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Review

How generalized CNS arousal strengthens sexual arousal (and *vice versa*)

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ABSTRACT

Heightened states of generalized CNS arousal are proposed here to facilitate sexual arousal in both males and females. Genetic, pharmacologic and biophysical mechanisms by which this happens are reviewed. Moreover, stimulation of the genital epithelia, as triggers of sex behavior, is hypothesized to lead to a greater generalized arousal in a manner that intensifies sexual motivation. Finally, launched from histochemical studies intended to characterize cells in the genital epithelium, a surprising idea is proposed that links density of innervation with the efficiency of wound healing and with the capacity of that epithelium to stimulate generalized CNS arousal. Thus, bidirectional arousal-related mechanisms that foster sexual behaviors are envisioned as follows: from specific to generalized (as with genital stimulation) and from generalized to specific.

Contents

Recently it was proposed that there exists a function in the vertebrate brain operationally defined as 'generalized CNS arousal," thought of as the most powerful and essential force in the nervous system for the activation of behavioral responses (Pfaff, 2006). We have an assay suitable for measuring generalized arousal in a genetically tractable animal, mice (e.g., Weil et al., 2010). Operating requirements (Table 1) of generalized CNS arousal systems have been presented (Quinkert et al., 2011). So far, three lines of evidence have been adduced to prove that a force called generalized CNS arousal actually operates in the brains of laboratory animals.

First, principal components analysis indicates that approximately 25%–40% of arousal-related variance, across a range of experiments, can be attributed to a generalized arousal component (Garey et al., 2003; Weil et al., 2010). Second, we are having partial success in breeding for generalized arousal (Weil et al., 2010).

Third, we already have a substantial amount of information about the neuroanatomical, neurophysiological and molecular mechanisms that produce generalized arousal. Neuroanatomical investigations have revealed five ascending systems (noradrenergic, dopaminergic, histaminergic, cholinergic and serotonergic, reviewed in Pfaff, 2006); several descending systems, including oxytocinergic, vasopressinergic and axons descending from hypocretin/orexin neurons; and a substantial number of large cells in the medullary reticular formation that have axonal divergences that would allow them to contribute both to ascending and to descending arousal systems (Scheibel and Scheibel, 1958; Valverde, 1961, 1962; Leontovich and Zhukova, 1963; Martin, Fontaine and Pfaff, submitted for publication). Medullary

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Table 1
Operating requirements for CNS arousal systems.

1. Provide alertness to sensory stimuli, body-wide, all sensory modalities.
2. Drive voluntary motor activity, body-wide, from fidgeting to marathons.
3. Fuel emotional reactivity, positive and negative.
4. For (1–3), be labile, 'hair triggered,' rapid, not sluggish.
5. For (1–3), be sensitive to the momentary state of the organism.
6. Convergence: All sensory stimuli activate the same sets of arousal subsystems, which, in turn, support each other.
7. Divergence: From arousal systems to activate cerebral cortex, autonomic nervous systems and endocrine organs thus to activate behavior.
8. Do not fail because survival of the organism depends on adequate CNS arousal.

(Adapted from Quinkert et al., 2011).

neurons in this same gigantocellular portion of the medullary reticular formation have the following neurophysiological properties that would allow them to act as 'first responders' to arousing stimuli: they have multimodal responses to sensory stimuli, their responses habituate, they are associated with activation of the cortical EEG and with neck muscle EMG and their increased firing rates precede the activation of behavioral responses from a state of quiescence (Martin et al., 2010). In terms of molecular mechanisms, among a large number of genes argued to be involved (Pfaff, 2006), the discoveries of hypocretin/orexins (Carter et al., 2009b) and their impacts on the wake/sleep cycle (Carter et al., 2009a; Blanco-Centurion et al., 2007; Anaclet et al., 2009) all clearly support the notion of a generalized arousal function. Furthermore, from a molecular point of view, arousal has been proven to be an experimentally tractable subject by gene knockout studies (Garey et al., 2003) and by molecular pharmacological approaches (Easton et al., 2006) and by antisense approaches (Mong et al., 2003b).

