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Invited review

Role of amygdala in mediating sexual and emotional behavior via coupled nitric oxide release[1]

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Abstract

Although the anatomical configuration of the amygdala has been studied a great deal, very little research has been conducted on understanding the precise mechanism by which this emotional regulatory center exerts its control on emotional and sexual behavior. By applying research methodology from the Neuroscience Research Institute, State University of New York, College at Old Westbury, we intended to demonstrate that much of the mediated effects of the amygdala, specifically the regulation of the male and female sexual response cycles, as well as related emotional considerations, exert their effects coupled to nitric oxide (NO) release. Furthermore, by using current anatomical and histological data, we demonstrated that amygdalar tissue rich in endocannabinoid and opiate, as well as catecholamine, receptors could exert its neurochemical effects within an NO-mediated paradigm. This paradigm, together with the existence of estrogen and androgen signaling within the amygdala, further lends credence to our theoretical framework. We begin with a brief anatomical and functional review of amygdalar function, and then proceed to demonstrate its relationship with NO.

Introduction to the structure and function of the amygdala

The region of the human brain commonly referred to as the amygdala comprises an area of approximately 3 cm^3 [1,2]. At the dorsal base of the brain, the elevation of the parahippocampus at the uncus is in part a result of the amygdala, which resides dorsal to it. Although neuro-anatomists often make reference to this portion as a single unitary structure, the amygdala is actually three distinct collections of nuclei. The largest portion of the amygdaloid complex is the basolateral nuclear group, consisting of the lateral nucleus, the irregular basal nucleus, and the accessory basal nucleus. The other major portion consists of the centro-medial group, which comprises the central nucleus and the medial nucleus. The centromedial group communicates via fibers of the stria terminalis to the bed nucleus of the stria terminalis (BST)[2] (Figure 1). Cell types in the BST are identical to those in the centromedial, causing the BST to be included in the classification of amygdalar tissue. The BST lies in the basal forebrain, which also contains the basal nucleus of Meynert, the nucleus accumbens, and the ventral portions of the putamen and globus pallidus. Anatomically, the smallest portion of the amygdaloid complex is the cortical nucleus; with primary input originating from the olfactory bulb and olfactory cortex, undoubtedly this plays a role in emotion-associated olfaction[2].

Nitric oxide correlates amygdalar function When we examine nitric oxide (NO) signaling, we notice two constitutive enzymatic components, the constitutive NO synthase (cNOS), including endothelial (eNOS) and neuronal (nNOS) isoforms. cNOS, as the name implies, is always expressed. When cNOS is stimulated, NO release occurs for a short period of time, but this level of NO can exert profound physiological actions for a long period of time[3]. NO not only is an immune, vascular, and neural autoregulatory signaling molecule, but also performs vital physiological activities via

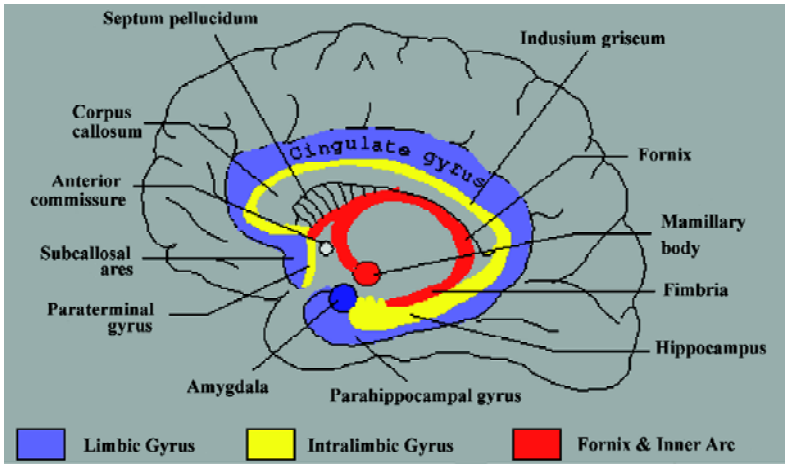

Figure 1. The limbic system.

its constitutive expression[4,5].

