Michele Iovino¹, Tullio Messana², Emanuela Iovino¹, Giovanni De Pergola³, Edoardo Guastamacchia¹, Vito Angelo Giagulli¹ and Vincenzo Triggiani¹,∗

¹Interdisciplinary Department of Medicine-Section of Internal Medicine, Geriatrics, Endocrinology and Rare Diseases, School of Medicine, University of Bari “Aldo Moro”, Bari, Italy; ²Infantile Neuropsychiatry, IRCCS – Institute of Neurological Sciences, Bologna, Italy; ³Clinical Nutrition Unit, Medical Oncology, Department of Internal Medicine and Clinical Oncology, School of Medicine, University of Bari “Aldo Moro”, Bari, Italy

Abstract: Objective: The aim of this narrative review was to analyze the role played by brain areas, neurohormones and neurotransmitters in the regulation of emotional and sexual behavior in the male.

Methods: We analyzed the currently available literature dealing with brain structures, neurotransmitters and neurohormones involved in the regulation of emotional and sexual behavior in the male.

Results: A common brain pathway is involved in these two aspects. The Hippocampus seems to control the signals coming from the external environment, while the amygdala and the hypothalamus control the response to social stimuli. Stimulation of amygdala in the animal models increases sexual performance, while it triggers violent emotional responses. Stimulation of the hypothalamus causes reactions of violent anger and increases sexual activity. Catecholaminergic stimulation of the amygdala and hypothalamus increases emotional and sexual behavior, while serotonin plays an inhibitory role. Cholinergic inhibition leads to a suppression of copulatory activity, while the animal becomes hyperemotive. Opioids, such as β-endorphin and met-enkephalin, reduce copulatory activity and induce impotence. Gonadal steroid hormones, such as estrogen in female and testosterone in male, which play a major role in the control of sexual behavior and gender difference have been highlighted in this review. Vasopressin, oxytocin and their receptors are expressed in high density in the “social behavior neural network” and play a role as signal system controlling social behavior. Finally, the neuropeptide kisspeptin and its receptors, located in the limbic structures, mediate olfactory control of the gonadotropin axis.

Conclusion: Further studies are needed to evaluate possible implications in the treatment of psychosexual and reproductive disorders.

Keywords: Sexual behavior, emotional behavior, hippocampus-amygdala, hypothalamus, social behavior neural network, adrenal steroids, neurotransmitters, motivational behavior.

1. INTRODUCTION

Several clinical observations indicate a close correlation between emotional disorders and sexual disturbances. Neuroanatomical and neurophysiological data showed that both emotional and sexual behaviors are controlled by a common brain pathway, as well as by the same neurotransmitters and neurohormones.

The role played by emotional disorders in human sexual behavior has long been recognized. In fact, in humans, they influence the secretion of gonadotropins and sexual steroids [1, 2], although hypothalamic-pituitary dysfunction alone cannot explain the correlations between sexual and emotional behavior. The mechanism of action of neuroleptics drugs, which intervene in neurotransmission, makes us understand the role played by some brain circuits in the complex relationships between emotional and sexual behaviors. The structures of the Central Nervous System (CNS) involved in the regulation of emotional behavior are part of a circuit of nuclei and brain areas called the Papez circuit [3]: hippocampus → fornix → mammillary bodies → thalamo-mammillary bundle of Vicq d’ Azir → thalamus → limbic gyrus including amygdala → hippocampus, in which the hippocampus plays the role in the reception of the signals, while the amygdala and the mammillary bodies play the role of effectors in the response. In experiments involving animals, the stimulation of these areas causes both reactions of anger and sympathetic responses, such as the pilomotor
activity, the increase in blood pressure and the aggressive-defensive behavior. Injury of the amygdaloid nuclei induces responses of anger and increases emotional reactions. These behaviors could be due to the removal of the inhibitory influences that originate in the hippocampus and amygdala on the hypothalamic mechanisms. Stimulation of the amygdala in the cat causes vegetative oral manifestations, such as chewing and salivation, motor disturbances, such as the facial expression of vigilance and fear for which the animal crouches on the ground or seeks to run away from sneak or angry, spitting with bristly hair and extended claws [4-6].

