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Cavernous Sinus and its Mysterious Physiological Functions: Facts And Hypotheses

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In the paper, facts are presented demonstrating that the retrograde transfer of neurotransmitters in the cavernous sinus is an important part of a universal physiological regulatory system, called the retrograde and destination transfer of hormones and other physiological regulators, which operates in humans and in animals (Krzymowski and Stefańczyk-Krzymowska, 2012). Thus, if the retrograde transfer of dopamine in the cavernous sinus operate in physiological conditions during one's whole life, the uptake and back transfer of dopamine to the brain result in a constant supply of dopamine metabolites to the brain capillaries, including capillaries of the cortex structures, in which dopaminergic neurons are located. We present an opinion assuming that under physiological condition unknown active substances produced under the influence of dopamine metabolites in the glial cells reach the dopaminergic neurons and inhibit the expression of the dopamine transporter (DAT). Disorder of dopamine retrograde transfer in the cavernous sinus and thus of the dopamine metabolites supply to the glial cells may be the main cause of dopaminergic system hyper- or hypo-functions, and therefore the cause of many motor and neuropsychiatric disorders, including Parkinson disease.

Key words: cavernous sinus, retrograde transfer, neurotransmitters, dopamine

INTRODUCTION

The cavernous sinus is placed in a very privileged position, being in the skull, but outside the dura mater. It is covered with a connective capsule and ten trunks of cranial nerves cross it. The neuroanatomist J. B. Winslow described the human cavernous sinus for the first time in the 18th century (Thakur et al., 2014).

Two cavernous sinuses, left and right, are connected by the intercavernous sinus. The left and right internal carotid arteries, which provide the main supply of the arterial blood to the brain, pass through the left and right cavernous sinuses. This fragment of the human internal

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carotid artery was identified as a part of the T6 (the sinus portion of the internal carotid artery) (Bouthillier et al., 1996). The sympathetic innervation of the internal carotid artery's fragment, passing along the cavernous sinus, is its special feature. A dense network of sympathetic fibers that form sympathetic carotid plexus and cavernous plexus, emanating from the upper cervical sympathetic ganglion and the sphenopalatine ganglion, covers this portion of the artery (Mariniello, 1994). (See Fig. 1)

The venous blood outflowing from the brain, the pituitary gland, and in part from the nose and the eye, fills the cavernous sinus, and a mutual approximation of the arterial and venous blood streams, flowing in opposite directions, takes place. The morphological adaptation of the vein and artery walls promotes this approximation. The vein walls in humans', rabbits', dogs', rats', and many other species' cavernous sinuses are changed into structures formed of fibrous trabecule and this enables a free, though slowed down, flow of the venous blood in the left and right cavernous sinuses and between the sinuses through the rostral and caudal (sometimes only the rostral) intercavernous sinuses. Only the endothelium remains from the vein's wall layers, and it directly covers the wall of the sinus portion of the internal carotid artery (Aquini et al., 1994; Mutus et al., 2001). The sinus portion of the human (Masuoka et al., 2010) and rabbit (Wong and Langille, 1996) internal carotid artery (T-6) loses the lamina elastica externa and the lamina elastica interna layers. Age-related changes in the size and number of pores in the lamina elastica interna were shown in rabbits, mice, and rats, and according to many researchers they facilitates the permeation of different chemical molecules through the vessel walls (Wong and Langille, 1996; Boumaza et al., 2001; Lee et al., 2005).

In many species of ungulates (ruminants, pigs, etc.) the sinuses were formed from the veno-venous network intertwined with the arterio-arterial network of the internal carotid artery (the rete mirabile caroticum) or with a network of the maxillary artery. The outer layers of veins and arteries combine in a common tunica adventitia (Khamas et al., 1984), and the inner muscular layer of arterioles is reduced to three to five layers of muscle cells (Santamaria et al., 1987).

