REVIEW ARTICLE

The Sexuality as the Less Known Feature of Human Life

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ABSTRACT

It was an illusion in the past years to try to explain the human sexuality in terms of the only sex steroid hormones, since the human sexual behavior has appeared to be under a complex endocrine, neuroendocrine, and nervous modulation, which reflects the psychological and spiritual status of subjects. According to the data available up to now concerning the human physiology, the sexual arousal and behavior is, namely, induced and amplify by oxytocin (OT), the endogenous cannabinoids, the most known of them are arachidonylethanolamide and 2-arachidonyl-glycerol, and the pineal indole and beta-carboline hormones, namely, melatonin, 5-methoxytryptamine, and pinealine. On the contrary, sexuality is, namely, inhibited by prolactin, while the mu-opioids may induce both inhibitory and stimulatory effects on the sexual behavior, but the suppressive action would be prevalent. Moreover, opioid-induced sexual pleasure would be different from that induced by oxytocin, by substantially consisting of a private personal pleasure, whereas that promoted by OT is constantly associated with good social relationships.

Key words: Beta-endorphin, cannabinoids, oxytocin, pleasure, prolactin, sex, sexuality

INTRODUCTION

Despite its great importance for human reproduction, pleasure, and self-realization, the human sexuality still persists to represent the most unknown aspect of the human life, since the knowledge of the neurochemical biochemistry responsible for sexual excitation, imagination, and satisfaction is still at the beginning.[1] Several endogenous molecules influence the sexual behaviour,[2-11] including LH RH, gonadotropins, gonadal steroids, PRL, oxytocin (OT), mu-agonist opioids, cannabinoids, the pineal indoles melatonin (MLT) and 5-methoxytryptamine (5-MTT), and the beta-carboline pinealine (PNL). Cannabinoids, OT, and pineal hormones may exert an antitumor activity, whereas PRL and mu-opioids may promote tumor growth". The results referred in the literature about the sexual effects of the different hormones, neuromodulators and neuropeptides are often contradictory, but this evidence is not surprising, since their influence on the sexual behavior may be dose dependent, and it could change in relation to the different experimental conditions and to the different animal species. However, despite the controversial results, it is possible to elaborate a preliminary biochemical system involved in the modulation of the sexual psychological and biological life, schematically represented by two opposite dynamics, provided by stimulatory or inhibitory effects on imagination and physical sexual potency.[2-11] The potentially stimulatory sexual system is consisted of LHRH, endogenous cannabinoids, the pineal indoles MLT and 5-MTT, the beta-carboline PNL, and the neurohypophyseal hormone OT. On the other side, the inhibitory sexual system is constituted by the endogenous opioids, namely, the mu-agonist ones, such as beta-endorphin, PRL, ADH, and catecholamines. Moreover, heart itself may indirectly participate to the regulation of the sexual life through the release of its main hormones, atrial natriuretic peptide (ANP)[12] and endothelin-1 (ET-1),[13] which are, respectively3 connected to the inhibitory and to the stimulatory functional systems on the sexual life. In fact, ANP is connected to both pineal gland[14] and OT secretion[15] by

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bidirectional stimulatory relationships. From a neuroanatomic point of view, amygdala would play a fundamental role in the modulation of the emotional and sexual life[16] through its connection with both the mesolimbic and limbic systems, as well as with the pineal gland.[9] Because of their involvement, respectively, in the control of mood and pleasure perception, serotonin and dopamine obviously play also a fundamental role in influencing the sexual profile.[2-11]