Originally conceived as a brain function universal among vertebrates, with a prime example of the most basic mechanism represented by Mauthner cells in the medulla of fish, the concept of generalized nervous system arousal has also come into play during studies of much simpler zoologic forms, such as Drosophila (van Swinderen and Greenspan, 2003; Anholt, 2004; Kume et al., 2005; Shang et al., 2008) and Aplysia (Jing et al., 2009). In the human brain, cerebral cortical electrical activity during 'resting states' in the absence of specific tasks are laid to a 'default network' that likely reflects the ascending influences of generalized arousal systems (Raichle et al., 2001; Kojima et al., 2009). Activity in this 'baseline' state depends on a certain baseline supply of brain energy (Shulman et al., 2009) and likely reflects local electrical field potentials in widespread areas of the cerebral cortex (Schölvinck et al., 2010). Disruptions of this distributed system may contribute to cognitive decline during aging (Andrews-Hanna et al., 2007), as would be expected if the 'default network' reflects the impact of generalized arousal systems. Thus, it appears to be the case across a wide variety of animals, including humans, that the activation of behavior reflects some kind of generalized arousal system.

Implicit in the theory of generalized CNS arousal was the prediction that increases of this universal function would augment the performance of specific motivated behaviors that depend on specific forms of arousal. Said another way, for example, increased levels of generalized arousal could result in a greater magnitude of sexual arousal. Conversely, sexually arousing stimuli could be potent drivers of the generalized arousal system (see below). These predictions are finding support in several studies of sexual behavior.

Here we propose, first, that generalized arousal transmitters activate preoptic and hypothalamic neurons that facilitate male and female sex behaviors, respectively, and that from the hypothalamus and basal forebrain axons descend to the brainstem and regulate those behaviors. But, then, second, we also chart ways of studying how signaling from a sexually aroused skin surface could influence generalized arousal—signals traveling in the opposite direction, ascending the neuraxis from the lumbosacral spinal cord toward the brain.

From generalized arousal to sexual arousal

Sexual arousal reflects states of heightened excitability in both males and females, states that likely depend on generalized arousal but that also require other environmental, neural and hormonal influences. In males, the evidence that heightened generalized arousal facilitates sexual arousal comes from genetic studies and from neuropharmacological studies.

Males

We sought to determine, by breeding lines of mice for high or low generalized arousal (GA), whether genetically-encoded differences in generalized arousal would translate into alterations in specific types of arousal-dependent motivated behaviors. To that end, we took the mice of generation number 6, in the breeding project, and divided them into two different ways, by 1) parental arousal—whether their parents were in the high or low lines and 2) offspring arousal—whether the animal in question (G6) was at the top or bottom of the arousal distribution (Weil et al., 2010). First, male mice were exposed to a sexually naïve conspecific (of the Het8 strain) on consecutive days until they mated. Males from the high line and those offspring who exhibited high levels of GA exhibited a specific pattern of sexual behavior associated with a higher level of excitability and sexual arousal. High arousal males exhibited more mounts before intromission and, then, fewer intromissions before ejaculating, and they ejaculated more quickly after the first intromission. In addition, the percentage of mount attempts that were successful in leading to intromission was significantly lower among male mice from the high arousal line. The pattern of sexual behavior indicates that high-arousal males were highly excitable in an inappropriate manner, as indicated by the very low intromission–total mount ratio. Importantly, as a form of control, the temporal structure of the mating bout was similar between the lines as there were no differences in the latency to mount or ejaculate between the genetic lines and between offspring high and low arousal groups. Thus, breeding males for high or low generalized CNS arousal produced animals whose sexual arousal was high or low, respectively (Weil et al., 2010).

The genes in these high GA males that we effectively have selecting for in our breeding project may well include that for hypocretin/orexin, a gene whose products are closely tied to CNS arousal. In male rats, activation of hypocretin neurons increases during copulation, whereas castration decreases then numbers of detectable hypocretin neurons (Muschamp et al., 2007). Deposited in the preoptic area, hypocretin-1 increases sexual arousal (Gulia et al., 2003), while in male rats already at a high level of sexual motivation, hypocretin decreases it (Bai et al., 2009). Arousing neurochemicals, as well, enhance male sexual behavior. Dopaminergic inputs to the preoptic area are perhaps the best established example of this phenomenon (reviewed by Hull et al., 2002; Hull and Dominguez, 2006). Likewise, drugs that release dopamine can facilitate sex behavior in male rats whose performance had been reduced by frontal cortical lesions (Agmo and Villalpando, 1995). Thus, according to several lines of evidence, it appears that heightening generalized arousal strengthens sexual arousal in males.