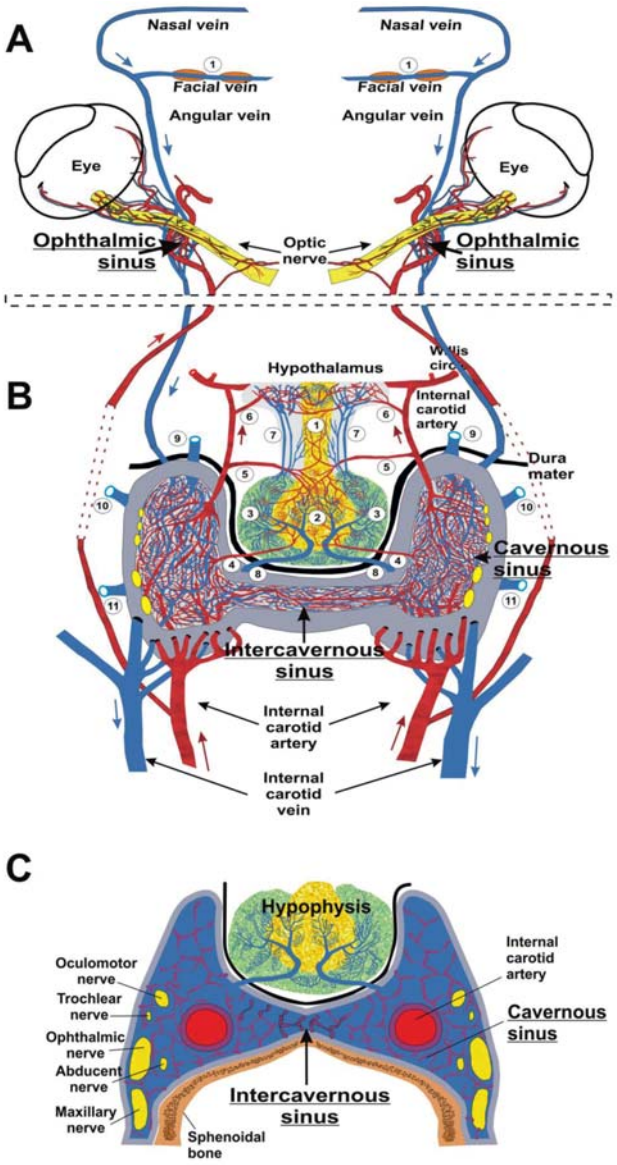

Fig. 1. Scheme of the ophthalmic sinus and cavernous sinus. A. Periophthalmic sinus: ophthalmic venous sinus and rete mirabile of the ophthalmic external artery. (1) "sphincters" created by part of the facial veins with well-developed multilayer tunica media react to steroids hormones and pheromones and regulate blood flow to the ophthalmic sinus and cavernous sinus or to the jugular vein. B. Cavernous sinus in animals with rete mirabile of internal carotid artery or maxillary artery (sheep, pig, and other species of Artiodactyla). (1) infundibulum, (2) neurohypophysis; (3) adenohypophysis; (4) inferior hypophyseal artery; (5) middle hypophyseal artery; (6) superior hypophyseal artery; (7) long portal veins; (8) inferior hypophyseal vein; (9, 10, 11) venous connections to the cerebral sinuses. C. Cavernous sinus in human, rabbit, dog, cat and many other species. Internal carotid artery without rete mirabile. Cranial nerves passing the cavernous sinus marked in yellow. Adapted, according to Krzymowski and Stefańczyk-Krzymowska (2012).

Venous blood is separated from the arterial blood by five or six relatively thin vascular layers.

Ten trunks of cranial nerves pass along the cavernous sinus in very close contact with the venous outflow from the brain and from the pituitary gland. The nerve trunks such as the oculomotor nerve (n. III.), the trochlear nerve (n. IV.), the maxillary nerve (n. V_2), and the ophthalmic nerve (n. V_1), which are branches of the trigeminal nerve (n. V.) and of the abducens nerve (n. VI), pass the cavernous sinus on each side of the head. The functional significance of these nerves' localization in the cavernous sinus has not been identified.

Physiological studies on the function and role of the cavernous sinus were conducted in the 1970s, mainly by Baker and Hayward, (1968; 1969). These authors postulated that in the cavernous sinus, cold venous nasal blood cools the arterial blood of the internal carotid artery that supplies the brain and pituitary, due to countercurrent heat exchange. However, new findings document the fact that the cavernous sinus does not play a considerable role in the heat exchange in protecting the brain against overheating under physiological conditions (Mitchell et al., 1997; Fuller et al., 2000; Fuller et al., 2011).

