The Pharmacology of Sexual Function and Dysfunction
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Physiological considerations and erectile function

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Introduction

Clinical physiological approaches to study and to diagnose male sexual organs and their dysfunctions have up until recent years been few and scattered and mostly concentrated on the penis when in the flaccid state or during the night when nocturnal erections, which are not sexually related, occur.

Most of the information needed to describe the physiology of the penis in the flaccid and, in particular, the erect state was based on anatomical and descriptive studies up until the mid-1970'es.

The traditional (somatic) field of medicine had no offers to perform diagnostic tests and the psychiatric field had no intention of such studies except to perform studies of the nocturnal penile tumescence periods. Such studies were based on a simple pletysmographic principle indicating changes in volume of the penis, but not in the rigidity. As lack of rigidity (stiffness of the shaft of the penis based on pressure increase intracavernosally) is the main problem in the majority of patients seeking help for erectile dysfunction, this parameter is crucial to study. However, the basic necessity to collect information for differential diagnosis is general knowledge of the normal function and where pathological processes may interfere in the series of events which leads to the normal function.

The two major male sexual complaints are erectile dysfunction and premature ejaculation, but only the first has been subjected to physiological and pathophysiological methods and only for a short period of time, i.e. less than twenty years.

Physiology of erection

A full, normal integration of cerebral, neural, vascular, and hormonal factors is essential. It is a highly complicated system and therefore vulnerable to environmental interferences as well as to structural pathological changes. For a recent review of the physiology of erection, see Andersson & Wagner [1].

The regulation of arterial inflow, the contractility and compliance of the smooth muscle of the intracavernosal trabeculae, and the regulation of the drainage ("venous outflow") are believed to be the crucial elements of the local function of the penis. The retractor muscle (smooth muscle) is present in most animals, but not in the human where the intracavernous smooth muscle exerts the function of keeping the penis flaccid by contraction.

However, two well-developed striated muscles surround the base and part of the shaft of the human penis. For decades, a discussion of the involvement of these muscles in normal erection has been going on.

Some basic misunderstandings seem to have hampered the discussion, mainly based on lack of physical argumentation. The interior of a non-distended, distentable cylinder does not obtain increase of pressure due to an external pressure. Only if the cylinder is completely filled and the next few millimeters of fluid are added, may an increase of pressure occur, cf. conventional volume/pressure curves for all hollow organs or ordinary length/tension diagrams valid for distensible tissues. The increment in volume, however, has to occur against a pressure gradient at this moment, as is the case of the cavernous tissue when the intracavernosal spaces have been filled up with blood and the trabecular tissue is extended and the tunica albuginea has been stretched to a point where tension will arise if further volume increment occurs. At this point, contraction of extratunical muscles, which are anchored to (and around) the tunica, will cause an increase in intracavernosal pressure.

Such contractions may occur as a reflex or as a voluntary contraction. If voluntary, it needs the full attention of the man at this point and will certainly distract his attention from other activities. Under experimental conditions when a full erection is obtained without the voluntary contraction, the intracavernosal pressure is around mean arterial pressure (85-100 mmHg) while the pressure may be increased to as much as 400 mmHg as long as the person is able to maintain full contraction of the involved striated muscles, which will be two minutes at the most. The somatic nerve innervating the muscles is the motor arm of the pudendal nerve.

Reflexogenic contraction may occur as well, but this will be of a short duration, maybe of approx. 1 second, and will therefore only bring about a short-lasting increment of intracavernosal pressure. The reflexogenic contraction is used clinically to ascertain the existence of the function of the sensory arm of the pudendal nerve (the dorsal nerve of the penis), its spinal relay and function of the motor nerve innervating the striated muscles.

The reflex (bulbocavernous reflex) may be evoked by a slight pressure upon the glans penis or by an electric stimulus of the glans area. Clinically, the contraction can be felt by palpation of the muscles and, more sophisticated, the latency period from stimulus to response can be measured. However, the relevance of the reflex for clinical evaluation of the patient with erectile dysfunction is obscure, see Buvat et al. [2].

From a functional point of view, the reflexogenic reflex may be of value at the very moment of vaginal intromission as the pressure exerted upon glans by the introitus of the vagina may increase the intracavernosal pressure momentarily, thus maximizing the rigidity of the shaft and facilitating full intromission [1].

Recent experiments in normal young men, who were aroused to penile erection by visual sexual stimulation, showed no electrical signals from electrodes placed in the ischio- and bulbocavernous muscles during tumescence and development of full rigid erection, Gerstenberg et al. [3]. The very same muscles, however, are involved in ejaculation and the necessary part of the expulsion of semen when they contract rhythmically during a (short) period before the external ejaculation and for a (longer) period thereafter.