The postero-ventral portion of the hippocampus is directly connected with the lateral septum, while the antero-dorsal portion connects above all with the mammillary bodies and the anterior thalamic nuclei through the fornix [7]. In addition, Raisman identified pathways arising from the septum projecting to the olfactory cortex and via the Medial Forebrain Bundle (MFB) to the Preoptic Area (POA), mammillary bodies and perifornical area [8]. Moreover, from amygdala to olfactory bulb [9]. Cholinergic stimulation of the rostral area of the hippocampus in rats develops a very characteristic hyper-reactivity which appears as an exaggerated reaction to normally non-noxious stimuli [10]. The section of the fornix, which interrupts some efferent pathways of the hippocampus, provokes very strong emotional reactions [11, 12]. The adrenergic stimulation of the amygdala and the posterior hypothalamus produces marked disturbances of both emotional and sexual behavior [13, 14]. Serotonin(5-HT)ergic neurons, located in raphe nuclei of medulla oblongata (B1-B4),pons (B5-B6) and midbrain (B7-B9), play an inhibitory role in sexual behavior. Electrical stimulation of median raphe nucleus (B8) following administration of 5-hydroxy-triptophan, the precursor of 5-HT, inhibits sexual behavior reducing copulatory activity, while Parachloro-Phenyl-Alanine (PCPA), inhibitor of 5-HT synthesis, stimulates sexual behavior. Dopaminergic neurons, located into midbrain (A8-A10), thalamus (A11) and hypothalamus (A12-A14), control, via A10 area, limbic system, cerebral cortex and pyramidal system. Administration of L-dopa or amphetamine stimulates sexual behavior, while DAergic antagonists, as α-metyl-para-thyrosine, haloperidol, sulpiride or phenthoazine play an inhibitory role [15]. Neurophysiological, neuroendocrine and neuropharmacological findings demonstrate the involvement of the hypothalamus, the amygdala, the hippocampus, the hypothalamo-hippocampal-adenal axis, and the vasopressinergetic and oxytocinergetic system of the Social Behavior Neural Network (SBNN) in the regulation of both sexual and emotional behavior.

2. BRAIN STRUCTURES REGULATING SEXUAL AND EMOTIONAL BEHAVIOR

2.1. Hypothalamus

The bilateral ablation of the posterior hypothalamus, which involves lateral mammillary nuclei and the perifornical area, immediately suppresses all sexual activities. In the presence of a female in estrus, the injured animal does not copulate and almost immediately the excitement turns into aggression. The administration of androgens and gonadotropins to lesioned male animals does not show a recovery of sexual activity. On the contrary, bilateral stimulation with electrodes implanted in the lateral mammillary nuclei and peri-fornical area leads to an increase in sexual activity. In fact, the number of ejaculations is significantly increased, as the refractory periods are significantly decreased.

It has been found that administration of Testosterone (T) into the hypothalamic preoptic region of castrate male rats results in the reappearance of sexual behavior thus showing the role primarily played by activation of androgen-receptor in the preoptic area but not in androgen-sensitive peripheral structures as seminal vesicles or prostate [16].

Lesions of the Medial Preoptic Area (MPOA) reduce significantly male sexual behavior in the rat. These lesions decrease sexual behavior altering hypothalamic neurotransmission rather than brain pathways. In fact, it has been observed that the neurotoxic agent ibotenic acid, administered into the MPOA, induces extensive degeneration of neuronal cell bodies, without damage of fiber systems synapsing in other hypothalamic nuclei, thus showing that the functional integrity of MPOA neurons is essential in sexual behavior. In addition, lisuride, a dopamine (DA) ergic agonist, restores sexual behavior in male rats with lesions of MPOA induced by neurotoxin indicating a possible role of DAergic transmission [17].

MPOA, located at the rostral end of the hypothalamus, and the ventral-hypothalamic input route plays an important role in the regulation of male sexual behavior [18]. Experimental data show an impairment of male sexual behavior following MPOA lesions and enhancement after MPOA stimulation. DA stimulates male sexual behavior in all species including rodents and humans. DAergic agonist administered into MPOA stimulates sexual behavior, whereas DAergic antagonist reduces copulation, genital reflexes and sexual motivation. In addition, increased levels of DA in the MPOA during copulation and in the presence of estrous female have been observed [19].