A completely new view on the function and physiological significance of the cavernous sinus was caused by the discovery of the permeation of neuropeptides (neurotransmitters) in the cavernous sinus from venous blood (venous outflow from the brain and from the pituitary) to arterial blood supplying the pituitary and the brain and the retrograde transfer of neuropeptides to the brain. A study on isolated pig heads supplied with their own blood through the carotid arteries demonstrated that after infusion of radiolabeled GnRH, beta-endorphin, or progesterone to the cavernous sinus, these hormones were found in the arterial blood that supplies to the brain and to the pituitary gland (Krzymowski et al., 1992). Subsequent studies performed on swine or on sheep using the isolated animal-head models perfused with autologous blood or on anesthetized animals demonstrated that after infusion into the cavernous sinus or into the nasal cavity of radioactive neurohormones or pheromones, such as GnRH (Grzegorzewski et al., 1997; Skipor et al., 1999), oxytocin (Grzegorzewski et al., 1995), dopamine (Skipor et al., 2001; Skipor et al., 2004), beta endorphin (Krzymowski et al., 1992; Skipor et al., 1997), and steroids i.e. progesterone and testosterone (Krzymowski et al., 1992; Skipor et al., 2000; Skipor et al., 2003) or male pheromone – androstenol (Krzymowski et al., 1999; Stefańczyk-Krzymowska et al., 2000; Krzymowski et al., 2001), these substances were found in arterial blood that supplied to the brain and to the pituitary gland, and in many brain structures. The role of the cavernous sinus was also shown in the local destination transfer of priming pheromones that permeate from the venous blood outflowing from the nose into the arterial blood that supplies to the brain. It has been postulated that physiological regulators, after reaching the hypothalamus and pituitary gland in this way, initiated endocrine reactions associated with reproduction (Krzymowski et al., 1999; Stefańczyk-Krzymowska et al., 2000; Krzymowski et al., 2001; Krzymowski and Stefańczyk-Krzymowska 2012).

Moreover, destination transfer through the cavernous sinus of male steroid pheromones absorbed in the nasal cavity and hormones applied on the nasal mucosa to the brain of gilts (Krzymowski et al., 1999; Skipor et al., 2000; Stefańczyk-Krzymowska et al., 2000; Skipor et al., 2003) is dependent on the function of the superficial veins of the nose and face. The vascular tension and contractility of the facial vein and of the frontal vein is regulated by steroid hormones and pheromones, and these veins function as vascular sphincters and regulate the influx of venous blood from the nose to the cavernous sinus (Grzegorzewski, 2005; Grzegorzewski, 2006; Grzegorzewski et al., 2010).

In 1996 D. A. Oren presented an inspiring hypothesis on a phototransduction and its functioning by the humoral pathway with the participation of the cavernous sinus. His concept assumed that energy from visible light stimulates the retina production of a neurogenic regulator – carbon monoxide (CO) (from the hem), which in the cavernous sinus permeates into arterial blood, and after reaching the brain causes several changes in its activity (Oren, 1996). A recent study by Koziorowski et al. (2012) confirm Oren's hypothesis and demonstrated that CO production in the eye depends on the intensity of

natural light reaching the retina, and its concentration in the venous blood outflow from the eye varies depending on the time of day and on the season (See Fig. 2).

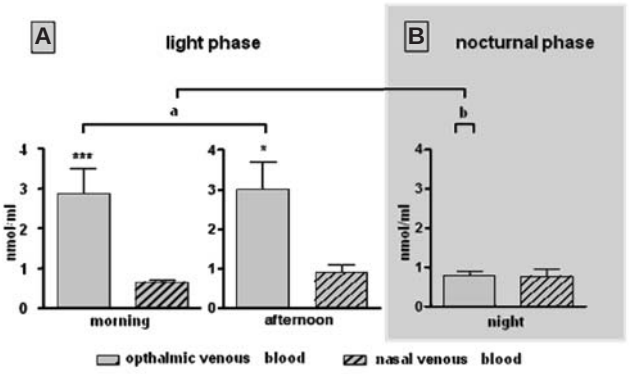

Fig. 2. Concentration of CO in the venous blood outflowing from the eye and nasal areas in male wild boar×domestic pig hybrids during the summer. A) light phase; B) nocturnal phase. *P<0.05; ***P<0.001; a/bP<0.001. According to Koziorowski et al. (2012).

