission increases in the nucleus accumbens of male

rats during their first exposure to sexually receptive female rats (Fibiger *et al.,* 1992; Wenkstern et al, 1993) and male rats (Damsma *et al.,* 1992; Pfaus *et al.,* 1990b).

Within the sex research literature, the roles of dopamine and glutamate, especially within the medial preoptic area, have been documented extensively. Interface between the medial preoptic area and nucleus accumbens have also been documented (Balfour *et al.,* 2004; Everitt, 1990; Pfaus *et al.,* 2012).

### Human studies

A direct measurement of serum testosterone level**s** in young men (who can express their feelings) showed that free testosterone levels were a strong predictor of sexual motivation and behavior. In order to separate hormonal from social effects on adolescent male sexual behavior, serum hormone assays were performed and questionnaire data on sexual motivation and behavior were collected on a representative sample of 102 boys in grades 8, 9, and 10 of a public school system. Free testosterone was a strong predictor of sexual motivation and behavior, with no additional contribution from other hormones. Including measures of pubertal development and age (indexing the effects of social processes) indicated no additional effects. Free testosterone, therefore, appears to affect sexual motivation directly and does not work through the social interpretation of the accompanying pubertal development (Udry *et al.,* 1985).

Young men's testosterone levels and their interest in visual sexual stimuli across three test sessions were measured within a 1 month period. Fifteen men aged 23-28 years viewed pictures of couples engaged in sexually explicit activity. Men's testosterone levels were assayed from blood spots obtained prior to viewing the pictures. Testosterone and viewing time were positively correlated. Testosterone level was strongly correlated with viewing time ($r=0.80$). This study demonstrated a direct but context dependent relationship between testosterone and sexual interest in healthy young males (Rupp and Wallen, 2007).

### Drug trials

Throughout history, palace "medicine men" have searched for the elusive aphrodisiacs for Kings, but the efforts have always ended in vain. The recent development of phosphodiesterase inhibitors has provided some relief for men but these agents are primarily aimed at erectile dysfunction. Many men, especially females with hypoactive sexual desire disorder need clinically proven agents that enhance sexual desire; however, almost all of the industry drug trials in this field have failed.

Currently, there is no proven FDA approved drug that enhances sexual motivation for male**s** or female**s** (except gonadal steroid preparations) even though the basic science knowledge in this field is deep. The molecular mechanisms of animal sexual motivation within the medial preoptic area are well established**.** (Alexander *et al.,* 1994; Becker, 1990; Blackburn *et al.,* 1992; Edwards and Einhorn, 1986; Erskine, 1989; Everitt and Stacey, 1987; Giuliano and Allard, 2001; Graham and Pfaus, 2010; Hansen and af Hagelsrum, 1984; Hansen *et al.,* 1982; Hart, 1986; Hoshina *et al.,* 1994; Hull, 2011; Hull and Rodriguez-Manzo, 2009; Hull *et al.,* 1995, 1989; Hughes *et al.,* 1990; Kato and Sakuma, 2000; Matuszewich *et al.,* 2000; Melis and Argiolas, 1995; Meisel and Sachs, 1994; Paredes and Baum, 1997; Pfaus, 1999 a&b, 2009; Pfaus and Everitt, 1995; Pfaus and Heeb, 1997; Pfaus *et al.,* 1990a, 2009, 2012; Pfaus and Phillips, 1991; Ryan and Frankel, 1978; Sachs and Meisel, 1988; Sakuma, 1995, 2008; Sanderson *et al.,* 2008; Sato and Hull, 2006; Sato *et al.,* 2005; Slimp *et al.,* 1978; Stefanick and Davidson, 1987).

Here we wish to review the historical background that may have contributed toward delayed development of the agents that are aimed at sexual desire disorders.

Through evolution, the human medial preoptic area connectivity and molecular regulation seem to have diverged from those of animals. One of the most noticeable changes can be seen in the vomeronasal organ and its afferent innervation to the Bed nucleus of the stria terminalis (Lesur *et al.,* 1989) and medial preoptic area. In animals, this organ provides powerful olfactory sensory inputs to the medial preoptic area that leads to proceptive behavior (Dulac and Torello, 2003; Luo *et al.,* 2003). In humans, this organ seems to have lost its function. There are clearly some hormonal/pheromonal inputs that do alter neuronal functioning (e.g., Preti *et al.,* 2003, Savic *et al.,* 2005).

Secondly, in animals, sexual motivation is primarily processed in the behavioral control column (Nieuwenhuys *et al.,* 2008) or in a series of cell masses within the preoptico-hypothalamic zone, most notably in the medial preoptic area. From an evolutionary standpoint, this is the most primitive part of the brain that regulates ingestive, agonistic and reproductive behavior. Additionally, there is increasing evidence that motivation is not only related to the previously mentioned areas, but also in the limbic system (e.g., amygdala, nucleus accumbens, and septum) and cortex (cingulate, piriform, and frontal). The motivation cue processing is different in some ways from that of the hypothalamus, but it ultimately generates wanting and liking, both of which are critical from an incentive motivational perspective.

