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Local transfer of substances between the blood vessels at the base of the brain

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ABSTRACT

Studies performed on a variety of species (pigs, sheep, rabbits, rats) indicate the existence of a local transfer system of substances between blood vessels located at the base of the cranium (the cavernous sinus - carotid artery vascular complex). This local transfer allows for some hormones synthesized in the brain and hypophysis, as well as biologically active substances absorbed from the nasal mucosa, and drained to the cavernous sinus to reach the brain vasculature in a concentration locally higher than that measured in systemic circulation. The present paper gives an overview of: 1. the major anatomical structure engaged in the transfer, 2. experimental evidence for substance transfer in the vascular complex, 3. factors affecting the transfer and 4. possible physiological importance.

KEY WORDS: carotid rete, cavernous sinus, local transfer, nasal administration, pheromones

INTRODUCTION

Regulation of the body functions is based on nervous signals and humoral messages. By tradition, the humoral signals are divided into cell-to-cell interaction (autocrine, paracrine), and hormones distributed by the circulatory system to the whole organism (endocrine). The “effective” level of a hormone in potential target cells depends on the balance between its uptake and removal. Changes in hormone concentration in the blood supplying the tissue are the main determinants of the

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hormones uptake. Some organs have a specific redistribution of hormones *via* the vascular system that allows for delivery of hormones to the target organs in a concentration higher than that measured in general circulation. This local redistribution is based on the morphological and functional adjustments of circulation in some areas, that allow for the transfer of substances from the venous blood and lymph to the arterial blood through the walls of the closely connected vessels. Physiologically, the transfer facilitates local feedback regulation of organ function in a process situated between general distribution of hormones through the general circulation and paracrine regulation. If the transfer takes place between the major in- and outflow of blood to an organ, the feedback will involve the entire organ and eventually, other organs supplied from the same artery, while if it concerns small organ blood vessels, the regulation will concern only those parts. So far, local transfer of substances between blood and lymph vessels as well as it importance in regulatory mechanisms was well documented for the area of the female and male genital tract (Krzymowski et al., 1990; Stefańczyk-Krzymowska and Krzymowski, 2002; Einer-Jensen and Hunter, 2005).

Krzymowski et al. (1992) discovered that the transfer of substances also take place between venous and arterial vessels located at the base of the brain - in the cavernous sinus (receiving an outflow from the pituitary and a part of the brain) - carotid artery/carotid rete (main vessels supplying the brain and hypophysis) vascular complex.

The present article attempts to describe experimental data concerning the evidence for local transfer of substances between the venous blood from the brain and nasal cavities to the brain arterial blood.

THE CAVERNOUS SINUS - CAROTID ARTERY/CAROTID RETE COMPLEX

Various authors have comprehensively described the structure and function of the vascular complex of cavernous sinus and carotid rete (Daniel et al., 1953; Godynicki et al., 1981; Ghoshal and Khamas, 1985; Simoens et al., 1987). Therefore, only information relevant to the understanding of the morphological and physiological factors affecting the transfer will be provided in the review.

The cavernous sinuses

The cavernous sinuses are paired venous channels in the dura located bilaterally on the cerebral surface of the basisphenoid bone, on both sides of the sella and pituitary gland. They are converted into complex neurovascular structures by the

numerous arteries and cranial nerves contained within their walls, and by their many venous connections. The right and the left cavernous sinus flank the corresponding aspects of the pituitary and are connected to each other by intercavernous sinuses (Figure 1). The venous channels converge around the carotid artery and its branches on several sites to form larger venous spaces, which might be termed “caverns”.