Both the amygdala and the hippocampus contain numerous receptors for varying neurotransmitters. The central nucleus of the amygdala is most strongly modulated by dopamine, norepinephrine (NE), epinephrine, and serotonin[6,7]. The basal nuclei receive moderately high inputs of dopamine, NE, and serotonin[6,7], each of which has been demonstrated to exert their desired effect via NO[4]. Taken together, we surmise that NE initially promotes a slight vasoconstriction of the artery during the amygdalar compensatory response, which is defined as the limbic system's inherent mechanism to maintain homeostasis and lower stress levels. This mechanism is indicated by a slight enhancement of sympathetic activity on stimulation (ie, emotional), and is immediately followed by the release of NO from the peripheral nitroxidergic nerve, which mediates a concentration-dependent vasodilation[5]. In primates, the cerebral arterial diameter, under resting conditions, is maintained by tonic release of NO from the nerve (10%–20%), or from the nerve and endothelium (30%)[8]. This observation is supported by other data from our laboratory because of the fact that basal NO is cNOS-derived and keeps particular types of cells in a state of inhibition[5]. Endogenous superoxide dismutase in the cerebral artery appears to protect the relaxation induced by NO from perivascular nerves from the NO scavenger action of superoxide anions[9]. This NO then produces the longer-lived phenomenon of smooth muscle relaxation. In another report, it was found that NE vascular hyperresponsiveness in hypertension was dependent on an impairment of NO activity that was realized through NE-induced oxygen free radical production[10], providing an important contribution to the understanding of this regulatory process.

Amygdalar NO release and its relationship to sexual behavior

In addition to NO and the amygdala, new knowledge has emerged concerning the role of hypothalamic, limbic, and brainstem structures, neuropeptides, and brain monoamines in the control of partner preference, sexual desire, erection, copulation, ejaculation, orgasm, and sexual satiety – the details of which are discussed below. At least one important sex difference exists between the male and female amygdala of many species. Owing to the interplay of the differing sex hormones, males and females will experience pleasure from differing experiences (eg, it has been shown that males are more visually stimulated than females[7,11]). In addition, modulating the concentration of testosterone may cause a male to partake in stereotypical "male behavior." Likewise, modifying the concentration of estrogen may cause the female to partake in specified, stereotypical "female behavior"[7,11]. The amygdala is intimately involved in sex and sexuality. It is important to note that the male amygdala is slightly bigger than that of the female. The medial part of the female amygdala plays an important role in pregnancy and appropriate coordination of the endocrine system. Stimulation of the amygdala will produce penile erection, sexual sensation, representations/memories of intercourse, and orgasm[7,12,13]. Furthermore, precortical region epilepsy has been shown to elicit spontaneous sexual arousal and orgasm, thus clearly demonstrating the role of the amygdala in sexual pleasure[12,13].

Stimulation of the corticomedial amygdala has been shown to induce ovulation in the female, and cutting the stria terminalis abolishes this effect. The introduction of tract lesions to the rat amygdala, including the medial nucleus, eliminates male libido, but not female libido[2,7,11,14]. In humans, temporal lobe epilepsy has been associated with sexual

arousal in women to the point of orgasm; however, evidence of this in men is unsubstantiated[12,13].

Nitric oxide release has been demonstrated as the critical link between corticomedial stimulation and its relationship with the densely packed estrogen/androgen regions within the amygdala[15–19]. NO has been shown to be crucial for the occurrence of basal luteinizing hormone (LH) release in males[15], and for the LH surge in ovariectomized females treated with estradiol plus progesterone[16–18]. Furthermore, NO donors induce an LH surge in estradiol-treated ovariectomized females[16–20], and thus, have a progesterone-like effect. Concomitant findings show that estradiol stimulates nNOS expression in the preoptic area and exerts a helping influence on NO-producing neurons[17]. The released NO appears to be able to modulate the activity of gonadotrophic releasing hormone neurons (GnRH)[17]. These observations implicate neuronal NO in the regulation of GnRH cell activity in the preoptic area[20–23]. It is important to note that some studies suggest that at the median eminence (ME) level, the NO implicated in the modulation of GnRH release is endothelial in origin, rather than neuronal[23]. This is consistent with the fact that, unlike in the preoptic area where GnRH perikarya are surrounded by nNOS-containing cells, nNOS fibers and GnRH fibers in the ME are distributed separately in the internal and external zones, respectively[19]. Furthermore, in the ME, eNOS immunoreactivity is observed in endothelial cells of the pituitary portal blood vessels[20], located in immediate proximity to the GnRH terminals[21]. The endothelial origin of NO secreted from ME fragments is further substantiated by the results of prior reports that show that central administration of eNOS antisense is more efficacious than nNOS antisense administration in suppressing an estradiol-/progesterone-induced LH surge in ovariectomized females[21]. These findings are directly related to amygdalar function by way of neuronal projections extending from the amygdala precortical region to the ME (interestingly, this relationship can be made without regard to whether ME signaling occurs via neuronal or endothelial NO). Thus, we can hypothesize a more robust signaling system involving both NO from amygdalar origins, as well as hypothalamic hormonal relationships.