THE MAIN ENDOGENOUS FACTORS STIMULATING THE SEXUAL LIFE

The hypothalamic neurohormone LHRH, in addition to its stimulatory activity on the hypophyseal release of gonadotropins LH and FSH, could at least in some experimental conditions to exert a direct psychological stimulatory action on the sexual excitation, whereas the actions of FSH and LH would be primarily limited to the regulation of the only reproductive life. On the contrary, the neurohypophyseal hormone OT has been clearly shown to promote sexual behavior in an emotional empathic manner and to stimulate sexual pleasure.[4] In fact, OT blood levels have been proven to enhance during the sexual activity, with maximal values at the orgasm phase in both women and men.[17] Moreover, OT has appeared to induce penile erection.[18] In addition to its promoting effect of the sexual arousal and pleasure, OT tends to inhibit the memory processes, and this finding is not surprising, since the memory of pleasure would reduce the potency of pleasure itself. In any case, OT has been proven to stimulate the sexual relation, but within a general amelioration of the social and affective relationships.[4] The endogenous cannabinoids, as well as the exogenous ones, represent the most potent agents in enhancing the sexual pleasure by amplifying the imagination potency of the sexual fancies,[7] either directly or through its connections with the pineal gland,[18] which also play an important role in the control of mood and pleasure perception.[9] OT and MLT secretion have appeared to be linked by reciprocal stimulatory mechanisms.[19] On the same way, both OT-ANP relationships[14] and MLT-ANP interactions[15] are consisting of bidirectional stimulatory dynamics. Then, heart itself, in addition to its fundamental hemodynamic function, may be indirectly involved through its endocrine activity in the regulation of the psychological and spiritual aspects of the human sexuality. Finally, the beta-carboline PNL, namely, produced by the pineal gland, would enhance the consciousness of own sexual fancies and pleasure perception, mainly in women.[11]. The importance of OT in activating the sexual life is also suggested by the evidence of abnormally low levels of OT in women experiencing sexual problems, as well as by that any factor which interferes with the secretion of OT can cause sexual dysfunctions, including depression and other psychiatric disturbances, while some recreational psychoactive drugs, such as 3,4-methylen-dioxy-metamphetamine, the so-called ecstasy, have appeared to stimulate OT secretion.[20]

THE MAIN ENDOGENOUS FACTORS INHIBITING THE SEXUAL LIFE

One of the first and more investigated endogenous factors suppressing the sexual behavior is probably PRL itself.[3] From a biological reproductive point of view, PRL plays an anti-sexual activity by inhibiting FSH and LH hypophyseal secretions, with erective dysfunction in men and amenorrhea and sexual anhedonia in women. However, some other endogenous factors have been proven to exert a preferential inhibitory action on the sexuality, despite the controversial results reported in the literature, in particular the opioid peptides.[20] The endogenous opioids would play a preferential suppressive activity on the sexual life, and this effect would primarily depend on the mu-opioid agonists, such as beta-endorphin, while the role of delta-opioid agonists, such as met-enkephalin, and the kappa agonist ones, such as dynorphin, would be less evident. The main role of endogenous mu-opioid agonists in mediating the inhibitory role of stress on the sexual interest is also documented by the evidence that the concomitant administration of mu-opioid antagonists, such as naloxone or naltrexone, may abolish the negative effects of stress on the sexual performance.[21] The pro-gonadotropic activity of mu-opioid antagonists is documented by their ability to increase LHRH release from the hypothalamus. Moreover, low-dose naloxone has appeared to exert both stimulatory and inhibitory effects on orgasm and pleasure in women, depending on the schedule of treatment.[22] Then, the opioid agents may play both inhibitory and excitatory effects on the sexual arousal, according to a parabolic profile of action. Exercise may stimulate beta-endorphin secretion, which may acutely induce a transient stimulatory effect on the sexual activity by inducing a well-being status, as well as on some immune cells, such as NK cells, but in any case, the chronic use of opioid drugs has been proven to reduce the sexual performance and interest, namely, in male subjects, with low levels of testosterone,[20] as well as in the immune performance.[23] If we consider that mu-opioid agonists may exert suppressive effects on both sexuality[20] and on the immune response, namely, on the anticancer immunity,[23] we start to understand the relation existing between sexual pleasure and cancer development and progression, as proposed by Wilhelm Reich more than 50 years ago.