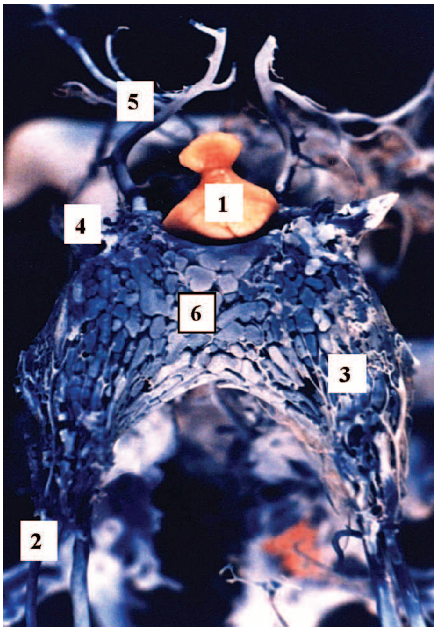

Figure 1. Corrosion cast of the cavernous sinus and rete mirabile epidurale in pigs. Pituitary gland - 1, ascending pharyngeal artery - 2, carotid rete (thin, white vessels between oval shape blue structures) - 3, internal carotid artery - 4, rostral cerebral artery - 5, cavernous sinus (oval shape structures filled with blue Merkox) - 6. prepared by W. Grzegorzewski and photographed by A. Penkowski

Some of the veins form a mesh and allow blood to flow in multiple directions. The afferents to the cavernous sinus come from the pituitary and base of the brain, but most of them drain extracranial areas. The concentration of hypothalamic and pituitary hormones in blood of the cavernous sinus is high. In horses concentration gradients between the intercavernous sinus and the jugular vein exceed 40-fold for LH, 50-fold for ACTH and even 500-fold for vasopressin (Redekopp et al., 1986). In sheep, the amplitude of LH and FSH pulses measured in the blood collected from the cavernous sinus exceed that measured in blood collected from jugular vein 9 and 1.5 times, respectively (Clarke et al., 2002). Some of the drainage to the cavernous sinus originates from the nasal cavity (Ghoshal and Zguigal, 1986).

The carotid artery and carotid rete

The arteries supplying the mammalian brain arise from the circle of Willis giving off branches that run deep into the nervous tissue. In man and other primates as well as in rodents, the circle of Willis is supplied by the paired internal carotid arteries and the vertebral-basilar system (Simoens et al., 1987). The pig, sheep and other animals of the Artiodactyla order possess the carotid rete located in the main blood supply to the circle of Willis (Simoens et al., 1987). The carotid rete is an intracranial arterial plexus that consists of a large number of short, thin, and parallel arteries that merge into one vessel before leaving the cavernous sinus. The rete arteries have a well developed elastic lamina, and a tunica media consisting of three to five (goat and pig) or six to eight (cattle) smooth muscle layers (Santamaria et al., 1987). The adventitia is rich in collagen and covered by a single layer of endothelium which forms the lining of the cavernous sinus. This construction creates a huge area with a small diffusion distance between arterial and venous blood that offers the possibility of heat exchange and substance transfer.

EXPERIMENTAL EVIDENCE FOR SUBSTANCE TRANSFER IN THE VASCULAR COMPLEX

Many substances representing several chemical groups (Table 1) were studied in two groups of animals: those with a well developed carotid rete (pigs, sheep)

Table 1. Studies of transfer of biologically active substances from venous blood of the cavernous sinus to arterial blood supplying the brain

Investigated substance	Species	Transfer	References
Water	Rats[a]	Y	Einer-Jensen and Larsen, 2000b
Propanol	Rats[a]	Y	Einer-Jensen and Larsen, 2000b
Tyrosine	Rats[a]	Y	Einer-Jensen and Larsen, 2000b
Dopamine	Sheep	Y	Skipor et al., 2001, 2004b
Progesterone	Pig, sheep	Y	Krzymowski et al., 1992; Skipor et al., 2003
	Rats	Y	
Testosterone	Pig	Y	Skipor et al., 2000
Androstenol	Pig	Y	Krzymowski et al., 1999, 2001; Stefańczyk-Krzymowska et al., 2000
Oxytocin	Pig	Y	Grzegorzewski et al., 1995
β-endorphin	Sheep	Y	Krzymowski et al., 1992; Skipor et al., 1997
LHRH	Pig, Sheep	Y	Krzymowski et al., 1992; Grzegorzewski et al., 1997; Skipor et al., 1999
Prolactin	Sheep	N	Skipor et al., 2004a
LH	Sheep	N	Skipor et al., 2004a
Diazepam	Rats[a]	Y	Einer-Jensen and Larsen, 2000a
Cocaine	Rats[a]	N	Einer-Jensen and Larsen, 2000a
Sumatriptan	Rats[a]	N	Einer-Jensen et al., 2001
Naratriptan	Rats[a]	N	Einer-Jensen et al., 2001