Opioids in the MPOA impair sexual performances. β-endorphin microinjected into the MPOA reduces the copulatory activity. Enkephalergic neurons, located as endorphinergic neurons in several brain areas, including thalamus, hypothalamus and limbic system, induce impotence and extension of the refractory period of copulatory activity. These effects are antagonized by pretreatment with naloxone [20].

Noradren(NA)ergic mechanisms are also involved. NA injected into the MPOA stimulates sexual behavior by improving sexual arousal and copulatory activity. Instead, propranolol impaired male sexual behavior thus suggesting that β-adrenergic mechanisms play a role in the elaboration of male sexual behavior [21].

In experiments involving animals, lordosis is used as a model of female reproductive behavior. Lordosis, the body posture for sexual receptivity to copulation, is an estrogen-dependent reflexive behavior involving neurons located into the hypothalamic ventromedial nucleus (VMN), the midbrain central gray, the reticulospinal tract and spinal cord. The stimulation of lordosis by estrogens is activated by a signal transduction pathways involving a specific G protein and the activation of protein kinase C [22].
2.2. Amygdala

A significant density of gonadal steroid receptors is present in Medial Amygdala (MA). An in situ hybridization study showed the brain distribution of androgen- and estrogen-receptors primarily in the MA [23]. Lesions of amygdaloid structures produce sexual behavior deficits, resulting in severe impairment of copulatory behavior in males of many animal species [24, 25].

The MA plays a key role in sexual behavior [26]. Androgen receptors are present in the MA and male sexual behavior is stimulated via T-induced changes in the morphology of the MA [27], while it is inhibited following blockade of androgen receptor in the MA [28]. However, T delivered directly into the MA is unable to stimulate male sexual behavior without the presence of an estrous female thus showing the role played by olfactory bulbs in the circuit subserving sexual behavior [29]. These data indicate that olfactory information critical to male sexual behavior is processed in the MA, which is an androgen-binding brain area. Therefore, the MA acts as synaptic station through which olfactory information influences the neurotransmission in the preoptic area and the bed nucleus of the stria terminalis (BNST), the areas involved in the sexual behavioral circuit.

Kisspeptidergic neurons show steroid androgen sensitivity and anatomical relationship with the hypophysiotropic GnRH 1 neurons [30]. In addition, kisspeptin receptor knockout (KO) mice display no sexual behavior [31], and intracerebroventricular administration of kisspeptin in male rats stimulates LH and T release [32] as well as in man following intravenous infusion [33]. Moreover, a significant increase of plasma LH concentration has been observed when kisspeptin 1 is administered directly into the MA thus showing a role of kisspeptin 1 in male sexual behavior via the MA [34]. Therefore the system MA-kisspeptin is considered essential for mammalian reproduction.

2.3. Hippocampus

The hippocampus seems to play a stimulatory role in the copulatory activities [35]. In untreated rats, it was observed that the copulation stimulates the hipoccampal activity as demonstrated by the synchronization of electrophysiological (EEG) recordings. Various drugs have shown improved sexual activity in male rats, especially para-chloro-phenylalanine (PCPA), an inhibitor of serotonin (5-HT), which has been shown to increase all sexual behavior constituents within 24 hours of administration. The hippocampal EEG recordings after PCPA demonstrated a continuous synchronization, a clear sign of the hippocampal neuron activation [36]. In contrast, administration of the cholinergic antagonist atropine causes desynchronization of hippocampal neurons and suppression of sexual activity. Therefore, a significant increase in sexual activity is accompanied by an activation of hippocampal neurons, while an absence of sexual activity is accompanied by desynchronization of these neurons [37].

