Because Sex Matters: the case of female sexual response

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Abstract

In recent years, the Food and Drug Administration approved two drugs for the treatment of hypoactive sexual desire disorder in premenopausal women which have been tested in preclinical tests with positive effects on some appetitive sexual behavior in female rats. Some years after their commercial release, the effectiveness of both drugs in women is not clear. In the present chapter, we present some considerations regarding preclinical studies of copulatory behavior, most of them conducted in female rats. Although knowledge of the neurobiological basis of copulatory behavior in the female rat is still growing, the extent to which these findings might be applied to women´s sexuality is unknown. On the other hand, sexual response in women is flexible and less hormone-dependent compared with men. Moreover, sociocultural factors deeply influence sexuality in women, and they might contribute to the development of sexual dysfunctions. Additionally, the kind of model that better describes sexual response in women seems to be individual and fluctuating. We briefly mentioned some of the most used methods for measuring genital arousal, putting out the need for developing better strategies to get objective and replicable results. We conclude that the contribution, if any, of animal models of sexual response in female rodents is modest. After the questionable approval and the lack of efficacy of drugs to treat sexual desire issues, it is necessary to realize that the more we understand the female sexual responses, developing better ways to evaluate them, the more we might explain, and eventually treat their dysfunctions.

Key words: female sexual response, sexual arousal, female sexual dysfunctions

Introduction

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) classified female sexual dysfunctions (FSD) into three main categories: a) sexual interest/arousal disorder, b) orgasmic disorder and c) genitopelvic pain/penetration disorder[1]. The prevalence of each FSD varies depending on instruments applied, the hypoactive sexual desire disorder (HSDD) shows the highest rates (12-20%), followed by the orgasmic disorder (6-12%) and sexual arousal disorder (5-11%) [2]. Additionally, the presence of a FSD also might negatively affect other aspects of sexual response, thus the presence of more than one FDS in the same woman is common.

The Food and Drug Administration (FDA) approved flibanserin in 2015, and bremelanotide in 2018 for the treatment of HSDD in premenopausal women. Flibanserin acts on serotonergic and dopaminergic systems and was initially developed for the treatment of depression. Bremelanotide is a melanocortin receptor agonist, originally designed for sunless tanning. Both drugs have positive effects on some appetitive sexual behaviors in sexually experienced and hormone primed female rats. Chronic treatment (14 days of 45 mg/kg/p.o.) of flibanserin, and acute bremelatonide (100/200 µg/kg s.c.,five minutes before a mating test) enhance solicitation behavior [3].

Some years after their commercial release, actual effects of both these drugs on sexual functions are still a matter of controversy [4]. For example, clinical studies show that 1.75 mg s.c. bremelanotide on demand, adds one enjoyable sexual experience every two months, whereas the effect of 50-100 mg of flibanserin daily is even more discrete than that. In a meta-analysis by Jaspers et al., (2016), they compared flibanserin and placebo effects and

included data from published reports and registries from trials. Authors found that the dropout rate in the flibanserin group was twice that found in the placebo group. The reasons were, among others, dizziness (odds ratio, OR= 4), somnolence (OR=3.97), and nausea (OR=2.35) [5]. Post-marketing reports regarding these adverse effects led to modification of the safety labeling of flibanserin, especially concerning its concomitant use with alcohol [4, 6–9]. As showed, the failure to develop efficient drug treatment for female HSDD may be related to a faulty model of the female sexual response.

In the present chapter, we present some considerations regarding preclinical studies of copulatory behavior, most of them conducted in female rats, to continue mentioning critical aspects of female sexual response (FSR) in women described recently, emphasizing peculiarities and sociocultural factors involving FSR. As will be noted, this field is still growing with the need for studying FSR directly in the subjects of interest, i.e., women.