ORGASM-RELATED HORMONAL CHANGES

The human orgasm is the end result of several interactions involving hormones, neurohormones, neurotransmitters, and neuromodulators. Orgasm has appeared to be associated with an increase in the blood levels of PRL, OT, catecholamines,

as well as beta-endorphin in the only women,[20] and this evidence could explain at least in part the different orgasm phenomenology between men and women, in whom the experience of orgasm is generally associated with a decrease in self-consciousness status. In fact, the opioid agents decrease the status of self-consciousness. The controversial results concerning the effects of beta-endorphin and most in general of the mu-opioid agonists may be explained by the fact that some of the opioid effects on sexuality are mediated by other endocrine or neuroendocrine agents, whose secretion may be stimulated or inhibited by the same opioid substances.

THE PSYCHIC SEXUAL IDENTITY

The psychological sexual identity, with the following sexual preferential orientation, does not primarily depend on the simple male and female gonadal steroid concentrations into the blood, but it would be mainly due to female and male gonadal steroid concentrations at brain level, which depend on the content of the two main enzymes responsible for sex steroid metabolism, including aromatase and 5-alpha reductase.[24] Testosterone is generally considered as the male sexual hormone, but in the reality, it simply represents the androgenic hormone, from which both male and female sexual hormones may originate, consisting of 17-beta-estradiol for females through the action of the enzyme aromatase and dihydrotestosterone (DHT) for males through that of 5-alpha-reductase. Moreover, in contrast to the common popular imagination, it has been shown that the female sexual hormone may paradoxically pilot the sexual orientation of men in heterosexual way, and on the same manner DHT, the active form of the male sexual hormone may direct the sexuality of women in heterosexual sense. Within the whole brain, one of the main nervous centers involved in sexual identity and orientation, is represented by the hypothalamic anterior interstitial nucleus, whose aromatase content has appeared to be highest in heterosexual males, to be lowest in women and intermediate in homosexual men.[25] Then, the evidence of low levels of brain aromatase in men, namely, in the hypothalamic anterior interstitial nucleus, would predispose to the homosexual orientation, as well as that of low levels of 5-alpha reductase in women may allow a lesbian behavior. Therefore, from this point of view, the administration of 5-alpha reductase inhibitors, such as finasteride, which induces a decline in DHT concentrations, may allow a heterosexual profile in homosexual men, and in a specular manner, the treatment with aromatase inhibitors may activate the sexual interest for men in lesbian women.[25]

THE HORMONE OF LOVE

Within the great number of hormones and neuroactive agents potentially able to influence the human sexuality, the most identified and investigated is OT.[4,26-28] In fact, it addition to its most popularly known fundamental role in promoting both maternal and paternal emotional behavior, namely, by stimulating dopamine release in the hypothalamic paraventricular nucleus and in nucleus accumbens, OT has been proven to promote social relationships, and in particular the sexual affective ones, which allow to define OT as the hormone of love or happiness hormone.[4] The stimulatory effect of OT on the sexuality would be due to several mechanisms, including anxiolytic, anti-stress, and antidepressant activity, as well as to a direct modulation of amygdala functionless, by reducing the fear response of amygdala, which plays a fundamental role in influencing the emotional responses in relation to the past experience of the affective life.[29] Then, OT would contribute to realize the freedom of human subjects by counteracting the emotional unconscious influence of past experiences on the present life. In any case, in addition to its fundamental influence on the sexuality in humans, OT would also play an essential role in the modulation of the consciousness states, as suggested by the evidence of an endogenous deficiency of OT in psychiatric disorders, such as the autistic syndrome.[30] In more detail, OT has been shown to play a role in memory processes by inhibiting memory fixation, in the perception of pleasure, also due to its connection with the pineal gland, and in the dynamics of self-identity.[4] According the knowledgments available up to now, it is possible to conclude that in addition to the role played by the sexual steroids, the psycho-neuro-endocrine regulation of the sexual life is mainly modulated by OT and the opioid peptides,[20] with a constant stimulatory effect exerted by OT released from the neurohypophysis, and with a dual inhibitory and stimulatory action of the opioid peptides, depending on the area of brain. In more detail, the mu-opioid agonists would inhibit the sexuality by acting on the medial pre-optic area and paraventricular nucleus, while they may play a promoting effect by acting on the ventral tegmental area and activating the mesolimbic dopaminergic system, which is related to pleasure perception. In contrast, OT would mainly act by modulating the function of the amygdala, as confirmed by the evidence of a high OT receptor expression at amygdala level.[20] Then, amygdala would represent the main brain target organ for OT action. Therefore, if we take into consideration the fundamental role of amygdala in modulating the emotions and the emotional response to the different social and environmental stimulations, we can understand the essential role of OT in the modulating the psychological, spiritual, and social life on humans.