The control column faithfully controls designated missions, but the missions are carried out under the predetermined animal instinct. For example, reproductive mission is carried out not through a voluntary choice but through instinctual forces. If animal sexual desire is generated within the medial preoptic area the desire needs to mediate a copulation strategy to copulation. But, within this structure, there is no such mechanism to develop a strategy. So, animals are forced to follow specific proceptive behavioral patterns such as hops and darts, ear wiggling or pacing. This suggests marked spatial and temporal limitations in accomplishing the copulation goal. In other words, without perhormone scent or hops and darts, rats have a limited chance of accomplishing copulation. Humans do not seem to possess either, yet humans have the most flexible and vastly improved opportunities to accomplish sexual goals (see below). Rats can also use a variety of non-hormonal or pheromonal cues, which are learned by Pavlovian associations, to determine the sexual status of a partner.

If human sexual motivation is generated in the medial preoptic area how might humans guide the motivation? The medial preoptic area and hypothalamus are tightly linked to the rest of the limbic system called the telodiencephalic reproductive complex (Nieuwenhuys, 2008). As such, the nucleus accumbens is an integral part of the reproductive system. It seems that without the vomeronasal organ and somatic motor pattern generator (hops and dart), humans began to incorporate the nucleus accumbens to enrich

and accomplish their reproductive goal (hypothesis).

The incorporation of the nucleus accumbens changes the scope of reproductive behavior significantly. As mentioned earlier (see the Neural basis of non-sexual desire section) the nucleus accumbens is the anatomical crossroad where signals coming from the medial prefrontal cortex (goal oriented strategies), basolateral amygdala (cue related sensory inputs), ventral subiculum (contextual memories), brain stem nucleus (incentive signals) are integrated (Sesack and Grace, 2010, see pages 31-33; Humphries and Prescott, 2010). Thus, the scope of maneuverability and adaptational value is vastly improved in comparison to the animal signals that come from the prelimbic area or area 32 in the case of monkeys (also see the papers on the limbic system by Pfaus, 2009; Pfaus *et al.,* 2010).

Humans have Brodmann areas 9, 46 and 10. Brodmann area 10 is a "treasure house" when it comes to accomplishing goals (Burgess *et al.,* 2007; Charron and Koechlin, 2010; Gilbert *et al.,* 2006; 2007; 2010; Koechlin and Hyafil, 2007; Koechlin *et al.,* 1999, 2003; Kouneiher *et al.,* 2009; Okuda *et al.,* 2011; Ramnani and Owen, 2004).

Haber stated "Tracer injections into dorsal and lateral area 10 projects to the medial wall of the rostral caudate (Ferry et al, 2000). Based on these data, one might assume that the medial and ventral area 10 would terminate in the nucleus accumbens. Thus, the nucleus accumbens in primates receives input most likely from area 10" (Haber and Knutson, 2010, see page 8). This suggests a direct anatomical innervation from the Brodmann area 10 to the nucleus accumbens. This is in contrast to what some authors have argued that the frontal pole region is connected only to other supramodal areas in the prefrontal cortex (Burgess *et al.,* 2007; Ramnani and Owen, 2004). All human dreams have traversed through this passage; genesis and fulfillment of sexual desire have left irreversible marks on this road.

The concept of self and the concept of future comes from this area (Buckner *et al.,* 2008; Christoff *et al.,* 2011; Gusnard and Raichle, 2001; Raichle, 2010; Raichle *et al.,* 2001). Rats or monkeys do not have self as an autonoetic entity (awareness of oneself as a continuous entity across time) that

encompasses past, present and future (D'Argembeau *et al.,* 2008; Tulving, 2002).

Monkeys have the Brodmann area 10, but monkey Brodmann area 10 appears to be the functional analog of the human ventromedial prefrontal cortex to monitor action outcomes (Tsujimoto, 2011). The human dorsolateral Brodmann area 10 (monkeys do not have this part of the brain) appears to subserve unique anthropoid function, providing cognitive flexibility that leads to emergence of human reasoning and planning abilities (Koechlin, 2011).

Through this anatomical arrangement humans can link sexual motivation to an almost unlimited number of strategies that will trump temporal and spatial limitations. For example, rats cannot say "Let's meet again next week at the corner ice cream parlor".

In humans, sexual desire that emerges during adolescence parallels the development of self-concept. From this point on, a person (self) makes a conscious (volitional) decision to have or not to have sex, a Shakespearean metaphor but based on scientific evidence (see Koechlin's work above).