2.4. Hypothalamo-pituitary-adrenal Axis and Gonadal Steroids

Gonadal steroid hormones, as estrogen and progesterone, play a major role in the control of female sexual behavior. However, several evidences showed also that non-ovarian steroid hormones, such as adrenal steroids, are involved in the control of female sexual behavior. In humans and other primates, orchidectomy or testicular dysfunction decreases sexual interest [38]. Instead, ovariectomy induces little or no effect on sexual interest in human and primate female [39-41]. On the other hand, adrenalectomy provokes a profound decrease in sexual activity of both human [39-41] and other primate females [42]. Androstenedione, as replacement therapy, is able to restore sexual receptivity in female [42]. In addition, in normally-cycling female rats, adrenalectomy plays an inhibitory effect on sexual maturation by interfering with LH secretion and hence on the estrous cycle [43]. Adrenalectomy or suppression of adrenal cortical function with dexametazone (DXM) suppresses the period of receptivity seen in normal female rats, desynchronizes the preovulatory release of LH, and reduces significantly the increase of progesterone release prior to estrous [44]. It has been hypothesized that adrenal progesterone secretion triggers the initiation of LH release from the adenohypophysis [45], a hypothesis supported by the observation that estrogen stimulates the release of ACTH which activates adrenal cortical hormone synthesis [46]. Therefore, female sexual behavior and normal estrous cycle are the results of synergic mechanism between endogenous estrogen and adrenal progesterone. Other data suggest that GnRH may have a direct effect on sexual receptivity since the increase of hypothalamic GnRH before the LH release does not involve adrenal progesterone at all [47]. However, DXM suppresses adrenal function but inhibits, also, LH release, via downregulation of adenohypophysyal cells to GnRH [48], thus showing that both adrenal progesterone and GnRH might be involved in female sexual behavior. In addition, gonadotrophin-releasing hormone (GnRH) agonists inhibit anxiogenic and depressive mood effect induced by corticotrophin-releasing hormone in rodents [49, 50], while gonadotrophin-inhibitory hormone (GnIH) reduces sexual motivation [51]. Estrogens play also antidepressant effects [52] and improve sexual arousal in hypogonadal women [40]. Testosterone induces fear and anger via amygdala activation [53] and sexual desire in men and women [54].

2.5. The Vasopressin (VP)-ergic and Oxytocin (OT)-ergic System in the SBNM

VPergic and OTergic neurons of the hypothalamic supraoptic (SON) and paraventricular nuclei (PVN) project to several brain areas [55]. Moreover, VP, OT and their receptors are also localized into forebrain structures as amygdala, hippocampus, septum, and striatum. Although the major role of these neurohypophyseal hormones is the release of VP in response to osmotic and hypovolemic stimuli whereas OT is involved in lactation and parturition [56-58], the presence of these neuropeptides in limbic areas indicates also a role in the control of social behaviors. In fact, anxiogenic and depressive effects, as well as aggressive-defensive behavior and involvement in memory processes for VP, and anxiolytic and antidepressive effects, protective aggression and maternal behavior for OT [59-65] have been reported. VP has been localized within circuitry of limbic areas that constitute the SBNM. This circuitry is composed of groups of neurons located into the ventral forebrain, as the medial and central amygdaloid nuclei, BNST, septum, medial prepoptic area.
(MPOA), hypothalamic VMN and periaqueductal gray. Several experimental data, in mammalian species, show the role of VP and VP receptors (V1R) played in the regulation or activation of social behaviors and aggressive-defensive behavior. VP acts in SBNN to regulate social behaviors by modulating the response to sensory information and triggering complex motor reactions.

Behavioral involvement of VP and OT has been observed in the pathophysiology of psychiatric disorders [59, 60, 64, 65]. In mammals, it has been identified four G-protein-coupled receptors (GPCRs) of the VP/OT system: V1 vascular (V1R), V2 renal (V2R), V3 pituitary (V3R) and OT (OTR) subtypes [66-68]. The V1R and OTR are found in high density in several brain areas [68] and play an important role in social behaviors [69].

Newman [70] first proposed the term SBNN indicating a brain circuitry composed of groups of neurons or “nodes” that are reciprocally connected, expressing gonadal steroid receptors, and constituting an important site of regulation or activation of multiple forms of social behaviors. This circuitry controls sexual, parental and aggressive-defensive behavior [71, 72]. Hormonal and chemosensory signals reach neurons of medial extended amygdala, via olfactory bulb, where neurons with androgen and estrogen receptors modulate the neurotransmission in this circuitry. Gonadal steroids influence VP expression in forebrain neurons increasing significantly VP concentration and its carrier protein, neurophysin II, in the presence of aromatizable androgens or estrogens [73], probably via direct action on hypothalamic VPergic neurons [74]. In addition, gonadal hormones influence, also, VP receptors mainly V1R [75].

