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The role of Nitric Oxide (NO) in Gravity and Life management in the Myofascial System

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ABSTRACT

This paper presents the hypothesis that Nitric Oxide (NO) mediates the adaptation to gravity of the Myofascial System, as the sexual molecule about which Sigmund Freud and Wilhelm Reich speculated about in their research. Starting from an experiment with Viagra on cut flowers, the paper extends these results to the Human Body. In the last section is proposed an experiment in order to confirm this theory.

Keywords: Nitric oxide, Myofascial system, Viagra, Myofibroblasts, Gravity

INTRODUCTION

This paper presents the hypothesis that Nitric Oxide (NO) mediates the management of Gravity and Life in the Myofascial System.

Working with cut flowers Siegel and Itzkovich in 1999 first noted this effect after the administration of 1 mg of Viagra (Sildenafil), a drug that exerts its action protecting cyclic Guanosine Monophosphate (cGMP) from the breakdown by the phosphodiesterase 5 (PDE5). The final physiological molecule responsible for gravity and life management is cGMP which is obtained after Nitric Oxide binds to its target soluble Guanylate Cyclase (sGC). Evidences of the adaptation to gravity mediated by Nitric Oxide and cGMP in plants have also been reported by Weiming et al. (2008).

In the Human Body, Sildenafil by itself, which only protects cGMP from breakdown, does not produces a penile erection without sexual stimulation, so a molecule responsible for Sexual Stimulation is needed. In this paper I put forward the hypothesis that the molecule which mediates Sexual Stimulation is Nitric Oxide.

Extending such a role of Nitric Oxide to the entire Myofascial System, I claim that this molecule mediates gravity adaptation togheter with the so called Elan Vital, i.e. the tendency to Life, and this is in agreement with what was proposed by Sigmund Freud and Wilhelm Reich about such functions.

VIAGRA

Generalities

Sildenafil, sold under the brand name Viagra among, is a medication used to treat erectile dysfunction and pulmonary arterial hypertension. It is taken by mouth or injection into a vein. Onset is typically within 20 minutes and lasts for about 2 hours (Goldstein et al., 2018).

Mechanism of action

Sildenafil acts by blocking phosphodiesterase 5 (PDE5), an enzyme that retards the breakdown of cGMP, which production is mediated by Nitric Oxide, regulating the blood flow in the penis.

More specifically, Sildenafil protects cyclic guanosine monophosphate (cGMP) from degradation by cGMP-specific phosphodiesterase type 5 (PDE5) in the corpus cavernosum. Nitric oxide (NO) in the corpus cavernosum of the penis binds to guanylate cyclase receptors, which results in increased levels of cGMP, leading to smooth muscle relaxation and vasodilation of the intimal cushions of the helicine arteries. This smooth muscle relaxation leads to vasodilation and increased inflow of blood into the spongy tissue of the penis, causing an erection (Webb et al., 1999).

The molecular mechanism of smooth muscle relaxation involves the enzyme cGMP-dependent protein kinase, also known as PKG. This kinase is activated by cGMP and it phosphorylates multiple targets in the smooth muscle cells, namely myosin light chain phosphatase, RhoA, IP3 receptor, phospholipase C, and others. Overall, this results in a decrease in intracellular calcium and desensitizing proteins to the effects of calcium, engendering smooth muscle relaxation (Francis et al,. 2010).

Sildenafil is a potent and selective inhibitor of cGMP-specific phosphodiesterase type 5 (PDE5), which is responsible for degradation of cGMP in the corpus cavernosum. The molecular structure of sildenafil is similar to that of cGMP and acts as a competitive binding agent of PDE5 in the corpus cavernosum, resulting in more cGMP and better erections. Without sexual stimulation, and therefore lack of activation of the NO/cGMP system, sildenafil should not cause an erection.