Animals will never kill themselves (willfully) out of romantic fallouts. Countless numbers of young people have done just that when their intense love fell apart. Why does this happen? This happens because human strategies and human identity (self) are one and the same. They both originate within the executive regions; especially in the Brodmann area 10 (see the references above). "Self" is an abstract representation of accumulated episodic memories. Humans have a monster called "self". Each and every decision has to be filtered through the self. It is the self that makes decision to kill the self; animals do not have a sense of self, so animals die only when they run out of food, or are killed by a predator, or by accident, but humans commit suicide even if plentiful amounts of food are available to them. In this regard, the methods of engineering human sexual desire are significantly more complicated than those of animals.

How might one cast a new concept to solve this dilemma that has plagued the human race for millennia? Most of the drugs that have been tested thus far belonged to the biogenic amine class. In most cases, biogenic amines are not created to carry messages; they are created to modulate messages. The legendary investigator Holstege stated that descending fibers from the raphe nuclei do not produce specific movements (in the case of muscle fibers) but act as a "level-setting" (modulating) system (Holstege, 1991; Holstege *et al.,* 1996). Boyd Hartman received the A.E. Bennett Research Award in 1971 by presenting evidence that biogenic amines are signal modulators rather than signal carriers, as such they should not be viewed as creating sexual motivation, but rather are agents that make sexual motivation stronger or weaker. How about glutamatergic or GABAergic agents within the reproductive complex? These agents may bring about improved treatment outcome when it comes to sexual desire. Gonadal hormones, no doubt play important roles as well. Gonadal hormones seem to create an optimal environment for glutamate to do its work within the telodiencephalic complex (Boulware and Mermelstein, 2009; Mermelstein, 2009).

In this regard, researchers involved in non-sexual motivation research have arrived at a different conclusion when compared to sexual motivation researchers, that is, the former found glutamate within the core of nucleus accumbens as the obligatory molecule while the latter found dopamine in the medial preoptic area as the primary molecule. When biogenic amines are involved, the magnitude of the symptom modulation is usually small as originally intended, and this is why we do not see dramatic improvement from decreased sexual desire, depression or hypertension when one of these agents is applied clinically (not necessarily true in animal research).

Among the most available (if not all) over-the-counter aphrodisiacs studied, only Tongkat Ali seems to have credible evidence of clinical effects (Ang *et al.,* 2003; 2004). The Tongkat Ali tree root that comes from Southeast Asia seems to increase testosterone levels if taken over ten days.

Until now, almost all drug companies, if not all, have targeted a specific disorder defined in the DSM manual. In this approach, investigators are assuming that hypoactive sexual desire disorder is a homogeneous disease. This is like saying breast cancer is a homogenous disease. It is critically important that investigators define pharmacological mechanisms of a specific drug and target it to a specific subset of sexual disorder to match the

pharmacological mechanisms to the pathophysiology of an underlying sexual disorder. For example, if a test shows low testosterone level, Tongkat Ali might be a reasonable agent to test (the authors have no financial interest in Tongkat Ali).

## Endopeptidase inhibitors

Vasoactive intestinal peptide is one of the major vasoactive neurotransmitters found in the vasculature of the vagina. It is a potent vasodilator that is postulated to have a role in the control of vaginal blood flow (Hoyle *et al.,* 1996; Ottesen *et al.,* 1983). Vasoactive intestinal peptide is a 28 amino acid peptide, which is unsuitable as an oral therapy for female sexual arousal disorder because of a combination of high clearance and low predicted oral bioavailability common to many peptide agents (Brown *et al.,* 2007). Neutral endopeptidase is a principal degrading enzyme of vasoactive intestinal peptide, which is also present in vaginal and clitoral tissues. The hypothesis being tested is that inhibition of neutral endopeptidase will increase circulating levels of vasoactive intestinal peptide and thereby facilitate increases in vaginal and clitoral blood flow in the presence of sexual stimulation. Both Pfizer and Solvay expressed interest in this area in recent years.

## Other peripherally acting agents

L-Arginine is well established as an endogenous precursor to the potent vasodilator nitric oxide. Phosphodiesterase 5 inhibitors are known to enhance the nitric oxide-signaling pathway by preventing breakdown of cyclic GMP by phosphodiesterase 5. A double blind placebo controlled study of the L-arginine containing therapy ArginMax has recently been reported (Ito *et al.,* 2006). Several other peripherally acting agents have been reported to be undergoing clinical trials for female sexual dysfunction including NMI-870 (arginine plus Yohimbine, NitroMed); REC2615 (an a1 adrenoceptor antagonist from Recordati) and phentolamine (a non-selective a-adrenoceptor antagonist) (Brown *et al.,* 2007).