Despite the neuropeptides VP and OT are synthesized in the same hypothalamic nuclei, SON and PVN, differing only for two amino acids, and are able to activate each other’s receptors, V1R and OTR, they show opposite behavioral effects. Neuman and Landgraf [59], as reported above, observed anxiogenic and depressive effects of VP, while OT provokes anxiolytic and antidepressive responses. These actions produced by VP and OT might be induced within the SBNN because these two hormones excite two distinct neuronal groups in the central amygdala [76]. In fact, Viviani and Stoop [77] observed that OT stimulates GABAergic neurons, located in the lateral part of the central amygdala, synapting to neurons of the medial part of the central amygdala where they inhibit VPergic neurons thus modulating emotional expression of a fear response.

2.6. Relationship between Sexual and Emotional Behavior

Stimulation of the amygdala increases sexual performance, while it triggers violent emotional responses [78, 79]. On the contrary, the destruction of the amygdala eliminates mating behavior, produces docility and attenuates the hyperemotionality produced by septal lesions [80].

The hippocampus seems to play the role of moderator interfering with the Mesencephalic Reticular Formation (MRF) that controls the vigilance responses [81]. Stimulation of the posterior hypothalamus, involving mamillary nuclei and peri-forehinal area, causes reactions of violent anger and increases sexual activity, while its ablation abolishes the two types of response [82]. Hence the posterior hypothalamus represents the final pathway in complex behavioral motor activities.

Cholinergic inhibition with atropine suppresses copulatory activity while the animal becomes hyperemotive. These effects can be ascribed to some modifications of the hippocampal control, which is considered part of the cholinergic limbic system [83, 84]. In fact, atropine determines a desynchronization of hippocampal EEG, while increased sexual activity after administration of Para-Chloro-Pheny-Alanina (PCPA), the inhibitor of brain serotonin (5-HT), is accompanied by synchronization of hippocampal electrical activity, thus showing a key role of the hippocampus in the modulation of cholinergic and 5-HTergic inputs. Catecholaminergic activation with amphetamine or NA dramatically reduces copulatory activity and at the same time causes very violent emotional responses. These observations can be linked to the amygdaloid stimulation which is particularly sensitive to the NAergic action [78, 85, 86].

Stress stimulates cortisol release that provokes increased anxiety and suppresses hippocampal neuronal plasticity. Sexual behavior, a natural rewarding experience that although increases plasma glucocorticoids levels, is able to stimulate hippocampal neurogenesis and the growth of dendritic architecture. These data indicate that sexual stimuli, in contrast to aversive stress experiences, promote neuronal proliferation in the hippocampus and reduce anxiety despite the increased adrenal cortical function [87].

3. DISCUSSION

Sexual, emotional, aggressive-defensive and food-intake behavior must be considered as a dialogue of the organism with the external environment. Therefore, signals arising from the external environment are continuously encoded and analyzed in the hippocampus and then circulated through the limbic system in the form of an internal representation of the external world. At the same time, the limbic circuits receive also information of visceral events through the amygdala. The behavior is, therefore, the set of reactions of an individual to a stimulus. The reaction, hence, needs to be received, to be transformed in the message, in turn, the message is stored in the limbic system by synaptic inputs and at the end, the order is carried out through the pyramidal system. The temporal connections between visceral and environmental data can constitute the development of conditioned reflexes.

When an animal placed on a floor with electric wire (hippocampal information) before the electric shock (amygdaloid information) shows signs of fear (hypothalamic response), but if previously conditioned it will adopt an avoidance behavior, it will jump on a non-electric platform. Furthermore, if the animal is stimulated on the platform (hippocampal information), where it has never previously received a shock (amygdaloid information), it will show signs of relaxation and sleep.

Motivated sexual, maternal, aggressive-defensive and food-intake behavior, depends on a motivational state of the brain that determines the response. So the determination of a state depends on motivation. The term motivation refers to
two closely complementary concepts: the “motor”, that is the production and endogenous conversion of a more or less specific energy required to trigger and maintain a behavioral sequence; and that of the “motive of action” which encompasses both the processes by which an action, of appetitive or aversive nature, is progressively conferred on a certain stimulus or situation which was initially neutral, and those to which this action can then be evaluated by reference to the traces left by past experience.