Females

In females, as well, generalized arousal helps to energize sexual behavior. Female rats administered methamphetamine systemically, as would clearly raise arousal levels, not only showed higher amounts of lordosis behavior (Holder et al., 2010) but also displayed more courtship behaviors (Holder and Mong, 2010) and sexual motivation (Holder and Mong, 2009) perhaps because of the greater activation of neurons in the medial amygdala and the ventromedial nucleus of the hypothalamus (VMN) and because of dopamine release onto D1 receptors in the medial preoptic area (Graham et al., 2009; Matuszewich et al., 2000).

Exactly how do compounds that alter generalized arousal affect female sexual behavior? Biophysical studies have revealed four independent physical chains of events by which arousal-related neurochemicals act on nerve cells in VMN in such a manner as to regulate sexual arousal and lordosis behavior: increasing arousal would increase lordosis, while decreasing arousal decreases lordosis. First, norepinephrine increases the excitability of VMN neurons by reducing a specific, voltage-dependent fast-acting potassium current, likely an A-type current (Lee et al., 2008a,b), even as greater binding at norepinephrine alpha-1b receptors is associated with greater sexual receptivity (Etgen, 2002). Second, histamine (HA) causes VMN neuronal depolarization acting through H1 receptors by reducing a potassium current, a current that in female rat neurons seems to involve calcium activation (Dupré et al., 2010, Kow et al., submitted for publication) but in female mouse neurons does not involve calcium activation (Zhou et al., 2007). HA elevates lordosis behavior (Donoso and Broitman, 1979), but new work must be done with specific H1 receptor agonists. Third, a mu opioid receptor agonist decreases VMN neuronal excitability (Devidze et al., 2008?), even as its administration in VMN decreases lordosis behavior (Pfaus and Pfaff, 1992). Fourth, prostaglandin D synthase (PGDS) is an enzyme that produces a somnogen in a nerve cell group, the ventrolateral preoptic area, associated with decreased arousal. That is, PGDS catalyzes the isomerization of the common prostanoid precursor prostaglandin H2 to prostaglandin D2. When administered into the cerebrospinal fluid, prostaglandin D2 promptly puts the experimental animal to sleep, i.e. reduces arousal. Prostaglandin D2 also reduces lordosis behavior as shown by the fact that microinjection of locked antisense oligonucleotides to PGDS into the preoptic area, in order to reduce the amount of functional mRNA for this enzyme, significantly increased lordosis behavior. (Mong et al., 2003a). Furthermore, estrogen treatment of ovariectomized females decreased PGDS mRNA levels in the preoptic area, thus providing a potential mechanism for estrogen-induced increases in arousal and lordosis behavior (Mong et al., 2003b). Thus, convincingly, generalized CNS arousal is associated with sexual arousal in the female.

In addition to the biophysical studies quoted above, a cell nuclear molecular route by which estrogens act in the hypothalamus to increase sexual arousal and female sexual behavior requires estrogen-dependent transcription (Pfaff, 1999; Pfaff, 2002). Recent studies of transcriptional mechanisms have emphasized the importance of changes in chromatin, histone proteins that are basic and that regulate access to gene promoters. It is clear that changes in histone chemistry in limbic–hypothalamic systems involve chemical modifications of histones (Hunter et al., 2009). Now, we are studying changes in the acetylation and methylation of histone tails in VMN as a function of estrogen treatment (Weil et al., 2009; Gagnidze et al., 2010).