## Centrally acting agents

Sildenafil (Pfizer, Pfizer is also evaluating a dopamine 3 receptor agonist), a phosphodiesterase 5 inhibitor; topical alprostadil (Vivus), a prostaglandin E 1

agonist; topical REC 2615 (Recordati), an a1 antagonist; bremelanotide (Palatin, under clinical trial, subcutaneous injection to minimize hypertensive episodes; Amgen, Merck, Proctor and Gamble also have similar compounds), a mixed melanocortin receptor agonist; apomorphine (Various), a pan dopamine agonist; bupropion (GlaxoSmithKline), a pan dopamine agonist; flibanserin (Boehringer Ingelheim), a 5-HT1A agonist/5-HT2A antagonist; OPC-14523 (Pharmos and Otsuka, now called VPI-013), a 5-HT1A agonist are under evaluation (Brown *et al.,* 2007).

**Table 2.** Hypotheses associated with sexual desire.

| |
|---|
| **Gonadal steroid hypothesis –** This is by far the most important hypothesis and plays the most important role in sexual desire. Males with lower testosterone levels may find effective treatment through testosterone replacement. For those with normal levels of testosterone with decreased sexual desire, supplemental testosterone may pose serious adverse reactions, especially in older males. In females, estrogen has led to inconsistent results, in part, due to the more complex neurobiological mechanisms. |
| **Glutamate hypothesis –** The roles of glutamate and/or GABA may be relevant in regulating sexual desire within the telodiencephalic complex. |
| **Dopamine hypothesis -** To enhance sexual desire through increased dopamine function in the nucleus accumbens or telodiencephalic complex. Consummatory behavior is also closely associated with the medial preoptic area for males and the ventral medial nucleus of hypothalamus for females (lordosis) (see page 39). |
| **Prolactin hypothesis –** Decreased prolactin level has been proposed to enhance sexual desire but further studies are needed (Dosa *et al.,* 2013). |
| **Melanocortin hypothesis –** Melanocortins have been tested in animals and humans with positive findings (Pfaus, 2009). |
| **Orexin hypothesis –** Relatively newly introduced molecule that augments sexual desire by activating dopamine neurons in the ventral tegmental area and enhancing dopamine function within the nucleus accumbens (see page 36). |
| **Gastrin-releasing peptide hypothesis –** The gastrin-releasing peptide system within the lumbar spinal cord (L3-L4 level) may affect sexual desire and orgasm (see Figure 4 on page 13). |

## Hormones

Tibolone is a synthetic steroid that is used for the control of menopausal symptoms such as hot flashes, but also has the benefit of progesterone-like and testosterone-like activities (Genazzani *et al.,* 2006; Steckelbroeck *et al.,* 2004). There is also evidence that tibolone may have beneficial effects in improving desire and arousal in post-menopausal women. In a double-blind crossover study of postmenopausal women tibolone increased vaginal blood flow above placebo when women fantasized about sex (Laan *et al.,* 2001). A recent study demonstrated efficacy in post-menopausal

women suffering from female sexual dysfunction (Nappi *et al.,* 2006). Table 2 shows a summary of the hypotheses associated with sexual desire.

## Sexual desire and orgasm

Most recently, Georgiadis and colleagues reported discrete anatomical and molecular distinctiveness among sexual motivation, pleasure and learning (Georgiadis *et al.,* 2012).

The available evidence suggests that brain mechanisms involved in fundamental pleasures (food and sexual pleasures) overlap with those for higher-order pleasures (for example, monetary, artistic, musical, altruistic, and transcendent pleasures) (Kringelbach, 2010). Appetitive and pleasurable behaviors involving feeding and the full range of sexual activity can also emerge inappropriately during sleep (which itself is an intrinsic, appetitive behavior), with individual patients demonstrating either or both feeding and sexual behavior during sleep, as reported and reviewed (Cicolin *et al.,* 2011; Schenck *et al.,* 2007).

In conclusion, it is not a coincidence that our most intense pleasurable feelings, such as orgasms, are evoked when we are closest to perpetuating our genes (Johnston, 2003). The neural substrates for orgasm may be localized to a single location or are distributed. It is clear that wide-ranging CNS regions show altered brain activity, but these changes can be secondary to a specific brain region that processes orgasm.

## Summary and outlook

Some medical and psychiatric disorders engender sexual dysfunction including sexual desire disorders. Pharmaceutical industries have not neglected or ignored these disorders. However, years of clinical trials involving many different molecules have eluded promising agents except in the domain of erectile dysfunction. We still do not have effective agents to treat male or female hypoactive sexual desire disorders. In this paper, we have reviewed the neural systems that regulate sexual functions. We have also reviewed the genetic, molecular and environmental inputs to the system and how they are integrated within the system. By exploiting these vastly advanced knowledge base, and by adhering to the neural system based neuroscientific approach (instead of the old biogenic amine concept as has been the case for most of the drug trials), researchers are now better equipped to discover new molecules than at any other time in history.

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