Hepatic metabolism

Sildenafil is broken down in the liver by hepatic metabolism using cytochrome p450 enzymes, mainly CYP450 3A4 (major route), but also by CYP2C9 (minor route) hepatic isoenzymes. The major product of metabolisation by these enzymes is N-desmethylated sildenafil, which is metabolised further. This metabolite also has an affinity for the PDE receptors, about 40% of that of sildenafil. Thus, the metabolite is responsible for about 20% of sildenafil's action. Sildenafil is excreted as metabolites predominantly in the feces (about 80% of administered oral dose) and to a lesser extent in the urine (around 13% of the administered oral dose).

MYOFIBROBLASTS

Myofibroblasts are mobile cells which are able to exert a contractile force of 4,1 μN on the ECM that is, four times the force exerted by common Fibroblasts thanks to the presence of stress fibers made up of ASMA (α-Smooth Muscle Actin) (Figure 1).

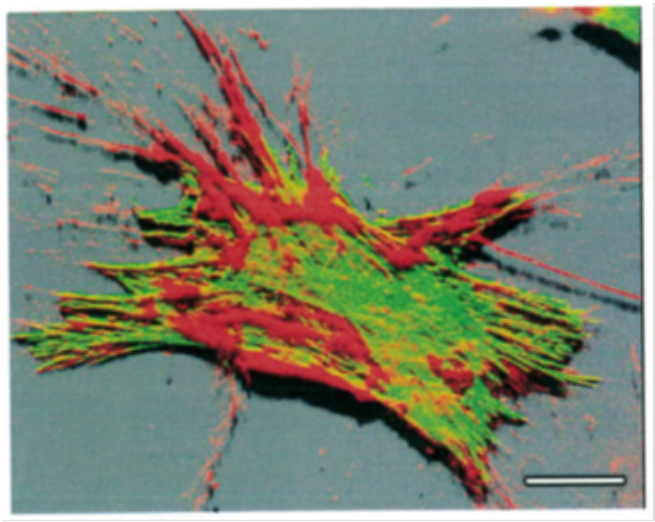

Figure 1: Myofibroblast with Stress Fibers highlighted in red, marker 20 m

The MFBs are arranged in linear syncytia from which the contractility of the fascia is guaranteed. They can exert a slower contraction (about 5-30 minutes for the activation) compared to the muscular contraction, developing prolonged traction actions (up to more than an hour) that contract collagen fibers and eventually cause the entire ECM to contract. This possibility of fascia to regulate and adapt its stiffness depending on different situations is an advantage for the organism: during fight-or-flight reactions, for example, a more rigid fascia prevents the body from physical traumas. A lot of MFBs are situated near capillar blood vessels, from which they can easily get all the chemicals needed for their functioning, including:

- Nitric Oxide (NO) stimulating relaxation;
- Inflammatory molecules (e.g TGF-1, cytokines, histamine and oxytocin) which stimulate contraction.

On the contrary, MFBs are not resposnsive to other neurotransmitters such as Acetylcholine and Adrenaline and not even to molecules blocking the calcium channels (e.g. angiotensin, caffeine). Besides being the main chemical regulatory agent of MFBs' activity as it promotes the intracellular accumulation of contractile proteins in Fibroblasts, TGF-β1 promotes a greater collagen density within tissues. With regard to histology, MFBs are a sort of link between smooth and connective muscle tissue; several MFB phenotypes exist, ranging from cells which are very similar to smooth muscle to cells which are more similar to fibroblasts. The maximum density of MFBs in the Fascial System can be found in the Perimysium. Within the ECM, Myofibroblasts are located between Smooth Muscle Cells, innervated by the autonomous nervosus system, and a common fibroblast, acting as a linking element. The control of this type of cells is involuntary (Figure 2).