Estrogenic effects on sexual arousal are not unique—estrogens also heighten several other aspects and manifestations of behavioral arousal: pain locomotion, aggression, anxiety and the sleep/wake cycle. We deal with these five aspects, in order: (i.) Estrogens can increase pain sensitivity (Claiborne et al., 2009; Hucho et al., 2006; Dina et al., 2001; LaCroix-Fralish et al., 2005) working through estrogen receptor alpha (even as they decrease pain sensitivity through ER-beta). (ii.) Clearly, estrogens elevate arousal as measured by the initiation of locomotor activity, acting through ER-alpha (Ogawa et al., 2003) perhaps because they lower adenosine 2A receptor gene expression in the ventrolateral preoptic area (Ribeiro, et al., 2009). In fact, viral vector mediated overexpression of ER-alpha in the striatum increases estradiol-induced motor activity (Schultz et al., 2009). (iii.) New results suggest that, even as the long term effects of estrogens on aggression through ER-alpha depend on the sex of the animal studied (Ogawa et al., 2004), acute activation of ER-beta increases specific aspects of aggressive behaviors in mice, namely, those aggressive responses that are not directly involved in attacks. (iv.) Estrogenic effects on anxiety and fear are complex and appear to depend both upon the assay used and on the ER subtype through which estrogens are operating (Lunga and Herbert, 2004; Hiroi and Neumaier, 2006; Lund et al., 2005). (v.) Finally, in laboratory animals, estrogens are associated with decreases in slow-wave sleep (Li and Satinoff, 1996; Colvin et al., 1969; Colvin et al., 1968) perhaps because of the ability of estrogens to suppress the activity of neurons in a sleep-producing neuronal group, the ventrolateral preoptic area (Peterfi et al., 2004; Mong et al., 2003a,b; Hadjimarkou et al., 2008; Devidze et al., 2010). Neurochemically, it has been shown that estrogens and orexin interact in their effects on measures of arousal in female mice (Easton et al., 2006). In women, under certain conditions, estrogens clearly heighten mood (Sundermann et al., 2010; Ng et al., 2010; Maki et al., 2010; Gillies and McArthur, 2010) and increase blood perfusion of cortical areas involved in cognitive tasks (Dietrich et al., 2001).

Finally, an entirely different way of connecting generalized arousal to sexual arousal has nothing directly to do with sexual behaviors. It turns out that there is a large and convincing literature on the relations between sex hormones and drugs of abuse. In fact, some drugs of abuse may be tempting precisely because they arouse states in a pleasing way. Becker and her colleagues have shown that the estradiol enhances behavioral sensitization to cocaine during experiments with rats (reviewed, with new data, in Zhao and Becker, 2010), although results in primates may be more equivocal (Evans and Foltin, 2010) and progesterone has exactly the opposite effect (Quiñones-Jenab and Jenab, 2010). Segarra et al (2010) emphasize that the major enhancing effect with cocaine has to do with animals' responses to repeated cocaine administrations. Whether or not stimulants of CNS arousal or depressant drugs affect sex behavior and sexual reward depends on several factors including, at least, the animal's initial level of sexual behavior, hormonal status, the exact measure of sex behavior or sexual preference used and the time course of drug administration (Pfaus et al., 2010; Guarraci, 2010). The differences in methodological requirements for studies with humans as compared to laboratory animals have been noted (Frohmader et al., 2010). Finally, in a comprehensive review, Carroll and Anker (2010) leave no doubt that there are sex differences in various forms of drug dependence.

In summary, it is clear from a variety of genetic, pharmacological and biophysical studies that heightened generalized CNS arousal can foster increased sexual arousal and the reverse. Therefore, the prediction from generalized arousal theory is satisfied, that its perturbations should be able to alter motivated behavior.

Up to this point in the present paper, mechanisms have been considered that are operational in the hypothalamus and basal forebrain, and subsequent hormone-dependent signals descend toward the brainstem in order to generate reproductive behaviors. Another approach is to work in the opposite direction, to start at the opposite end of the neuraxis, with cellular mechanisms in those areas of skin most intimately connected to sexual arousal.