During the same time, the rigidity of the penis decreases as some blood excapes the cavernes into the venous system concomitant with a decrease of the tension of stretched trabeculae which is followed by an active contraction of the smooth muscle cells in order to bring the penis back to its resting state. Almost no in vivo studies exist on this phase of erection and the above theory is mainly based on in vitro studies of cavernosal tissue

[1]. Rigidity to a certain extent without filling of the intracavernosal spaces of blood does occur when the smooth muscle inside the corpus cavernosum contract maximally, as can be observed during low temperature or fear. Most likely, the stiffness of the penis might be sufficient for vaginal penetration, but at this stage the size of the penis would be insufficient for proper copulation.

Normal erection and ejaculation as well as the flaccidity are obviously dependent on an interaction between the striated and smooth muscle in which both are regulated by involuntary mechanisms.

Cell communication

The roles of endocrine factors in regulation of penile function will not be dealt with here, but rather it should be emphasized that the cell communication among the smooth muscles inside the corpus cavernosum seems to be the crucial key in the normal function of the tissue and that malfunction of such communication systems may easily lead to erectile dysfunction.

One particular difference between striated and smooth muscle is the way in which they are innervated. Where each muscle fiber receives a neurone in striated muscle, only one of many smooth muscle cells is innervated by one nerve fiber and the signal from the nerve terminal has to be transmitted from cell to cell by some intercellular communication system in order make the tissue function synchronously. Furthermore, the smooth cells of the cavernous tissue are lined by endothelial cells which are known to be essential in the regulation of the state of the muscle cells, and as only a certain proportion of the cells have direct contact with the endothelial cells, an intercellular messenger system has to exist to make this system work also.

The current debate whether the tissue is "richly" or "sparsely" innervated may be futile to further the understanding of a functional asynchrony or synchrony being it a signal of contraction or relaxation to be conveyed between the cells.

Signal transduction within the cavernous tissue could occur by electrical impulse propagation, by gap junction (chemical transduction) or by traditional apocrine function [1,4]. Discrepancies of the findings in the literature could be due to differences in tissues and in methodology. In cultured, human cells from corpus cavernosum, no electrical signals could be demonstrated [4] while it was possible to pick up electrical signals (cc-EMG) from intact animals as well as from the human [5]. Pick-up electrodes in the human do not need to be intracavernosally placed electrodes, but can be surface electrodes placed on the skin on each side of the penis.

In the flaccid state, some electrical activity exists, usually not regularly, while the activity subsides when a tumescence is to occur as a sign of reduced contractile activity necessary for stretching the smooth muscle tissue during filling up of the cavernes preparing for the erection. Similarly, a reduction is noted after intracavernosal injection of vasoactive compounds with smooth muscle relaxatory effect.

Thus, when this technique is refined and fully interpreted, it might be an important addendum to diagnostic procedures in evaluation of erectile dysfunction.

Conclusion

From what has been discussed above, it seems clear that the neurotransmission locally in the penis and the cell-to-cell communication are of utmost importance to get fully elucidated, especially when it comes to pharmacological intervention. Further research into these phenomena is necessary to pave the road for highly selective compounds that can be used for pharmacological therapy.

References

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Discussion - PHYSIOLOGICAL CONSIDERATIONS AND ERECTILE FUNCTION

M. Murphy

I would like to go back to the bulbocavernosus reflex. It has been reported that this reflex is absent in subjects with primary anorgasmia. Do you have any comments on that?

G. Wagner

I actually wrote to the author of this paper to ask him if he ever saw a case of primary and total anejaculation. That is what I call it, anejaculation. I once saw one case. The patient was 28 and he had never had any ejaculation, diurnal or nocturnal. This patient did have this bulbocavernous reflex and he responded to vibration, and the child now is 4 months and they are going for the next child. He has not had any ejaculation except with vibration, using the device that we developed. So my answer is, I do not have an explanation: I do not see it together.

P. *Gutiérrez*

The absence of this reflex has also been reported in women, so I cannot agree that primary anejaculation is the correct term, because women fail to have orgasms, if they lack this reflex. Do you have any comment on that?

G. Wagner

No. As I told you I have seen one case after many years in the area and I called for help. I did not get a response that satisfied my particular question. I thought that this patient that I mentioned might have an anatomical explanation, with closed tubules or whatever. And then he ejaculated and he did not have an orgasm, he ejaculated and that was all over because it was all in such a short time. And then we started up a series of vibrations and after five or six times he started to have something that he now felt pleasurable as orgasm which was quite an interesting development. And the ordinary commercial vibrators did not work, it was only our own old-fashioned model that really gives the amplitude in frequency which is necessary.

P. Gutiérrez

Taking into account the importance of the venous flow through the tunica albuginea and the good elasticity of the corpora cavernosa tissues in a good erection, can you comment on the problems associated with the surgical approach to venous leakage? Usually, obstruction of the vein at the base of the penis leads to a good erectile function for a few months, but then it gets impaired again.