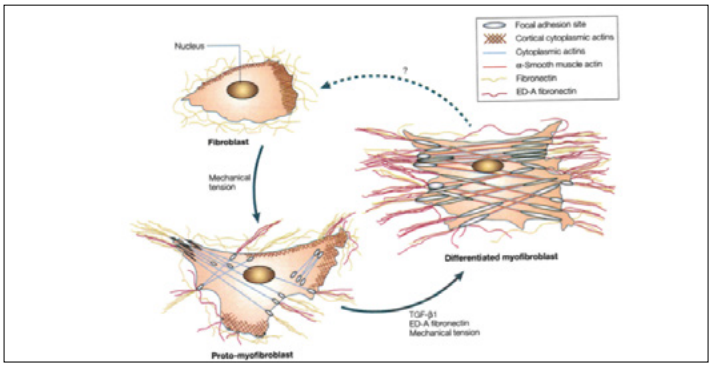

Figure 2: Differentiation of a Myofibroblast

When a fibroblast is solicited by a non-physiological mechanical stress, it differentiates into a proto-myofibroblast, which produces filaments of ASMA actin in order to form adhesion complexes and structural fibers so as to guarantee the external anchorage to ECM. If stress persists, the complete differentiation in a MFB will take place with the formation of an organized network of connections with the ECM through the cellular membrane, due to the presence of ASMA filaments directly connected with the cytoskeleton.

The phenomenon of Myofibroblasts' Differentiation depends on:

- the mechanical stress in the tissues;
- the proinflammatory chemical milieu;
- the chemical acidity, since a lower pH level than the physiological one stimulates the Contraction of MFBs.

MECHANICS OF MYOFASCIAL CONTRACTILITY

The main functions of Myofascia, i.e. the Fascia of Skeletal Muscle, are (Petrogalli, 2019):

- to manage the adaptation of muscular fibrocells in a gravitational field
- to mantain the sarcomeres at an optimal lenght in order to provide the maximal force of contraction
- to allow the volumetric expansions which occur during muscle contraction and that are particculary evident and violent during tetanic contractions

The first two functions are possibile thanks to the capability of Fascia to contract in a smooth-like manner, due to the presence of Myofibroblasts. The third function implies that during the contraction of a muscle Fascia has to relax and its relaxation is mediated by Nitric Oxide (Schleip, 2006 and Petrogalli, 2019) which acts on Myofibroblasts in the same manner it provides the relaxation of smooth muscle cells.

GRAVITY AND LIFE MANAGEMENT BY NITRIC OXIDE

In the Human Body Nitric Oxide is the molecule that manages gravity within the Myofascial System, providing the gravitational adjustment of the tissues in the gravitational field of the Earth, bringing them to a minor or to a major gravity field, i.e. to a lower or higher curvature of spacetime.

Resuming

- when a muscle contracts, the concentration of Nitric Oxide increases, providing the relaxation of the Fascial Tissue
- when a muscle undergoes an eccentric elongation, the concentration of Nitric Oxide decreases and consequently the Fascia contracts

When the interested muscle is an extensor, its contraction is an Erection against gravity (i.e. to a lower curvature of spacetime), which I call Erection "alla Petrogalli".

When the interested muscle is a flexor, its contraction is pro-gravity (i.e. to a higher curvature of spacetime).

Versari et al. (2007) found that Hypogravity stimulated endothelial growth and enhanced Nitric Oxide production, while Hypergravity did not affect endothelial growth and enhanced Nitric Oxide synthesis, results that indicate that cytoskeletal alterations and increased nitric oxide production represent common denominators in endothelial responses to both hypogravity and hypergravity. This support my thesis that a greater or minor gravitational field (i.e. a greater of minor curvature of spacetime) influences the concentration of Nitric Oxide in the tissues.

Karlsson et al. (2009) reported that exhaled Nitric Oxide is lower in microgravity and higher in hypergravity than in normal gravity and that these data are consistent with the hypothesis that alveolar NO uptake is increased in microgravity and decreased in hypergravity. However, changes in lung diffusing capacity can't explain neither the full extent of the lowered exhaled NO in microgravity nor the leveling off of exhaled NO from 2 to 3 G, so further studies are required to find additional mechanisms. My Mechanism could be the key to resolve this issue, considering the role of Nitric Oxide in breath mechanics which is a particulary interesting topic which esulate from the aim of this paper.