Arousal signaled from genital epithelia: from sexual arousal to generalized CNS arousal

Actions of the cutaneous receptors and the other biochemical properties of epithelial tissue of the vulva, genitalia and vagina help to stimulate sexual arousal. These genitosensory fields deliver sensory information to the CNS by a series of complex integrative mechanisms. After tactile stimulation of the genital epithelium, specific changes in genital structures occur (increased clitoral length and diameter, labial blood engorgement and increased vaginal luminal diameter) and lead to increasing arousal in the female. In males, similar processes control penile erection. (Schober and Pfaff, 2007). As in male genital tissue, the richest network of nerve bundles and their terminal branches are associated with neural nitric oxide synthase (nNOS) immunostaining in the cavernous tissue of the body of clitoris. (Martin-Alguacil et al., 2008a,b,c,d). Our histochemical evidence

suggests that ER-alpha can mediate the short-term effects of estrogen on endothelial NOS enzymatic activity and it may assist vasodilatation by NO synthesis or activation. Estrogen causes rapid endothelial NO production because of the activation of plasma-membrane-associated ER coupled to endothelial NO synthase through Gai. This rapid effect, initiated in the endothelium, also suggests an active role of the vulvar endothelium in arousability. (Martin-Alguacil et al., 2006). Through all of these mechanisms, tactile stimulation of the genital epithelium is beginning to be characterized as a precursor to sexual arousal in both males and females.

As we work to demonstrate histochemical mechanisms underlying and influencing receptivity from these distal areas, our focus has been the establishment of genital epithelium not only as a receptor for tactile stimulation but also as a site of action for sex steroid hormones. Relationships to nNOS and eNos are also critically inherent to the transmission of impulses along the neuraxis. Toward this end, we have established critical neural and hormonal receptor locations within the clitoral, labial and penile epithelium, in both human and animal models (Martin-Alguacil et al., 2008a,b,c,d; Schober et al., 2010; Cooney et al., 2010).

With regard to the clitoris, murine tissue study has demonstrated that the most distal epithelial innervation is derived from one of three nerve bundles: one related to the perineal region, one through the corpus cavernosum and the third between the dorsal part of the clitoris and the urethra. Communicating nerve fibers were identified between the perineal, the corpus cavernous nerve (CN) and the dorsal nerve of the clitoris. Immunostaining for nNOS showed that the CN sends nNOS-positive fibers to join the dorsal nerve of the clitoris. In the same distal area of the clitoris, the connecting branches between the perineal nerve and the dorsal nerve of the clitoris are also nNOS positive (Martin-Alguacil et al., 2008a,b,c,d). Nitric oxide's control of vasodilatation and neuronal signalling between the CN and the dorsal nerve of the clitoris could contribute to the engorgement and subsidence of clitoral tissue. This would support the initiation of sexual arousal by tactile stimuli. We note that the distribution pattern of both general and peptidergic innervation in the murine clitoris is generally similar to that of the penis.

With regard to the labia minora, ER-alpha nuclear staining was found in the stroma of the labia minora close to the clitoris and basal and suprabasal in the epidermal cells membrane restricted to superficial sections of the labia minora. ER-beta was found in the stroma of the labia minora closer to the clitoris and in superficial sections, in the basal epidermal cells membrane and apocrine glandular epithelial cells membrane. There was also ER-beta cell membrane staining in the basal and suprabasal epithelial cells and fibroblasts in the lamina propria (Martin-Alguacil et al., 2008a,b,c,d). In other studies of pubic skin of adult women, transition from vagina to vulva was marked by a decrease in ERs. (Hodgins et al., 1998).

With regard to innervation, vascular and lymphatic plexes lie within the reticular dermis, along with a dense mesh of nerve fibers. There is a higher concentration of nerve fibers at the level of the subepithelial plexus. Dense innervations are located at the epidermis, extending along the basal and spinous layers of the epithelium of labia minora. Nerve bundles in the papillary dermis are associated with sebaceous and eccrine glands and nerve terminals located throughout the epithelium. The introital epithelium of the labia minora is highly innervated with widespread and intense staining, detected in the introital border of the labia minora versus the external one. The dermis displayed S-100 and nNOS immunolabelling, with S-100 also immunopositive in the epidermis (Schober et al., 2010). A relative decrease in nerve density has been established when moving from distal to deep within the vagina. In a female cadaveric study, terminal nerve branches in the vaginal wall were found to be most dense at the second 1/5 partition from the inferior anterior wall. Density started decreasing and became scarce at the fourth and fifth 1/5 partitions from the bottom (Song et al., 2009).