Further research *in vivo* shown that carbon monoxide infused into the cavernous sinus reaches the suprachiasmatic nuclei, the location of the main biological clock, and alters the expression of the clock genes *Per and Cry* and their transcription regulators, which modulate the circadian and the seasonal cycles (Gilun et al., 2013). It has been demonstrated that exogenous CO added to the blood or produced in the eye is transferred from the venous blood to the arteries supplying the brain and modulates the function of the biological clock in the brain (Koziorowski et al., 2012 ; Gilun et al., 2013). These data proves that the CO as a physiological regulator transferred from the cavernous sinus venous blood to arterial blood produces a definite effect on the function of specific brain structures. (See Fig. 3).

The above evidence shows the importance of the countercurrent transfer of neurotransmitters in the cavernous sinus. The transfer is a part of a universal physiological regulatory system, called "the retrograde and destination transfer of hormones and other physiological regulators," and it functions in humans and in animals (Krzymowski and Stefańczyk-Krzymowska, 2012). Particularly noteworthy is the dopamine. The dopamine as a neurotransmitter and the dopaminergic system

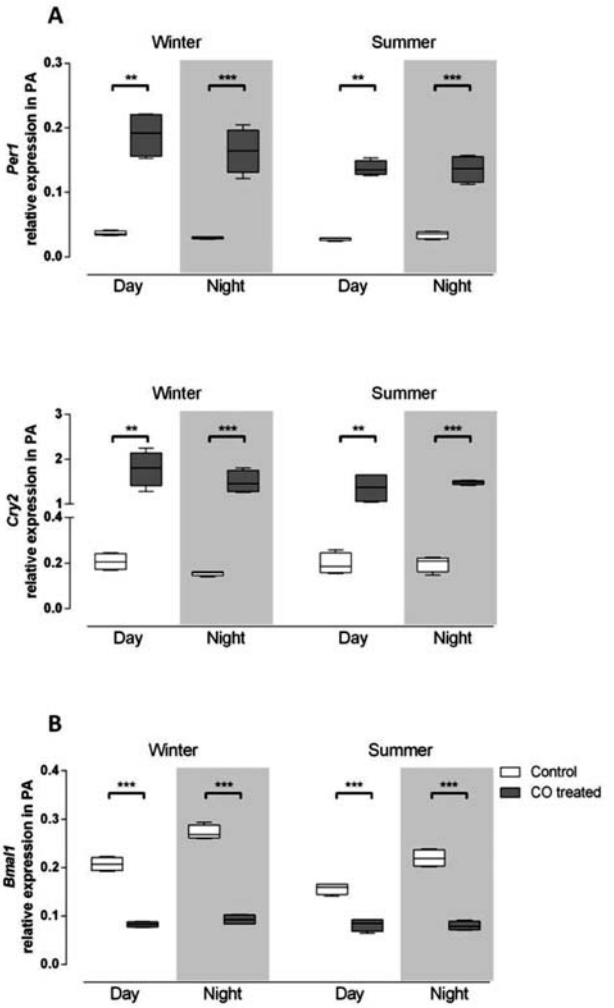

Fig. 3. Effect of exogenous CO on the expression of clock genes *Per* and *Cry* (A) and regulatory gene *Bmal1* (B) in the preoptic area of male wild boar×domestic pig hybrids. Transparent boxes – control; gray boxes after infusion of CO into the cavernous sinus. **P<0.01; ***P<0.001. According to Gilun et al. (2013).

are involved in many basic functions of humans and of animal organisms such as motivational and emotional behavior, control of involuntary and rapid motor functions, and neurosecretion associated with the physiological rhythms, the biological clock, and reproduction (Skipor et al., 2001; Skipor et al., 2004; Gilun et al., 2013). Things of particular interest in the human dopaminergic system result from the occurrence of serious neurological disorders, due to dysfunctions of the system i.e. hypo- or hyper-function, such as ADHD (Attention Deficit Hyperactivity Dis-

order), which is most common in young people; depression, present in people of all ages; schizophrenia, in adults; and Parkinson disease, in older people (Bjorklund and Dunnett, 2007; Meiser et al., 2013; Money and Stanwood, 2013; Sulzer and Surmeier, 2013; Vaughan and Foster, 2013).

The main groups of the dopaminergic neurons lie in the midbrain in the substantia nigra, in the nucleus interpeduncularis, in the abdominal area of the tegmentum of the base of the brain, and in the hypothalamus (Ciliax et al., 1995; Bjorklund and Dunnett, 2007). The axons of dopaminergic neurons located in the midbrain project to the striatal, limbic and cortical area. The dopamine released in hypothalamic dopamine neurons affects the hypothalamic neurons synthesizing neurohormones, but also penetrates the portal vessels and reaches the adenohypophysis, and from there may reach the cavernous sinus with venous blood. In the cavernous sinus, the dopamine may permeate to the arterial blood and participate in the regulation of reproductive processes (Skipor et al., 2001; Skipor et al., 2004).