In conclusion, Nitric Oxide is the molecule responsible for the adjustment of the Myofascial Tissues in a gravitational field and for their vitality, resulting this last function a sexual one, not only from a psychological point of view as Freud and Reich speculated in their psychiatric researches, but also from a molecular perspective, as I claim.

EXPERIMENTAL HYPOTHESES

Electrochemical NO detection

Use of various electrodes for electrochemical detection of Nitric Oxide *in Vivo* is widely employed. The choice of electrode is of great importance for detection of NO, since the electrochemical process takes place at its surface and its quality influences the charge transfer process between target analyst and Electrode material. Carbon and noble metal electrodes are most commonly used for NO detection.

The basic of NO detection using amperometric method is the current generated on the surface of electrode due to oxidation of NO. A typical system for NO detection includes use of working (coated with platinum or Teflon) and reference electrodes (Ag/AgCl) immersed in solution containing NO.

The application of positive potential (800–900 mV) causes NO to be oxidized at the surface of working electrode by generating a redox current. The oxidation occurs via electrochemical reaction followed by chemical reaction. One electron transfer from NO molecule to electrode constitutes the electrochemical reaction which generates nitrosonium ion (NO+). This cation reacts with OH^- to form nitrite (NO_2) which further gets oxidized to nitrate. NO meter measures the amount of NO oxidized which is proportional to the current flow between working and reference electrodes. An internal electrolyte is enclosed in the NO gas selective permeable membrane of the working electrode. Current due to oxidation gets generated at the surface of working electrode when NO gas passes through the membrane and the electrolyte (Goshi et al., 2019).

The use of NO specific electrodes has seen a successful graph in the recentnpast for monitoring NO in vivo.

Recently, amperometric NO release was viewed in real time

at the stimulated acupoints in rats inserted with an acupuncture microsensor needle made up of gold film and doped with ironporphyrin functionalized graphene composite (Tang et al., 2017). These electrochemical sensors are known to have a response time of few seconds with good sensitivity, real-time monitoring and the capability to measure slight changes of NO concentration.

6.2 The experiment

Using an acupuncture microsensor needle, as the ones adopted by Tang et al. (2017), to measure NO concentration in the Trapezium Muscle, when a Human Being assumes an attitude in which the shoulders fall as if they were lifeless, as shown in the Figure 3, my theory predicts that the concentration of NO must decrease after a certain time.

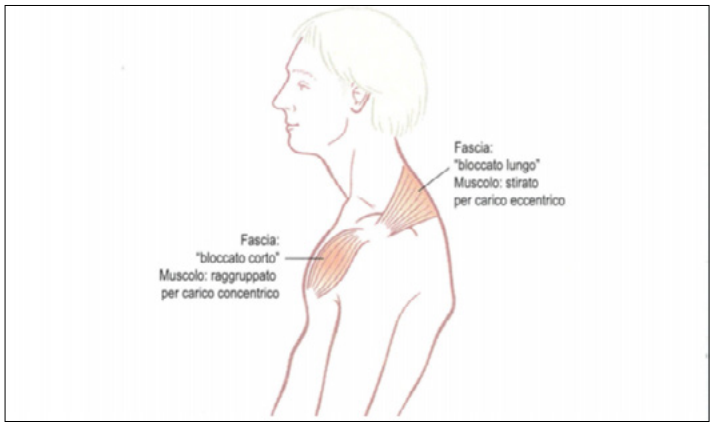

Figure 3: Human Being assumes an attitude in which the shoulders fall as if they were lifeless

Viceversa, when the muscle Contracts extending itself against gravity, NO concentration must increase, as also reported by Lau et al. (1998). The experiment can be reproduced with a flexor muscle, e.g. Pectoralis Major, and the result must be an increase in NO concentration when the muscle contracts and a decrease when it remains elongated as it was lifeless.

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