2. Basic considerations regarding copulatory behavior in the female rat

Studies about the mechanisms involved in the dramatic behavioral changes observed between non-sexually receptive and sexually receptive female rats were relevant for extending our understanding of the neuroendocrine and physiological processes underlying these drastical changes. These studies were focused on how sex hormones, such as estrogens, in the central nervous system, induced estrous behavior whereas, in the periphery, they increased the skin´s sensitivity of the pudendal nerve field which, in sum, induce and enhance female copulatory behavior[10–12]. During behavioral estrus, rats present two relevant behaviors: receptivity and paracopulatory (formerly proceptive) behaviors. Receptivity manifests itself in a complex neuromuscular reflex, that produces immobilization with flexion of the back, rump elevation, and extension of the neck. The

lordosis posture is triggered by tactile stimulation of the flanks and enables penile intromissions into the vagina. Paracopulatory behaviors involve a range of behavioral patterns that females usually display towards the male during estrus, such as hopping, darting, and ear wiggling. A detailed description of FSB in the rat is found elsewhere [13].

With the unprecedented success of sildenafil (Viagra; Pfizer) for treating erectile difficulties in men, the interest for developing new pharmacological treatments for sexual dysfunctions increased, and many researchers shifted their interest to developing new animal models of sexual dysfunctions, especially regarding erectile and ejaculatory responses [14–16].

For decades, studies about FSB were conducted in small uni-compartmental arenas. Under this condition, a sexually experienced male and a sexually receptive female are placed together., There are a few options, if any, for other interactions but sexual [17, 18]. Research was focused mainly on neuroendocrine mechanisms behind the sexual responses. Since this experimental setup is far from a representative design, i.e., a procedure resembling conditions in the wild, comparisons between different species (e.g. rats and humans) were of limited value [17].

Later, studies concerning other aspects of copulatory behavior in the rat, such as sexual reward and sexual motivation, became available. In this regard, it is worth to mention that robust evidence demonstrating sexual reward in females that paced the mating was published in the late ’90 s [19–22]. Soon after, the endogenous opioid system was identified as relevant for this effect that also induces neurogenesis in some brain areas, mainly in the accessory olfactory bulb, which is critical in species such as rodents for identifying sexual cues [23–25]. Olfactory cues are critical and required in combination

with other sensory stimuli (visual, auditory) to induce a female´s approach behavior to a potential mate in rats [26].

The sexual incentive motivation test was proposed as a feasible and specific way to measure sexual motivation in rats [27]. Pharmacological studies used this paradigm to explore the role of neurotransmitters such as serotonin in sexual motivation. For example, the effect of selective serotonin reuptake inhibitors (SSRI) were evaluated, since inhibitory effects on sexual desire have been reported by women taking these drugs for the treatment of depression. Most evidence suggests that increased serotoninergic activity is related to inhibition of approach behaviors in female rats, as a reflection of decreased sexual motivation. Although there is no published data regarding the effect of the current FDA-approved drugs to treat HSDD in procedures especially designed for evaluating sexual motivation, it might be feasible way to evaluate these drugs in this kind of preclinical tests. Detailed analysis of modeling sexual motivation in rats and humans is found elsewhere [14] and an extensive analysis of that issue goes beyond the scope of the present chapter.

Studies of mating behavior in rats, under seminatural conditions, where a group of males and females are housed together in a spacious arena during some consecutive female estrous cycles. Thus, animals are in contact during transitional periods between receptive and unreceptive status, and conditions enable them to express different behaviors beyond sexual. Contrary to the uni-compartmental condition, the seminatural environment has external validity, i.e., it resembles what occurs in the rats´ natural habitat, and results can be generalized to situations outside the specific laboratory setting [17]. Under this condition, the experimental subjects showed a slower rate of copulation and the time spent in mating was less than one percent of the total duration of estrus [14]. Additionally, males and

females initiated and maintained sexual interactions equally, not female-dominated as stated previously, and the intensity of paracopulatory behaviors was partially related to female sexual motivation. The results suggest that it is necessary to re-evaluate the previous assumptions regarding the meaning and function of paracopulatory behaviors [28, 29]. Detailed methods for tests are available elsewhere in the present book. Although knowledge of the neurobiological basis of copulatory behavior in the female rat is still growing, the extent to which these findings might be applied to human sexuality is unknown, mainly because we are continually learning about the bases of the human sexual response and its peculiarities.

3. Female sexual response and some of its peculiarities

Our understanding of FSR is growing, and the evidence shows that FSR presents some exceptionalities, which are important for triggering and/or maintaining some FSD. We will discuss some of them in the following sections.