It is worth noting that all the cranial nerves passing the cavernous sinus i.e. nerves III, IV, V_1, V_2, and VI, emanate from neurons located in the midbrain, i.e. the area containing the greatest groups of dopaminergic neurons (the substantia nigra and ventral tegmental area). We emphasize this because of the results of Johnston et al. (Johnston et al., 2007) who documented for the first time the possibility of the movement of chemicals along the cranial nerves, mainly along the epineurium and the perineurium. They demonstrated that Microfil (the substance used to fill the blood and lymphatic vessels) penetrates the branches of the trigeminal nerve to the cavernous sinus after its introduction into the cerebrospinal fluid of the cisterna magna in sheep. The high concentration of extracellular dopamine in the midbrain dopaminergic nuclei (Rice and Cragg, 2008) suggests the possibility of dopamine penetration along the cranial nerves from the midbrain to the cavernous sinus. This dopamine concentration is about 40 times higher in the substantia nigra than it is in the extracellular concentration in the striatum, whereas the rate of its reuptake from the synaptic clefts into flasks is 200 times lower in the substantia nigra than it is in the striatum (Rice and Cragg, 2008). Our recent pilot study showed that when radiolabeled dopamine was infused for 20 minutes into the ventral tegmental area in a bled rabbit, high radioactivity was found in the cavernous sinus 30 minutes after the end of the infusion (unpublished data). We hypothesized that cranial nerves III, IV, V_1, V_2, and VI, originating from the midbrain and passing along the cavernous sinus, might be the pathway by which the dopamine penetrates to the venous blood of the cavernous sinus, to be able to permeate into the arterial blood supplying the brain and to reach the cortical structures of the brain.

In accordance with the general opinion, the activity of dopaminergic neurons is primarily dependent upon the operation of the dopamine transporter (DAT) belonging to the family of neurotransporter proteins. In humans, the DAT is composed of 620 amino acid residues. The DAT is located mainly in the membrane of the presynaptic dopaminergic neuron and effectively acts in the dopaminergic synapse (Gainetdinov and Caron, 2003). The dopamine released into the synaptic cleft affects the second dopaminergic neurons by specific dopaminergic receptors belonging to the membrane receptors of the G-protein-coupled family. Simultaneously, extracellular dopamine is moved from the synaptic cleft back to the synaptic flask by the DAT. This is the re-uptake and the retrograde transfer of dopamine (Mateo et al., 2004; Torres, 2006), which not only reduces dopaminergic stimulation but also reduces the synthesis and storage of the dopamine in the synaptic flask vesicles (Giros et al., 1996). When DAT has been genetically determined to be absent in mice, they have a 300-fold increase of dopamine residence in the synaptic cleft (Jones et al., 1998). The dopamine is transported by the DAT through the cell membrane using the energy of the electrochemical gradient of Na^+ / Cl^- (Nelson, 1998). Excessive concentrations of dopamine in the dopaminergic neuron cytoplasm first led to the formation of toxic hydroxyl radicals followed by alpha-synuclein protein. The alpha-synuclein composed of 140 amino acid forms a stable complex with DAT. This results in the formation of Lewy's bodies and of neuron degeneration typical of Parkinson disease (Kahling and Galli, 2003).

Our recent study demonstrated permeation of dopamine in the cavernous sinus from the venous blood to the arterial blood supplying the brain in

rabbits (Muszak et al., 2014). However, approximately 60% of the dopamine, which permeated from the cavernous sinus to the arterial blood of the rabbit, reached the brain in a form of dopamine metabolites (Muszak et al., 2014). Un-metabolized molecules of dopamine present in blood reaching the brain capillaries are retained in the glial cells, and converted to dihydroxyfenylacetic acid, vanillic acid, or methoxytyramine (Meiser et al., 2013). The numerous data support the concept that DAT is indirectly regulated by dopamine metabolites. Repeated short periods of exposure to dopamine metabolites cause rapid decrease in the activity of the DAT (Saunders et al., 2000; Afonso-Orama et al., 2010; Gulley et al., 2012).