This “memory of experience” reaches the reticular mesencephalic formation and then, after being analyzed here, is transferred to reticular thalamic formation which allows the motor behavior to be programmed for avoidance responses. Moreover, this “memory of experience” reaches also the hypothalamus that will produce behavioral reactions, especially emotional ones.

In the determinism of a motivational state, two complementary aspects must be considered: (a) changes in the “milieu interieur” (internal environment), such as glycemia, plasma osmolality, circulating gonadal hormones, temperature, etc., which induce a more or less specific behavioral awakening. These fluctuations are detected in particular by hypothalamic neurons; in fact, the hypothalamus plays an essential role in the adaption of the behavior to the physiological state present in the organism. (b) the “memory of experience” that represents the adaption of the behavior to the past experience of the subject. Here intervenes the limbic system which plays an important role in the constitution of the “memory of experience”.

The hypothalamus participates to emotional and social reactivity. Practically we have two motivational behavior: through sensory information and past experience. The behavior depends on the memory of experience and the “milieu interieur”, which always intervenes in a combined way. The emotional, sexual, maternal and food-intake behavior represent the expression of a behavioral awakening and of a biological need, created by particular energetic, osmotic or endocrine conditions of the “milieu interieur”. In other words, in the case of behaviors as sexual, emotional or food-intake behavior, the limbic system modulates, by giving them a historical dimension and a certain personality of the behavior, whose the triggering and nature depend essentially by hypothalamic and mesencephalic mechanisms themselves brought into play by factors of the “milieu interieur” (Fig. 1).

As far as sexual behavior is concerned, the stimulation of the hippocampus is evoked by the sexual partner and by past experiences previously stored in memory; the stimulation of the amygdala is probably produced by hormonal conditions (circulating levels of gonadal and corticoid hormones), information deriving from genital structures and previous experiences of reward stored in memory. All of this integrated information is conveyed to the posterior hypothalamus and reticular formations where they are processed to give sexual responses. In all these conditions it is this or that parameter of the physiological state which plays a preponderant role in the determinism of the behavioral activity. But it is clear that references to past experiences are not absent from these behaviors: individual nuances modulate the stereotyped behav-

---

**Fig. (1). Relationship between internal and external environment with hypothalamus and limbic system.** The probability that a given sensory information triggers a certain behavioral response is determined by the motivating proprieties which are conferred to this information both according to the parameters of the internal environment, and by reference to the traces left by the past experience (s-r link: stimulus-response link).
ior and it is in particular the limbic system that allows the development of these aspects that translate the psychosocial personality of the subject.

Aggressive-defensive situation, or memory of it, can severely damage hippocampal information. Similarly, functional visceral abnormalities (endocrine failure, pain, etc.) cause amygdaloid hyper-stimulation. In both cases, an alteration of the stimulation balance prevents such behaviors, as sexual performance, through the induction of a “jamming effect” in the limbic circuits. All these circuits are saturated with information that are extremely intense, so there is always an emotional response. Certain types of male sexual impotence can be defined within these limits; in these cases, sexual impotence could be due to emotional hyper-excitability, as evidenced by a strong stimulation of hippocampus and amygdala.

The memory of past experiences and information (external or internal) on the current situation are conveyed simultaneously through limbic circuits of the hippocampus and the amygdala to the posterior hypothalamus and to the anterior portion of the mesencephalic reticular formation causing a stimulus or inhibition of the behavioral response. Finally, one can easily understand that factors that increase the excitability of the hippocampus or amygdala (neurostimulant drugs, endocrine dysfunctions, affective conflicts, neurotransmitter disorders, etc.) reinforce behavioral inhibition of emotional origin (Fig. 2).

However, it should be taken into account the SBNN. VP/OT system affect social behavior, social cognition, emotional and sexual behavior, by acting within the SBNN. The SBNN is composed of groups of neurons defined as nodes that are reciprocally connected, and express gonadal steroid receptors. Signals arising from AVP and OT modulate synaptic inputs within the SBNN that constitute an important site of regulation or activation of multiple forms of social behavior.