THE ENIGMA OF THE COCCYGEAL GLAND

It is known since a long time in the Indian and Tibetan tradition that the coccygeal gland is connected to the sexual energy, the so-called kundalini. However, until few years ago, the histological nature of the coccygeal gland

was still unknown, while at present, it has been identified as a chemoreceptor gland, with a great density of vessels, neuroendocrine cells around the vessels and nervous fibers directly activating the central nervous system, by influencing cardiac and respiratory frequency.[31] Coccygeal gland is under both sympathetic and parasympathetic regulations, and it has been proven to show a high acetylcholine content.[32] Moreover, a deficiency in coccygeal gland function has been shown to allow lymphocytopenia and increase in platelet and neutrophil counts,[32] and this finding could explain the possible influence occurring between sexual life and hematologic and immunological status of human subjects.[32]

A HYPOTHESIS ON THE ARCHETYPAL STRUCTURE OF THE HUMAN SEXUALITY

The recent advances in the knowledge of the neurochemical mechanisms involved in the mediation of the psychological and spiritual life would seem to confirm the prophetic Freud's vision of the human psychological life as founded on two main major principles, the principle of pleasure and love and that of death-like status of pleasure repression, the so-called principles of Eros and Thanatos, respectively. In fact, it is possible to identify two major biochemical systems influencing the sexual life, provided by stimulatory or inhibitory action. The sex inhibiting system is mainly constituted by PRL, mu-opioid peptides, ADH, and ET-1, whereas the stimulatory one would involve the endogenous cannabinoids, OT itself, the pineal hormones, both the indole hormones and the beta-carbolines, and LHRH. In the reality, Freud's vision would represent the simple evolute form of the natural Hebraic essenic tradition, which had identified into the human life two opposite ways of existence, the way of Life and the way of Death. The sex stimulating system may be considered as the way of Life and, on the contrary, the sex-inhibiting system the way of Death. However, it is probable that the activation of both systems may induce a some kind of sexual unconscious excitation and pleasure, but with opposite profiles, since opioid-related pleasure would simply consist of well-being and euphoria as a private status and with separation from the universal life, then without any expansion of mind, with probably sadic fancies during the sexual excitation, whereas the sexual pleasure promoted by OT, cannabinoids, MLT, and beta-carbolines tends to be associated with an improvement in the social relationships, as well as with an expansion of self-consciousness, with preferential sexual excitation-related masochistic fancies, as an psychosexual equivalent of the spiritual sacrifice for the free spiritual evolution of humans. In fact, preliminary study would suggest a greater dimension of amygdala in males than in females, and most in general in hypersexuality than in hyposexuality or normal sexual condition,[16] whereas the dimension of hippocampus would be greater in women than in men, and most in general in low religiosity conditions than in the presence of religiosity, by suggesting possible interactions between sexual and spiritual life.[33,34]

CONCLUSIONS

The knowledge of the neurobiochemical mediation of the human sexuality is still at the beginning, and it is very complex, since it does not involve the only sex steroids, as believed in the past, but a great number of neurohormones and neuropeptides with their multiple interactions. However, according to the still limited knowledge of the sexual psychobiochemistry, the more simple non-toxic human molecules to improve the sexual life in its pleasure and romantic dimensions may be represented by OT, the pinel indole MLT, the beta-carboline PNL, and the cannabinoid agents.

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