3.1 The flexibility of sexual behavior in women

Gonadal hormones, mainly estrogens released in the periovulatory period, are necessary to trigger and maintain copulatory behavior in non-primate mammals. However, in some female primates, including women, the role of gonadal hormones is not that determinant. Thus, the sexual response is more flexible and modulated by environmental and non-biological factors. Moreover, human sexual behaviors are shaped by sociocultural conventions. Therefore, humans are used to engage in sexual activities that follow social norms, which changes according to social dynamics [30].

From this perspective, the influence of gender roles, stereotypes, and violence on women´s sexuality is remarkable, and it is present in the establishment of some sexual dysfunctions, as will be mentioned in the following sections. In this context, biological factors participate marginally in the physiological aspects of sexual response in women, and expectations or previous experiences contribute to the development of women´s sexuality. In this regard, studies of sexuality in childhood consistently reported that children were able to respond genitally to sexual stimulation. Whereas masturbation in boys is commonly a discursive topic either negatively or positively, in girls, it is an unspoken issue that usually is discovered by self-exploration [31, 32]. It is possible that whereas boys acquire more experience and knowledge regarding their sexual response as they grow, girls lag in this process, creating a gender gap. Moreover, the importance given to penile-vaginal interaction as the main source of pleasure, in conjunction with the incomprehension about female anatomy and sexual arousal, enlarge this gap. In fact, penile-vaginal intercourse is far less efficient than some other sexual behaviors for leading to orgasm in women. The focus on penetrative sex as the main source of sexual satisfaction might explain, at least partially, the fact that lesbian couples are more likely to experience orgasms than women in heterosexual relationships [33].

Moreover, negative socio-cultural connotations, the lack of information, and weak positive encouragement about female sexual response increase the probability of developing sexual dysfunctions. Thus. the more we overcome these factors, the more possibilities we have to reduce this gender gap [34]. On the other hand, when humans engage in sex for reasons and consequences beyond recreation i.e., transactional sex, women´s reasons differ from those

of men since women tend to show more emotionally based motivations. However, the main reasons for having sex in both sexes are related to recreation [35, 36].

3.2 Female sexual response: models in different shapes and sizes

Different sequential models of female sexual response has become available ever since the one proposed by William Masters and Virginia Johnson [37]. Their unprecedented physiological studies performed in actual sexual intercourses undoubtedly established the basis for research in the sexology field. However, to date, no other laboratory has replicated or verified Masters & Johnson's findings, and conclusions derived from them usually are taken as reference in most studies regarding sexual response in the general population. Masters & Johnson´s convenience sample required masturbatory experience and the presence of regular coital orgasms [38]. Additionally, they included people with high levels of academic formation and good communicative skills to get a detailed description of their sexual responses [38–40]. Despite the limitations of the sampling procedure, mainly regarding women, Masters and Johnson´s model of sexual response in the female, and its later modifications, permitted us to make more precise definitions and classifications of sexual response stages and dysfunctions. Moreover, they established the basis of therapeutic approaches, many of them still used. Around 40 years later, Rosemary Basson proposed a model based on data from questionnaires and interviews with women in long-term relationships. According to Basson, there are four main omissions in previous models:

a) the lower urge for sexual releasing in women than men,

b) women reported non-sexual motivations for engaging in sexual activity,

c) for women, subjective sexual arousal might not be accompanied by genital sexual arousal, or the awareness of that arousal,

d) in women, the release of sexual tension induced by orgasm might or might not occur.

Basson´s model proposes that women might start from neutrality, to decide deliberately to engage in sexual activity, motivated by sexual and non-sexual needs. In this situation, some sexual arousal is present which might be enhanced by sexual stimulation and emotional needs such as closeness, love, and/or affection which enhance the awareness of being sexually aroused. Increased arousal with adequate and sufficient sexual stimulation might lead to orgasm and physical wellbeing. In this theoretical model, desire might precede or accompany arousal, and both elements are reciprocally influenced either positively or negatively by emotional factors, such as intimacy (fig.1) [41, 42].

Women's descriptions regarding sexual desire and sexual arousal suggest that these elements are experienced as the same construct, complicating their differentiation each other. that fluctuates with sexual experiences. The fluctuation of desire and arousal is highly variable, depending on relational and sexual outcomes. The results indicated that female sexual response could not fit into a single model since its variability in the same woman under different situations. Notably, women usually are aware of this variability, but it was not problematic for them. Authors proposed that sexual responses are as variable as women´s shapes and sizes [41]. The findings also led us to reconsider how we understand the female sexual response and if a single model can appropriately represent the variance of sexual responses in women.