Previously such a transfer of the dopamine was demonstrated in sheep (Skipor et al., 2001; Skipor et al., 2004). As described earlier (Muszak et al., 2014), the cavernous sinus morphology in sheep varies considerably compared to human and rabbit. The morphology of the cavernous sinus in rabbits and in humans is very similar. This allows us to assume that dopamine transfer and its participation in the regulatory process can also take place in humans. Therefore rabbits can be a good experimental animal model in further studies of this phenomenon. The counter current transfer of dopamine from the cavernous sinus to arterial blood and to the brain in rabbits is presented in Fig. 4.

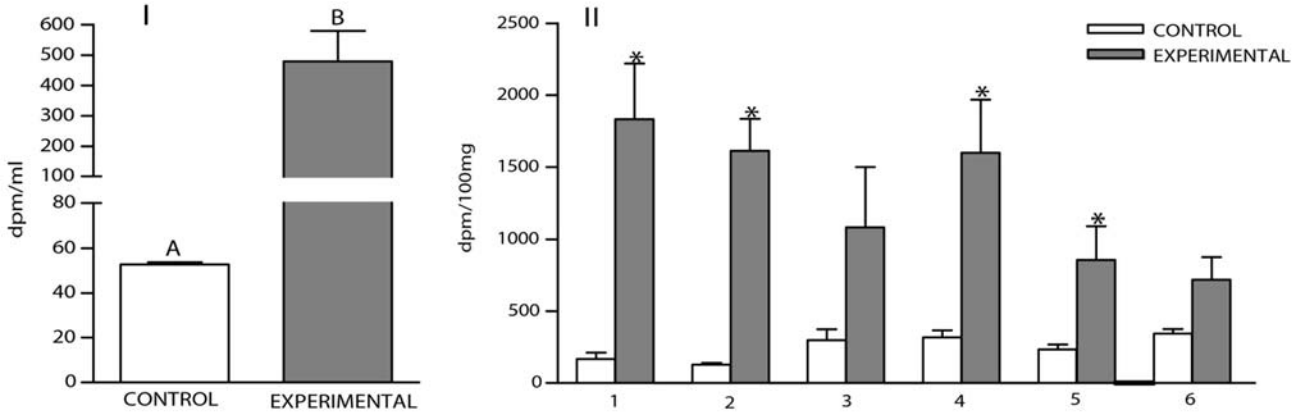

Fig. 4. Concentration of radioactivity during and after infusion of the radiolabeled dopamine into the rabbit cavernous sinus: (I) in the arterial blood supplying the brain (II) in some brain structures: (1) pia mater; (2) pons; (3) ventral tegmental area; (4) mammilary body; (5) hipocampus; (6) corpus striatum. According to Muszak et al. (2014).

CONCLUSIONS

- The retrograde transfer of neurotransmitters in the cavernous sinus is part of a universal physiological regulatory system, called the retrograde and destination transfer of hormones and other physiological regulators (Krzymowski and Stefańczyk-Krzymowska, 2012).
- It may be assumed that whether the retrograde transfer of dopamine in the cavernous sinus operates under physiological conditions during one's whole life, the uptake and transfer of dopamine to the brain results in a constant supply of dopamine metabolites to the brain capillaries of the striatal, limbic and cortical area where dopaminergic neurons are located.
- The numerous data have pointed to the fact that dopamine may reach the cavernous sinus not only with venous blood flowing out from the hypothalamus through the pituitary, but also along the epineurium and perineurium of ten trunks of the five cranial nerves (III, IV, V1, V2 , and VI). All these nerves have their origin in the midbrain, where the groups of dopaminergic neurons are largest and where extracellular dopamine concentration is highest. Moreover, these nerves pass through the cavernous sinus.