Emotional stressors mediated via amygdalar NO release

Morphine and related compounds mediating NO release within the amygdala The endocannabinoids, anandamide, and 2-arachidonyl glycerol, are naturally occurring, constitutively expressed, NO-stimulating signaling molecules[24]. Anandamide and morphine can also cause NO release from human immune cells, neural tissues, and human vascular endothelial cells[25]. Moreover, both anandamide and morphine can initiate invertebrate immune cell cNOS-derived NO[26]. Additionally, estrogen can stimulate cNOS-derived NO in human immune and vascular cells[27,28]. Anandamide, as part of the ubiquitous arachidonate and eicosanoid signaling cascade, serves to maintain and augment tonal NO in vascular tissues[24].

Both the hippocampus and the amygdala (particularly the lateral nucleus) contain high concentrations of receptors for the endocannabinoids[29,30]. In fact, reports have found endogenous morphine within the structure of the hippocampus[29,30]. In addition, this morphine activates pleasure pathways via NO and has been shown to do so in the rat brain hippocampus and amygdala[31–34]. Studies from our laboratory confirm the mediated release of NO via real-time amperometric measurement from the rat brain hippocampus[34] and amygdala[31]. This information can further be used to understand some of the pleasurable aspects of sexual activity that, indeed, are often found to have morphine-like properties and, perhaps, are mediated via these endocannabinoid and morphine laden amygdalar pathways[31,35]. Further credence to these findings stems from lesional data. Humans with amygdala lesions show a decrease in emotional tension and related sexual dysfunction[6,7]. It has been postulated that endocannabinoids and endogenous morphine may act on the lateral nucleus to prevent the linkage of sexual significance to sensory stimuli prior to conscious processing, thus interfering with the perception of sexually and emotionally charged stimuli[36].

Estrogen mediates NO release within the amygdala Estrogen, through NO release, provides an additional pathway by which the system can downregulate immunocyte and vascular function in women[37]. This may be because of both the immune and vascular trauma associated with cyclic reproductive activities, such as endometrial buildup, when a high degree of vascular and immune activities occur. Given the extent of proliferative growth capacity during peak estrogen levels in this cycle, NO may function to enhance down regulation of the immune system to allow for these changes. Therefore, enhanced cNOS activity would be a beneficial effect within the concept and time framework of amygdalar compensation (as defined earlier) and the subsequent sense of calm it induces. Thus, these signal molecules, especially endocannabinoid and opiate alkaloids, have the potential to make you "feel" good and relax[38] by releasing NO, which may once again be part of the sexual resolution (post coitus) phase of the sexual cycle.

Emotionally charged events mediating NO release within the amygdala Within this context of varying stimuli evoking

NO release, emotional stresses such as fear and anxiety can induce cardiovascular alterations, such as cardiac dysrhythmias. These are some of the same events that occur when one is exposed to sexually charged stimulus, or engaged in a sexual act[39–42]. These cardiovascular events are initiated at the level of the cingulated, amygdalar, and hypothalamic processes, as well as their projection into the higher level cerebral cortex, further altering the heart rate under stressful or sexually aroused conditions[43]. Neurons in the insular cortex, the central nucleus of the amygdala, and the lateral hypothalamus, owing to their role in the integration of emotional and ambient sensory input, may be involved in the emotional link to the cardiovascular phenomenon[44]. These include changes in cardiac autonomic tone with a shift from the cardioprotective effects of parasympathetic predominance to massive cardiac sympathetic activation[45]. This autonomic component, carried out with parasympathetic and sympathetic preganglionic cells via subcortical nuclei from which descending central autonomic pathways arise, may therefore be a major pathway in how emotional state may affect cardiovascular function. The importance of an elicited emotional response (and therefore limbic activation) was further demonstrated in ischemic heart disease when patients with frequent and severe ventricular ectopic rhythms were subjected to psychological stress[46]. The frequency and severity of ventricular ectopic beats increased dramatically during emotional activation of sympathetic mechanisms, but not during reflexively induced increased sympathetic tone. Perhaps we can even relate this mechanism to sexual orgasm, a process dominated by increased sympathetic tone.

The hard-wiring of emotional and sexual sensations coupled to cardiovascular neural processes probably involves many subcortical descending projections from the forebrain, midbrain, and, specifically, the amygdala[47–50]. Cardiovascular changes were observed in experiments where the motor cortex surface was stimulated, eliciting tachycardia accompanied by and independent of changes in arterial blood pressure[51]. The "sigmoid" cortex[52] and frontal lobe[53–55], and, in particular, the medial agranular region[56], subcallosal gyrus[57], septal area[58], temporal lobe[59], and cingulate gyrus[60–62] appear to be involved. The insular cortex in cardiac regulation is important because of its high connectivity with the limbic system, suggesting that the insula is involved in cardiac rate and rhythm regulation under emotional stress[53,54]. This form of regulation is mediated via a parasympathetic response, and is probably active in the resolution phase following orgasm[2,6,12,13].