[a] - male rats

and those without carotid rete (rats, rabbits). Most of the experiments in pigs and sheep have been performed on a model of the perfused isolated head (Krzymowski et al., 1992). The advantage of this model is the absence of recirculation through the general circulation. The head must be considered brain-dead since the circulation was stopped during the preparatory period, but the function of the vessels seemed undisturbed. *In vivo* model developed for rats (Einer-Jensen and Larsen, 2000a) and pigs (Stefańczyk-Krzymowska et al., 2000) utilizes transfer *via* venous drainage from the nasal cavity to the cavernous sinus and then to the brain and hypophysis. In anaesthetized rats or pigs parallel blood samples were collected from two catheters inserted into the same carotid artery; the two tips were pointing towards the head and the heart respectively. A head:heart ratio grater than 1.00 indicated that nasally infused substances were transferred locally in the circulatory system to the head.

FACTORS AFFECTING THE TRANSFER

Information is limited concerning the mechanism of the retrograde transfer of substances between the blood vessels at the base of brain. From the general point of view, transfer of substances between vessels is based on the anatomical structures, flow rates, and the physico-chemical properties of the substances.

Molecular size

According to previously published data (Grzegorzewski et al., 1995, 1997; Skipor et al., 1997, 2000, 2001, 2003, 2004a) we present calculations indicating that the passage of molecules through the walls of the cavernous sinus - carotid rete complex depends on the size of molecules (Figure 2). A sharp upper limit for the

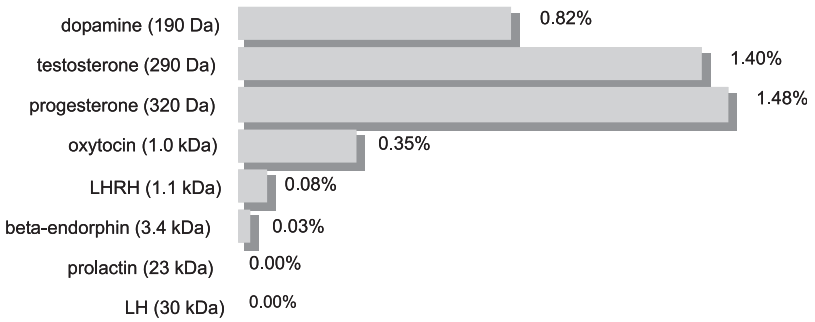

Figure 2. Estimated level of the transfer for labelled molecules with different molecular mass, presented as percentage of total infused dose. All molecules were infused into the cavernous sinus in the similar dose of 7.35×10^7 dpm for tritium labelled and 6.65×10^7 dpm for iodine labelled. Calculated on the base of the mean level of radioactivity in arterial blood and blood volume collected during 12 min of experiment

molecular size has not been established, but substances with a large molecular weight such as prolactin and LH are not transferred (Skipor et al., 2004a). Celia and Osol (2005) observed a similar relationship between molecular weight and the passage of substances through the uterine vein. The authors using two different molecular weight fluorescent dextrans, has demonstrated higher permeability of uterine vein to 3-kDa than 70-kDa dextran in both non-pregnant and late pregnant rats. There are two possible mechanisms for the passage of substances across the walls of the carotid rete and cavernous sinus: bulk flow through openings between cells (paracellular transport) and the active shuttling of molecules by transcellular transport. It has been demonstrated that blocking membrane Na^+, K^+ ATP-ase by ouabain reduced the transfer of β-endorphin in the perihypophyseal vascular complex in sheep (Skipor et al., 1997).