3.3 Women´s sexual arousal: The bipartite component and its discrepancy

Since sildenafil's release and its tremendous commercial success, the interest in developing analogous drugs in women made sexual arousal the most studied component of the female sexual response. Although sildenafil has shown inconclusive results and is not approved for female sexual dysfunction treatment, thanks to these studies, our understanding of female sexual arousal is still growing [43, 44].

As aforementioned, women might refer to sexual arousal as the primary mental or psychogenic process. However, experimental studies have reported two different elements that constitute the core of this response: genital arousal (i.e., vasocongestive changes in genitals with engorgement and perceptions of genital pulsing and warmth), and subjective sexual arousal (i.e., feeling 'turned on' during sexual activity) which usually are accompanied by extragenital changes, including skin flushing and nipple erection. Women´s descriptions support the interplay between both types of responses during sexual arousal, possibly each one enhances the other, like a positive feedback fashion, facilitating women's realization of being sexually aroused [44, 45]. However, for some women, both components are not related at all. Since the grade of synchrony between genital and subjective sexual arousal is not related to sexual function, its clinical relevance, if any, is unclear [44].

Preclinical experiments using tissue cultures, organ baths, or *in vivo* tests indicated that peripheral genital arousal in females is mediated by somatic and autonomic responses. Afferent signals from the genitals are conveyed by the pudendal nerve, to the spinal cord, where efferent spinal reflexes induce muscle contraction of the perineum. On the other hand, peripheral autonomic nerves, such as the hypogastric, pelvic and vagal, facilitate genital blood flow and genital smooth muscle relaxation through parasympathetic and

sympathetic influences, which favor vaginal and clitoral engorgement [43, 46]. Electrical stimulation of the pelvic nerve in female rats and rabbits induces hemodynamic changes with vaginal enlargement and increased vaginal wall tension. These responses are also partially mediated by several local mediators, including vasoactive agents such as neuropeptide Y, noradrenaline, vasoactive intestinal polypeptide, nitric oxide synthase (NOS), calcitonin gene-related peptide, and substance P. The role of each one of those in regulating vaginal and clitoral smooth muscle tone remains unclear [43].

Clinical studies in women revealed that the autonomous nervous system is involved in sexual arousal response. The role of generalized sympathetic activity has been demonstrated since a) noradrenaline plasma levels are higher in women sexually aroused, b) vaginal arousal induced by erotic films is higher after 20 min of intensive exercise than those presented after a non-exercise test, c) this effect was prevented by clonidine, an α-adrenergic receptor blocker [44, 47, 48]. On the other hand, evidence for the regulatory role of parasympathetic is based mainly on women with thoracic spinal injury, who refer getting sexually aroused without vaginal lubrication [49].

Estradiol and testosterone also contribute to genital arousal by regulating the activity of peptides in the vagina, including the vasoactive intestinal polypeptide (VIP) and nitric oxide synthase (NOS). Intravenous and intraepithelial administration of VIP increased vaginal blood flow, measured by heated oxygen electrode, in postmenopausal women, only if they received hormonal supplementation [50, 51]. Although comprehensive VIP mechanisms are not yet elucidated in sexual contexts, results indicate the interaction of endocrine and local factors in vascular vaginal response.

Opposite to genital arousal, which is an autonomic response, subjective arousal involves the experience and feelings of being turned on. Experiments indicate that attentional focus on

sexual arousing cues is required to enhance subjective arousal. Thus, distractors reduce subjective arousal in women and they include negative or autocratical thoughts such as situational elements and they are also modeled by psychosocial and cultural inputs [52]. Conventional experiments usually evaluate individual responses. However, growing evidence indicates that it is necessary to broaden our perspective and put on the discussion how personal history, including sexual abuse, and dynamics with the partner are critical for sexual functioning in women [44, 53, 54].