The amygdala, with respect to autonomic-emotional integration[63,64], is composed of numerous subnuclei, which play a major role in the elaboration of autonomic responses[65]. There are profuse inputs to this region from the insular and orbitofrontal cortices, the parabrachial nucleus, and the nucleus tractus solitarius[66]. Amygdalo-tegmental projections are viewed as a critical link in cerebral cortical control of autonomic function[8,67]. This level of input allows for cerebral control of sexual behavior, such as showing sexual restraint and the ability to pass on sexual gratification. Indeed, a great deal of research center on sex-offenders' inability for, or lack of, the above-mentioned amygdalo-tegmental projections[68,69].

Mechanisms of amygdala-induced emotional compensation

As noted above, once individuals are exposed to sexually explicit or emotionally charged information, they experience peripheral vasodilation: warming of the skin, an increase in heart rate, and an ensuing sense of agitation[5,70]. This experience is remarkably similar to the physiological state that exists throughout the sexual cycle, from initial arousal through to resolution. It is the function of the amygdala to aid in the relief of these altered states, through the amygdalar primary compensatory response as defined above[2,6,7,53]. In examining a potential mechanism for this relief, besides the overriding central nervous system output via the autonomic nervous system, peripheral neuro-vascular processes would appear to be important. We surmise that NO is of fundamental importance in this response because of the increase in peripheral temperature (ie, vasodilation[5]). For a complete review of possible related mechanisms as well as the related mechanisms outlined above, see the studies by Toda *et al*[8], Lembo *et al*[10], Okamura *et al*[66], and Toda[67].

We also surmise, based on current studies, that endothelial-derived NO, released through normal pulsations as a result of vascular dynamics responding to heart beat[38], as well as acetylcholine-stimulated endothelial NO release, may contribute to the effect of NO in inducing smooth muscle relaxation[5,70]. Furthermore, vascular pulsations may be of sufficient strength to also stimulate nNOS-derived NO release, limiting any basal NE actions[5,70]. Interestingly, nitrosative stress, mediated by involvement of the reactive nitrogen oxide species, N_2O_3, does inhibit dopamine hydroxylase, which, in turn, inhibits NE synthesis and contributes to the regulation of neurotransmission and vasodilation[5,70]. This system may provide an autoregulatory mechanism involved in the neuronal control of peripheral vasomotor responses and may, once again, aid in the resolution phase of sexual intercourse (Figure 2).

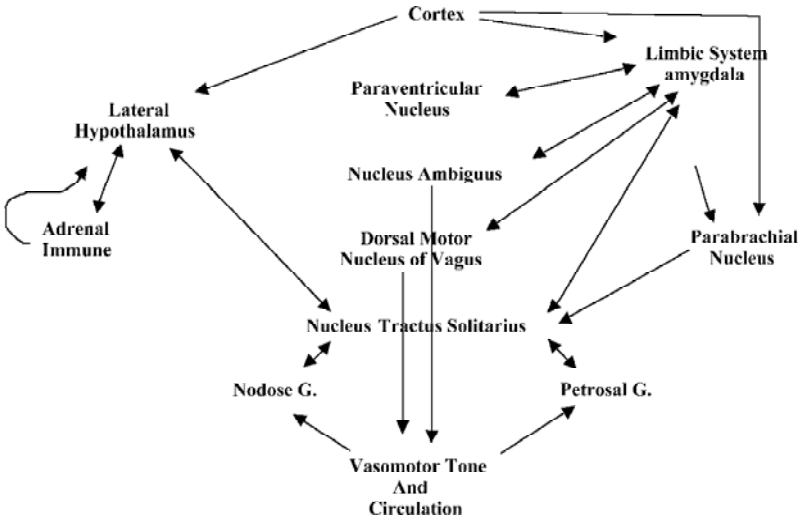

Figure 2. Summary of amygdalar projections involved in the amygdalar-induced compensatory response.

Conclusion

Our conclusion is two-fold. We demonstrate that amygdalar regulation of the male and female sexual cycle is medicated by estrogen-/androgen-related signaling molecules, both of which exert their respective influences on ovulation and sexual behavior via coupled NO release. Furthermore, we propose that amygdalar-induced homeostatic control mechanisms acting in response to emotionally charged stimuli, including sexually stimulating sensations, appear to be mediated by a system of regulation involving NO as a neurotransmitter and as a locally acting hormone. Hence, these two principal roles of the amygdala exert their respective behaviors via NO.

In final summary, we have demonstrated numerous mechanisms and neurochemical pathways with regard to both emotion and sexual behavior (ovulation, arousal, *etc*), and we have shown a link between each of these complex pathways systems, as well as the use of NO as a major biochemical messenger. Moreover, throughout each of the aforementioned pathways, we have attempted to offer a possible relationship to sex, either as a mediator of direct sexual activity, or as a mediator of an individual aspect of the sexual cycle.

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