G. Wagner

I have been involved in that discussion a couple of times because now the surgeons realize that they have been gone too far in reducing the venous outlet. First of all, is there such a thing as a higher than normal outflow during erection, which means a kind of abnormal drainage? If this condition is not visualized in one or two large veins the problem should not be approached surgically because what the patient has is an internal problem due to the failure of the smooth muscle to function normally, which is partly to be completely relaxed and/or not having any diseased areas like in Peyronie's disease. If there is an area with a plug under the tunica albuginea the venous drainage in this area is larger than normal. If you have a patient with Peyronie's disease and a slight erectile failure you may go in and localize and ligate the veins at that point.

P. Gutiérrez

Perhaps the problem with surgical approaches is that they have been introduced without enough knowledge of the vascular physiology. The relationship between elasticity and vascular function should be further explored, particularly in older men.

G. Wagner

I may not agree with you that we do not know enough about the vascular physiology. As a matter of fact, what we do not know is the aging process of the smooth muscle inside the corpus cavernosus and the more specific pathways and ways by which the cells are signalling. But that has nothing to do, should we say, with the major understanding of vascular physiology in the area because we have been through a development which is based on misunderstanding.

J. Bancroft

You talked about the various mechanisms involved in development of erection. You have talked about arterial dilation and an increase in the arterial flow as well as the relaxation of sinusoidal space and so on. I have observed in a number of occasions when doing duplex sonography that you can see increased arterial flow without any measurable increase in arterial diameter. In a non erect penis the artery, which is long enough for the erect penis, must be very convoluted. Does that reduce the amount of flow through the artery? And as the penis fills up and straightens, do you get a simple mechanical increase in the flow because the artery becomes straight rather than convoluted?

G. Wagner

This is an extremely difficult question to answer precisely, because whether a given convolution will give resistance will depend on the angles of this convolution and so forth. I am not able to oversee that. I think that the main resistance in the arterial tree is due to contraction as well as a closed outlet system. No doubt that at a very early stage, inflow resistance drops and pressure of the arterial tree is filled up all the way up to the mean arterial pressure due to the dilatation. But I don't understand what you said. You said that you see increases in the arterial flow before the diameter increases, is that what you said?

J. Bancroft

You can measure the diameter of the deep penile artery before and after the papaverine or prostaglandin injection. You can record an increase in the arterial flow through that artery without there being an increase in the diameter. Sometimes there is increase in the diameter but this is not always the case. Can that be explained because the artery is straightened out and there is less resistance to flow?

K.E. Andersson

I think that the sequence of events, hemodynamically, is not established but it has been well studied in several animal models and the first thing to happen is an increase in flow and then there is a shear stress in the artery. This leads to the release

of endothelial factors, an opening up of the helicine arteries and at the same time a relaxation of the sinusoids. There is a filling up and straightening of the arteries producing with compression of the outflow region, the subtunical small veins are compressed against the tunica and there is an increase the pressure. The result is an erection and then the contraction of the bulbocavernosus muscles provides an additional rigidity.

G. Wagner

And then the latest addition to that is that oxygen seems to be involved, because oxygen tension in the area dramatically shifts due to the increase of the arterial flow and therefore it facilitates the formation of NO.

D. Vanderschueren

We should recall that there is a lot of discussion about what parameters should be used. There is also a lot of discussion about how good the diameter is as a parameter, and I think most of the people just go for the peak flow and do not measure diameters any more because they cannot be measured very precisely.

B.D. Sachs

I would like to ask about the injection pharmacology with respect to the mechanics of erection. Many drugs have been used for injection in the corpus cavernosum, including papaverine, VIP, and I do not know how many others. Are they all thought to act only on relaxation of the cavernous tissue or are they simultaneously acting to increase arterial inflow. What is the mechanism of action?

G. Wagner

Papaverine relaxes all smooth muscles, which means that if you inject into the closed chamber of the corpus cavernosus and you have a restricted outflow you will only have papaverine in that area. However if you listen or you palpate the dorsal arteries which are outside the tunica albuginea, very soon after an injection of any of these substances you will be able to notice a change in the flow of these arteries. That means that somehow there must be local reflex within the arterial tree that also

produces dilatation of the arteries irrigating the glans and the spongious tissue. When you have such a provoked erection you will have a normal increase of size and some pressure increase in the corpus cavernosum which does not come up to the arterial pressure at all but is rather much about half, maybe 50 mm of mercury. This is an effect in the early stage; if there is a well developed pharmacological erection and an ejaculation, then you will see, not a fall of the erection of the corpus cavernosum, but a change and fall of the volume increase of the spongious body. So you will have at that time a differentiated situation, and this is disturbing to some men, so it is a matter of dosing correctly.

S. Erill

Have you ever checked the effect of antihistamines on erections induced by local administration of vasodilators? Many of these vasodilators are basic drugs and many basic drugs produce histamine release. A very simple experiment would indicate whether the systemic administration of an antihistamine blocks the secondary reflex.

A.J. Riley

There is quite a high concentration of mast cells in the penis and we know that H_2 blockers do impair erection, and there is quite a lot of data now being generated indicating that H_2 agonists promote erections given both orally and intracavernosally.