Kisspeptin and its receptors kiss 1 have been reported in the amygdala and hippocampus [88], and limbic structures, both playing a major role in sexual behavior, emotion and reproduction [89]. In addition, in rodents, amygdala kisspeptin neurons are necessary in reproduction as putative mediators of olfactory control of the gonadotropic axis [90]. Kisspeptin, enhancing limbic neurotransmission in response to sexual and emotional behavior [91], may be a potential therapeutic agent for psychosexual disorders, because it improves positive mood and reduces sexual aversion, and can be used to treat reproductive disorders such as male hypogonadism [92], hypothalamic amenorrhoea [93] and hyperprolactinemia [94].

CONCLUSION

Hormones, such as kisspeptin that reduces sexual aversion and depression in humans, GnRH that induces anxiolytic and anti-depressant effects in rodents, GnIH that reduces sexual motivation, estrogens that improve sexual arousal in hypogonadal women, testosterone that induces fearful and angry emotions, and improves sexual desire in hypogonadal men and women, OT that reduces anxiety and fear via amygdaloid GABAergic neurons, VP that stimulates aggressive-defensive behavior through stimulation of ACTH and cortisol, play a crucial role in brain circuits (Fig. 2) subserving sexual and emotional responses and demonstrating the close psychoneuroendocrine relationship between emotional and sexual behavior.

CONSENT FOR PUBLICATION
Not applicable.

FUNDING
None.

CONFLICT OF INTEREST
The authors declare no conflict of interest, financial or otherwise.
ACKNOWLEDGEMENTS

All the following individuals listed as authors have contributed substantially to the design, performance, analysis, and reporting of the work: Michele Iovino, Tullio Messana, Emanuela Iovino, Giovanni De Pergola, Edoardo Guastamacchia, Vito Angelo Giaguilli and Vincenzo Triggiani.

REFERENCES

[1] Mc Ewen, B.S. Endocrine effects on the brain and their relationship to behavior. In: Brain Neurochemistry, 8th ed; Brady, S.T.; Siegel, G.J.; Albers, R.W.; Price, D.L.; Eds.; Academic Press: Oxford, UK, 2012, pp. 945-965.
[2] Kalantarioud, S.N.; Makriangikas, A.; Zoumakis, E.; Chrousos, G.P. Stress and the female reproductive system. J. Reprod. Immunol., 2004, 62(1-2), 61-68.
[3] Shah, A.; Jhawar, S.S.; Goel, A. Analysis of the anatomy of the Papez circuit and adjoining limbic system by fiber dissection techniques. J. Clin. Neurosci., 2012, 19(2), 289-298.
[4] Miczek, K.A. The psychopharmacology of aggression. New Directions in Behavioral Pharmacology; Iversen, L.L.; Iversen, S.D.; Snyder, S.H. Eds.; Plenum Press: New York, London, 1987, Vol. 19, pp. 183-277.
[5] Gregg, T.R.; Siegel, A. Brain structures and neurotransmitters regulating aggression in cats: implications for human aggression. Prog. Neuropsychopharmacol. Biol. Psychiatry, 2001, 25(1), 91-140.
[6] Siever, L.J. Neurobiology of aggression and violence. Am. J. Psychiatry, 2008, 165(4), 429-442.
[7] Raisman, G.; Cowan, W.M.; Powell, T.P.S. An experimental study of the projection of the anterior thalamic nuclei to the accessory olfactory bulb and its relationship to the fimbria system to the control of rage responses in cats. Brain, 1966, 89(1), 83-108.
[8] Raisman, G. The connexions of the septum. Brain, 1966, 89(2), 317-348.
[9] Raisman, G. An experimental study of the projection of the amygdala to the accessory olfactory bulb and its relationship to the fimbria system. Exp. Brain Res., 1972, 14(4), 395-408.
[10] Liu, M.G.; Chen, J. Roles of the hippocampal formation in pain information processing. Neurosci. Bull., 2009, 25(5), 237-266.
[11] Rothfield, L.; Harman, P.J. On the relation of the hippocampal-fornix system to the control of rage responses in cats. J. Comp. Neurol., 1954, 101(2), 265-282.
[12] Cohen, R.A. Neural mechanisms of attention. The Neurophysiology of Attention; Cohen, R.A., Ed.; Springer: New York, 2014, pp. 229-233.
[13] Myers, R.D. Emotional and autonomic responses following hypothalamic chemical stimulation. Can. J. Psychol., 1964, 18, 6-14.
[14] Nagy, J.; Decsi, L. Simultaneous chemical stimulation of the hypothalamus and dorsal hippocampus in the waking cat. Pharmacol. Biochem. Behav., 1974, 2(3), 285-292.
[15] Hull, E.M.; Muschamp, J.W.; Sato, S. Dopamine and serotonin: influences on male sexual behavior. Physiol. Behav., 2004, 83(2), 291-307.
[16] Davidson, J.M. Activation of the male rat’s sexual behavior by intracerebral implantation of androgen. Endocrinology, 1966, 79(4), 783-794.
[17] Hansen, S.; Köhler, C.; Goldstein, M.; Steinbusch, H.V. Effects of ibotenic acid-induced neuronal degeneration in the medial preoptic area and the lateral hypothalamic area on sexual behavior in the male rat. Brain Res., 1982, 239(1), 213-232.
[18] Motoifei, I.G.; Rowland, D.L. The ventral-hypothalamic input route: a common neural network for abstract cognition and sexuality. BJU Int., 2014, 113(2), 296-303.
[19] Dominguez, J.M.; Hull, E.M. Dopamine, the medial preoptic area, and male sexual behavior. Physiol. Behav., 2005, 86(3), 356-368.
[20] van Furth, W.R.; van Emst, M.G.; van Ree, J.M. Opioids and sexual behavior of male rats: involvement of the medial preoptic area. Behav. Neurosci., 1995, 109(1), 123-134.
[21] Mallick, H.; Manchanda, S.K.; Kumar, V.M. β-adrenergic modulation of male sexual behavior elicited from the medial preoptic area in rats. Behav. Brain Res., 1996, 74(1-2), 181-187.
[89] Yang, L.; Comninos, A.N.; Dhillo, W.S. Intrinsic links among sex, emotion, and reproduction. Cell. Mol. Life Sci., 2018, 75(12), 2197-2210.