The oestrous cycle and reproductive activity

Strong evidence exists for an influence of the female reproductive cycle on the local transfer of neuropeptides and steroids between vessels in pigs and sheep (Krzymowski et al., 1992; Grzegorzewski et al., 1995, 1997; Skipor et al., 1997, 2003). In contrast, studies performed on female rats showed that progesterone transfer between vessels of the cavernous sinus - carotid artery complex in females is not affected by hormonal milieu (Skipor et al., 2003). In pigs, a subsequent comparison of the transfer of ^{125}I-oxytocin, ^{125}I-LHRH and ^{3}H-progesterone during different days of the oestrous cycle showed that both labelled neuropeptides transferred only on Days 1-3 and 12-14 of the oestrous cycle, while progesterone

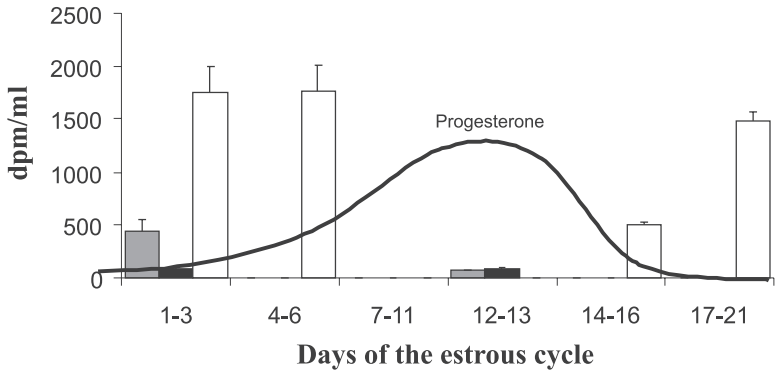

Figure 3. Mean radioactivity values for progesterone (white bars), oxytocin (grey bars), LHRH (black bars) in arterial blood taken from the carotid rete *via* the carotid artery in gilts on different days of the estrous cycle. Calculated from Grzegorzewski et al., 1995, 1997; Skipor et al., 2003

transferred on Days 1-6 and 14-21 (Figure 3). The data may indicate that in gilts an efficacy of progesterone transfer is opposite to its endogenous level during the oestrous cycle. However, it should be noted, that ^{3}H-progesterone (as well as other labelled molecules) might be considered only a marker of the permeation process and its intensity. Therefore, their mass corresponding to the values of radioactivity estimated in the blood, plasma or tissue samples did not represent the amounts of the hormone (endogenous and radioactive together) transferred from the venous blood of the cavernous sinus into the arterial blood supplying the brain and hypophysis. A reverse trend in the intensity of the steroid transfer comparing to their endogenous level may reflect therefore a competition between the endogenous cold steroids and the labelled steroids infused into the cavernous sinus.

It has been documented that in sheep the endocrine stage of the ewe also affected transfer of ^{3}H-dopamine. However, the effect of oestradiol treatment on the intensity of ^{3}H-dopamine transfer was observed only during anoestrus (Skipor et al., 2001). Therefore, the trend in the intensity of ^{3}H-dopamine transfer seems to be reverse of the dopaminergic tone of the medial basal hypothalamus and median eminence during anoestrus, when dopamine content in median eminence is high. Similar, seasonal variations in the intensity of the transfer were observed also for ^{125}I-LHRH and ^{125}I-β-endorphin (Krzymowski et al., 1992; Skipor et al., 1997). Transfer of these neuropeptides was present during reproductive season when during anoestrus was almost neglectible. In seasonally anoestrous sheep, transfer of ^{125}I-LHRH was restored after oestradiol benzoate was administered for five days (Krzymowski et al., 1992). On the other hand, in ovariectomized sheep oestradiol benzoate decreases the intensity of ^{125}I-LHRH transfer in the time when the endogenous level of LH was high due to the positive action of oestradiol benzoate on LHRH and LH secretion (Skipor et al., 1999). Moreover, this effect was potentiated by hCG, receptors of which were found in the walls of venous and arterial component of the periovarian vascular complex (Skipor et al., 1999). In ovariectomized gilts a higher intensity of ^{125}I-LHRH transfer was observed in animals treated with oestradiol benzoate (during the period of LH decrease) compare with an oil-treated animals (Grzegorzewski et al., 1997). These variations in the effect of oestradiol on the transfer of ^{125}I-LHRH could result from the use of ovariectomized vs intact animals and the time between oestradiol benzoate injection and experiment inducing negative vs positive feedback for LH secretion. In generally, the mechanism of oestradiol action is not known. It can be assumed that oestradiol affect LHRH transfer efficacy at least in two areas. In the vessels of the perihypophyseal vascular complex, oestradiol may participate in the regulation of vessel permeability, as it was suggested for other vascular beds (Van Buren et al., 1992), and at the hypothalamus and pituitary levels, regulating LHRH