Hormone-dependent neurophysiological measures may illustrate the roles played by sex hormones acting on receptive tissue of the genitalia, leading to sexual arousal (e.g., Kow and Pfaff, 1973). With respect to other causal routes, sex hormones alter cardiovascular responses to activation of medullary neurons in the arousal crescent and also address oxytocin neurons in the PVN of the hypothalamus which project back to the spinal cord and support engorgement or erection of the genitalia. (Papka et al., 1997; Zoubina and Smith, 2003; Mendelsohn and Karas, 1999; Jankowski et al., 2001; Nickenig et al., 2000; Ciriello et al., 2002; Rhodes et al., 1982; Meston et al., 1996).

In summary, estrogenic hormones affect the brain, spinal cord and peripheral sensory mechanisms that regulate acuity of sensory input in support of arousal. In both men and women, arousal is influenced by adrenergic, cholinergic and nitrergic activation mechanisms that control vascular changes and underlie vaginal lubrication and penile erection. These systems respond to descending brain and spinal influences that generate orgasmic responses. Disruptions of endocrine, neural or vascular response caused by aging, disease, surgery or medication have the potential to lead to lack of arousal and consequent sexual impairment (Schober and Pfaff, 2007).

A new theory

We propose that, across a range of epithelial surfaces on the human body or the body of a laboratory animal, there exists an unexpectedly strong correlation among three different properties: (a) density of innervation of the skin, (b) capacity for stimulating CNS arousal and (c) efficiency of wound healing. For this paper, the primary example of an epithelium high in all three properties would

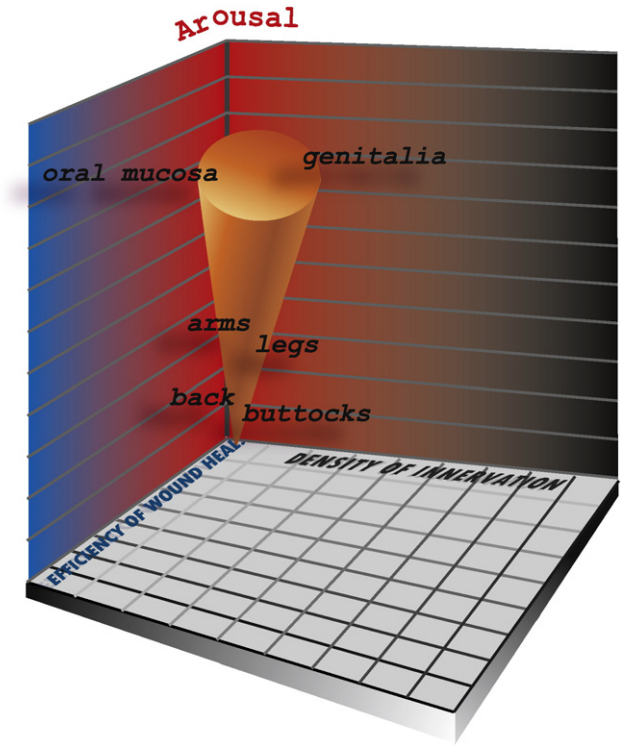

Fig. 1. Rendition of a theoretical proposal that envisions a surprising correlation among three properties of epithelia on the human body. In this three-dimensional illustration, density of innervation, efficiency of wound healing and (vertical dimension, red) capacity for triggering generalized CNS arousal are presented as independent axes. We suggest that epithelia such as the oral mucosa and genital epithelium are high on all three, whereas the buttocks and the back are low on all three, thus yielding the orange line that expresses the theoretical correlation. Importantly, interruption of signaling from heavily innervated genital epithelia, whether by peripheral or spinal injury, causes corresponding loss of sexual arousability from its sensory stimulation.

be the skin of the genitalia. Another example would be the lips. Low on all three properties would be the middle of the back (Fig. 1).

At one extreme, according to this somewhat surprising proposal, we emphasize that, even in adult humans, there are tissues that are capable of complete regeneration: the gums and gingival (interdental) papillae between the teeth will completely regenerate without scarring if excised. This regenerative mechanism is the basis of the clinical dental specialty of periodontics. In human adults, the oral mucosa and gums scar little (if at all) after surgical incision (Ferguson and O'Kane, 2004). Earlier resolution of the inflammatory reaction and reduced wound contraction may promote scarless oral mucosal wound healing. In addition, scar formation likely depends not only on the number of myofibroblasts but also on the extracellular environment which regulates their function (Mak et al., 2009).