[90] Pineda, R.; Plaisier, F.; Millar, R.P.; Ludwig, M. Amygdala kisspeptin neurons: putative mediators of olfactory control of the gonadotropic axis. Neuroendocrinology, 2017, 104(3), 223-238.

[91] Comninos, A.N.; Wall, M.B.; Demetriou, L.; Shah, A.J.; Clarke, S.A.; Narayanaswamy, S.; Nesbitt, A.; Izzit-Engbeaya, C.; Prague, J.K.; Abbara, A.; Ratnasabapathy, R.; Salem, V.; Nijher, G.M.; Jayasena, C.N.; Tanner, M.; Bassett, P.; Mehta, A.; Rabiner, E.A.; Hönigsperger, C.; Silva, M.R.; Brandtzæg, O.K.; Lundanes, E.; Wilson, S.R.; Brown, R.C.; Thomas, S.A.; Bloom, S.R.; Dhillo, W.S. Kisspeptin modulates sexual and emotional brain processing in humans. J. Clin. Invest., 2017, 127(2), 709-719.

[92] George, J.T.; Veldhuis, J.D.; Tena-Sempere, M.; Millar, R.P.; Anderson, R.A. Exploring the pathophysiology of hypogonadism in men with type 2 diabetes: kisspeptin-10 stimulates serum testosterone and LH secretion in men with type 2 diabetes and mild biochemical hypogonadism. Clin. Endocrinol. (Oxf.), 2013, 79(1), 100-104.

[93] Jayasena, C.N.; Abbara, A.; Veldhuis, J.D.; Comninos, A.N.; Ratnasabapathy, R.; De Silva, A.; Nijher, G.M.; Ganiyu-Dada, Z.; Mehta, A.; Todd, C.; Ghatel, M.A.; Bloom, S.R.; Dhillo, W.S. Increasing LH pulsatility in women with hypothalamic amenorrhoea using intravenous infusion of Kisspeptin-54. J. Clin. Endocrinol. Metab., 2014, 99(6), E953-E961.

[94] Sonigo, C.; Bouilly, J.; Carré, N.; Tolle, V.; Caraty, A.; Tello, J.; Simony-Conesa, F.J.; Millar, R.; Young, J.; Binart, N. Hyperprolactinemia-induced ovarian acyclicity is reversed by kisspeptin administration. J. Clin. Invest., 2012, 122(10), 3791-3795.