and LH release and therefore their concentration in the venous blood reaching the cavernous sinus.

THE POSSIBLE PHYSIOLOGICAL IMPORTANCE

The local transfer of biologically active substances in the perihypophyseal vascular complex raises the possibility that it may serve some physiological function. A humoral pathway for the priming action of male pheromone in female pigs is one very special function. Intraspecies communication by chemical signals (pheromones) plays important behavioural and physiological roles in coordinating reproduction in mammals. Pheromones act by stimulating the dendritic receptors of chemosensory neurones in the olfactory neuroepithelium in the nasal cavity, and in the vomeronasal organ. Such a mechanism seems to be well adapted for transmitting information induced by signalling pheromones, that are responsible for changes in behavioural and sexual activity. It has been demonstrated that in female pigs priming pheromone - androstenol, that set in motion a chain of neuroendocrine and endocrine events may use a local humoral pathway to reach the hypophysis and brain (Krzymowski et al., 1999, 2001; Stefańczyk-Krzymowska et al., 2000). In both *ex vivo* and *in vivo* experiments the resorption of ^{3}H-androstenol from the respiratory part of the nasal mucosa into the venous blood in the nasal cavity and its subsequent local transfer in the periohypophyseal vascular complex into the arterial blood supplying the brain, as well as its arrest in certain brain structures, were demonstrated. In anaesthetized gilts ^{3}H-androstenol was found in the anterior hypothalamus, i.e. at the site of LHRH, oxytocin and vasopressin synthesis, while was not present in the mediobasal hypothalamus where the transport and release of this peptides take place (Stefańczyk-Krzymowska et al., 2000). It was also found that intramuscular injections of androstenol stimulate the development and secretory function of the ovarian follicles in gilts during sexual maturation, during perioestrous period affect the ovarian morphology and influences hormonal regulation in hypoosmatic gilts (Stefańczyk-Krzymowska et al., 2002, 2003, 2005). It has been demonstrated, just recently, that androstenone and androstenol (pig pheromenes) directly affect the reactivity of the superficial veins of the face and nose in the female pigs that may play an important role in the mechanism regulating direction of venous outflow from the nose to the cavernous sinus (Grzegorzewski, 2005, 2006).

Although there is presently no experimental evidence for its participation in another regulatory mechanism it is worth considering that this phenomenon allows for some substances secreted from brain centres, the pituitary gland and the retina to reach the pituitary and other brain centres (if they pass the blood brain barrier) in a concentration higher than that measured in general circulation. The advantage

of the local transfer is an increase in specific impact since the message is not evenly diluted in the general circulation. It has so far been an overlooked method for distribution of humoral signals from one brain centre to other parts of the brain. In our opinion, it may be regarded as a semispecific intermediate between distribution *via* the general circulation and paracrine distribution. One brain centre will communicate, through the vascular system, with other centres; an example of this is the ability of LHRH, oxytocin, β-endorphin (released in neurohypophysis) to reach other brain centres with arterial supply. This has specific, but as yet not fully determined function in the regulation of reproduction or other physiological processes on the brain and pituitary level.

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