3.4 The role of intra and interpersonal influences on women's sexual response

Women are historically receptors of different types of violence throughout all their life stages. Up to 85% of women with sexual dysfunctions, mainly of these concerning desire and arousal, also report sexual abuse in childhood, twice as much as those without sexual abuse antecedent. Disruptive changes in sexuality in women with negative sexual experiences include, among others, sexual shame, lack of positive emotions towards sex, impaired attachment security, and negative sexual self-schemas. Those negative associations probably act as distractors that counteract subjective sexual arousal [44]. For this group, psychological therapy is particularly effective [55, 56]. In women veterans, sexual trauma in childhood or during military service was associated with low sexual satisfaction and especially with sexual pain. Future research is needed to understand this interaction.

Effective communication and the level of emotional intimacy with the partner influence sexual satisfaction in women, especially for those women in long-term relationships. In heterosexual couples, there are some correlations between sexual dysfunctions in the partners. For example, erectile dysfunction is related to low sexual satisfaction in the

female partner, whereas its effective treatment also improves females´ sexual life quality [57]. Additionally, a report showed that premature ejaculation might be related to vaginal penetration difficulties in the female partner [58]. The approach considering the couple as a relevant factor in the development, maintenance, and solution of some FSD is being more used [59].

4. Common methods for measuring genital arousal in women

Masters and Johnson proposed that besides the obvious anatomical differences, male and female sexual responses were parallel and similar from a physiological point of view [37].

Currently, researchers continue looking for the gold standard for measuring sexual arousal in women by evaluating different physiological parameters, among others: vaginal blood flow, volume and pressure of genitalia, lubrication, neural responses, and muscular activity. In the meanwhile, there are some available options, each one with strengths and opportunities, summarized in table 1.

4.1 Vaginal photoplethysmography

Sexual arousal is followed by vasocongestion of the vaginal capillaries that increases the transudation of plasma to create a lubricative film covering the vaginal walls. The grade of vasocongestive reaction is measured using a photometer with a source of infrared LED light and a phototransistor inside of a tampon-shaped probe, which is inserted into the vagina. Once the LED light is turned on, photons diffuse and reflect on the vaginal walls, which are captured by the phototransistor and transformed into electrical signals. The larger the blood volume in the vagina, the greater the amount of the incident light backscattered to the light detector. Two variables are obtained depending on the signal coupling: vaginal

blood volume (VBV) for direct current, and vaginal pulse amplitude (VPA) for alternating current. Although VBV and VPP are highly related to blood volume, vaginal photoplethysmography (VPP) is expressed in arbitrary units such as changes in mV or mm of pen deflection [61, 62].

Some advantages of using VVP are: the majority of reports have used VVP for measuring genital arousal and the probe can be placed by the participant. On the other hand, it is still unclear which is the physiological parameter measured by VPP and VPA. Additionally, the need for introducing into the vagina, it might not be feasible in genital pain or vaginismus; after each use, the probe needs to undergo disinfection. Another consideration is the lack of standard units and the high variability across studies, even in the same person.

4.2 Labial thermistor

Changes in the surface temperature of labia minora are measured by a small thermistor attached to a padded clip and placed on the labia minora. There is a positive correlation between temperature increase and subjective rating of sexual arousal in women, similar to which occurred with vaginal plethysmography. This technique also uses arbitrary units and results show high inter-subject variability but also across the day of the menstrual cycle.

4.3 Genital infrared thermography

This non-invasive technique also evaluates genital temperature by infrared light camera.

Similarly, with the labial thermistors, infrared thermography correlates with self-reported sexual arousal. Thermography also discriminates between erotic and non-erotic stimuli, making this approach promising to evaluate sexual arousal.

4.4 Lubrication

Vaginal fluid produced during sexual arousal is the result of sequential vasodilation (likely neural VIP-mediated) with vasoconstriction of veins that causes transudation of plasma and interstitial fluid to vaginal walls. Actual mediators of lubrication remain unknown and a report suggests that labia minora produce their lubrication, independent of the vaginal [63]. Although lubrication is considered a physiological response during sexual arousal, there are no reliable ways to measure it. Some reports have focused on vaginal pH changes using a glass pH electrode in the vagina showing that, during clitoral self-stimulation, vaginal pH increased up to 1 unit when the woman reached orgasm. Some preclinical reports have evaluated lubrication fluid by using tampons, but its use is limited in physiological research.