Likewise, anogenital traumas heal quickly, often without residual scarring (Heppenstall-Heger et al., 2003). Hymenal injuries heal rapidly and except for the more extensive lacerations left no evidence of a previous injury and no scar (McCann et al., 2007). In contrast, an identical surgical incision, such as a 1 cm cut, will scar much worse if made on the skin covering the deltoid region and sternum of the chest than for example on the face, abdomen or legs. It is clear that, even in man, there are tissue-specific and regional variations in regeneration and in the severity of scarring (Ferguson and O'Kane, 2004). Wound repair in human adult skin typically begins with hemostasis and inflammation followed by a proliferative phase, re-epithelialization and angiogenesis. This ends with some degree of scar in most areas. Animal and clinical fetal studies have shown that a different type of healing occurs in the first two trimesters of development: regeneration or repair with little or no inflammation, faster re-epithelialization and no scarring. (Wilgus, 2007). Scarless fetal skin wound healing is the ideal paradigm for ideal skin repair and is dependent on peripheral nerve function. Along these lines, fetal skin cells may express neurotrophins during skin development that regulate peripheral neuron formation (Antony et al., 2010).

Thus, for the stimulation of sexual arousal, it is important that anogenital epithelia are among the highest with respect to the theoretical correlation proposed in Fig. 1. At the other extreme, there are tissues that are less well innervated, have less dense blood supply, heal more slowly and would be less effective at stimulating generalized CNS arousal.

How does the correlation theoretically illustrated in Fig. 1 come about? Our current thinking focuses on the developmental biology of the skin, in which classical findings reported close associations between developing innervation and new vascularization. Albers and Davis (2007) have begun to chart the roles of various growth factors in the development in skin innervation, including nerve growth factor (Harrison et al., 2004), a glial cell-derived growth factor (Zwick et al., 2002) and NT3 (Krimm et al., 2004). But between innervation and vascularization during development, which leads to which? It has been well established that developing blood vessels and neuronal pathways "share guidance cues and cell-surface receptors" (Fantin et al., 2009). Studies with still another growth factor, VEGF, not only revealed that proper vascularization and neuronal development can be coordinated (Mukouyama et al., 2002) but also suggested that "nerve-vessel alignment is a necessary but not a sufficient condition for nerve-induced arteriogenesis" (Mukouyama et al., 2005).

Therefore, we now would hypothesize (Fig. 2) that denser innervation not only eads to the greater capacity for triggering CNS generalized arousal but also fosters vascularization that is, in turn, a positive factor for efficient wound healing. This series of events would explain the correlation proposed in Fig. 1.

This somewhat surprising theoretical idea is intended to deepen our understanding of the nature of the tissue whose stimulation heightens both generalized arousal and sexual arousal. Current work focuses on the histochemical characterization of epithelial cells and sensory end-organs in genital epithelial tissues that are crucial to the kind of cutaneous stimulation that triggers sexual behaviors.

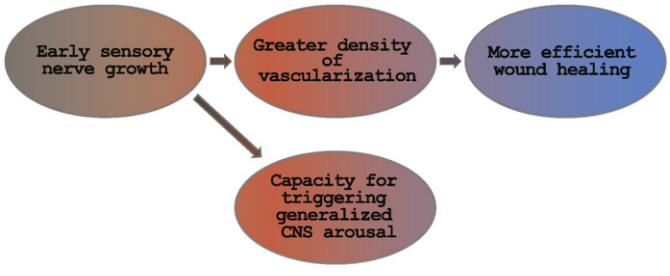

Fig. 2. To the extent that the correlation across epithelial surfaces presented in Fig. 1 actually exists, how does it come about? The molecular literature suggests that the first step involves sensory nerve growth. Sensory innervation is obviously linked to the capacity for triggering CNS arousal and also apparently promotes vascularization which, in turn, is theoretically associated with wound healing.

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