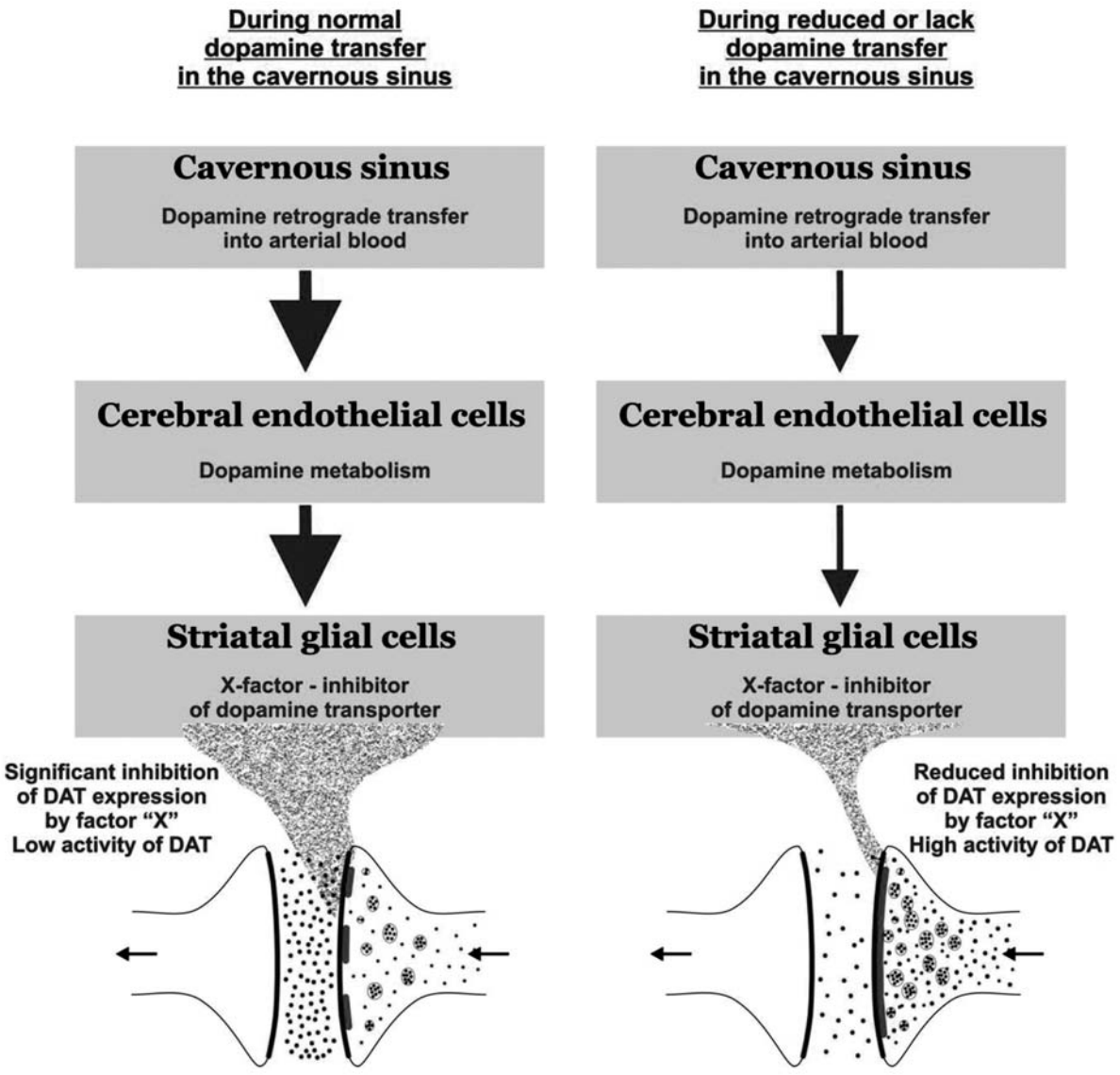

Fig. 5. The regulation of the dopaminergic system according to our hypothesis.

Based on the results of our own study and on data from previous studies, we present the following opinions:

a) Under physiological conditions, unknown substances produced under the influence of dopamine metabolites in the glial cells reach the dopaminergic neurons and inhibit the expression of the DAT. This regulation functions as the feedback loop.
b) Disorders of dopamine retrograde transfer in the cavernous sinus and thus of dopamine metabolites supply to glial cells, might be the main cause of the dopaminergic system hyper- or hypo-function, and therefore the inducer of many motor and neuropsychiatric disorders, including Parkinson disease.

Our conception of regulating the dopaminergic system function is presented in Fig. 5.

We think that when studying the causes of dopaminergic system dysfunctions, namely its hypo- or hyper-function, and the consequences, including the Parkinson disease, ADHD, schizophrenia, and many other mental disorders relat-

ed to the dopaminergic system, two areas must be involved:

- the cavernous sinus, where operates the uptake and retrograde transfer of dopamine from the cavernous sinus venous blood into the arterial blood supplying the brain;
- the brain and its dopaminergic structures, where the DAT meets the leading role in the regulation of the dopaminergic system function.

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