5. Conclusions

As we are still learning from sexual behavior in female rats, we also realize that making extrapolations to humans might not be feasible, mainly because sexual responses in women are so peculiar, variable, and strongly influenced by sociocultural factors. Moreover, our knowledge regarding basic anatomy is still growing nearly forty years after Masters and Johnson studies: in 2005, the most comprehensive study about the anatomy of the clitoris was reported at last [60]. Thus, the contribution, if any, of animal models of sexual response in female rodents is modest. After the questionable approval and the lack of efficacy of drugs to treat sexual desire issues, it is necessary to realize that the more we understand the female sexual responses, the more we might explain, and eventually treat, their dysfunctions.

Acknowledgements

Funding was provided by Programa de Apoyo a Proyectos de Investigación e Innovación Tecnológica, Universidad Nacional Autónoma de México (No. IA204321)

Table 1. Common methods to measure female sexual arousal in sexual research

Method	Physiological variable	Basic principles	Advantages	Disadvantages
Vaginal photoplethysmography	Genital blood flow	Tampon shape device containing a light source and a photosensitive cell. Light that is backscattered is correlated with vasocongestion	-The most extended method for assessing sexual arousal -Easily inserted in most of cases by participants -Feasible for long and multiple recordings correlates with self-report of sexual arousal	-Sterilized is needed after use -Not suitable for women with pain or vaginismus -Not clear what variable is measured -Highly inter-subject variable
Labial thermistor	Temperature changes in the labia minora	A padded clip attached to thermistors that detect temperature of the surface	-Minimally invasive -Correlates with self-report of sexual arousal	-Some participants found it highly aversive -Requires room temperature control - Movement artifact -Affected by body temperatures across the menstrual cycle
Thermography	Temperature changes in the genitals	Thermograms by infrared camera	-Non- invasive -Correlates with self-report of sexual arousal -Objective scale of measures	-Expensive devices -Requires room temperature
Lubrication measures	pH and amount of lubricant fluid	An electrode placed into the vaginal detect changes in the pH. Components and the amount of vaginal fluid can be measured by filter papers and tampons	-Unexpensive -Ease of use	Somewhat invasive -Scarce use in research -Results might be affected by vaginal infection and menstruation

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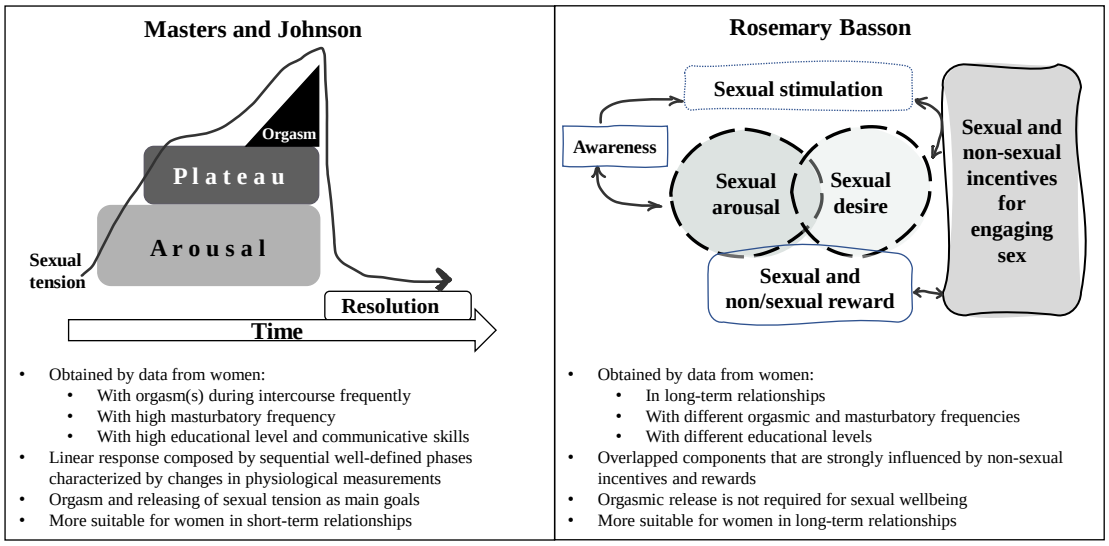

Figure 1. Comparison between two different models for female sexual responses. Modified from Masters and Johnson (1966) and Basson (2000).