Annals of Veterinary Science
Review Article

# A Scoping Review of Research on the Cranial Molecular Counter-Current Transfer in Mammals

**Xinyu Liu[1*], Chris Araujo[2], Pawel M Bartlewski[2]**

[1]Shenyang 204 Hospital; Hemu Bei 2 Lu, 2 Hao, Dadong District, Shenyang, Liaoning, PR China

[2]Department of Biomedical Sciences, Ontario Veterinary College, University of Guelph, Canada

**Received**: 18 July, 2018; **Accepted**: 24 July, 2018; **Published**: 27 July, 2018

***Corresponding Author:** Liu X, Shenyang 204 Hospital, Shenyang, Liaoning, China.
E-mail: 13889106685@hotmail.com



## Abstract

Various cephalic sites of the molecular transport and counter-current transfer have been identified in mammalian species, including the choroid plexus blood-cerebrospinal fluid barrier (CPB-CFB), the cavernous sinus-carotid rete complex as well as the nasal vasculature exchange pathway. The present literature review has been conducted to incorporate articles highlighting the key findings, conclusions, and the anticipated impact of studies aimed to elucidate the counter-current transfer processes in the brain. Although cephalic sites of the molecular counter-current transport of biologically active substances have been clearly defined and their undeniable importance for neurohomeostatic regulations and reproductive physiology has been recognized, a scarcity of most recent reports have slightly dampened the optimism that in the nearest future these sites will be exploited to their full therapeutic potential.

**Keywords:** Counter-Current Exchange; Brain; Choroid Plexus; Cavernous Sinus; Carotid Rete; Cerebrospinal Fluid; Nasal Cavity

# Introduction

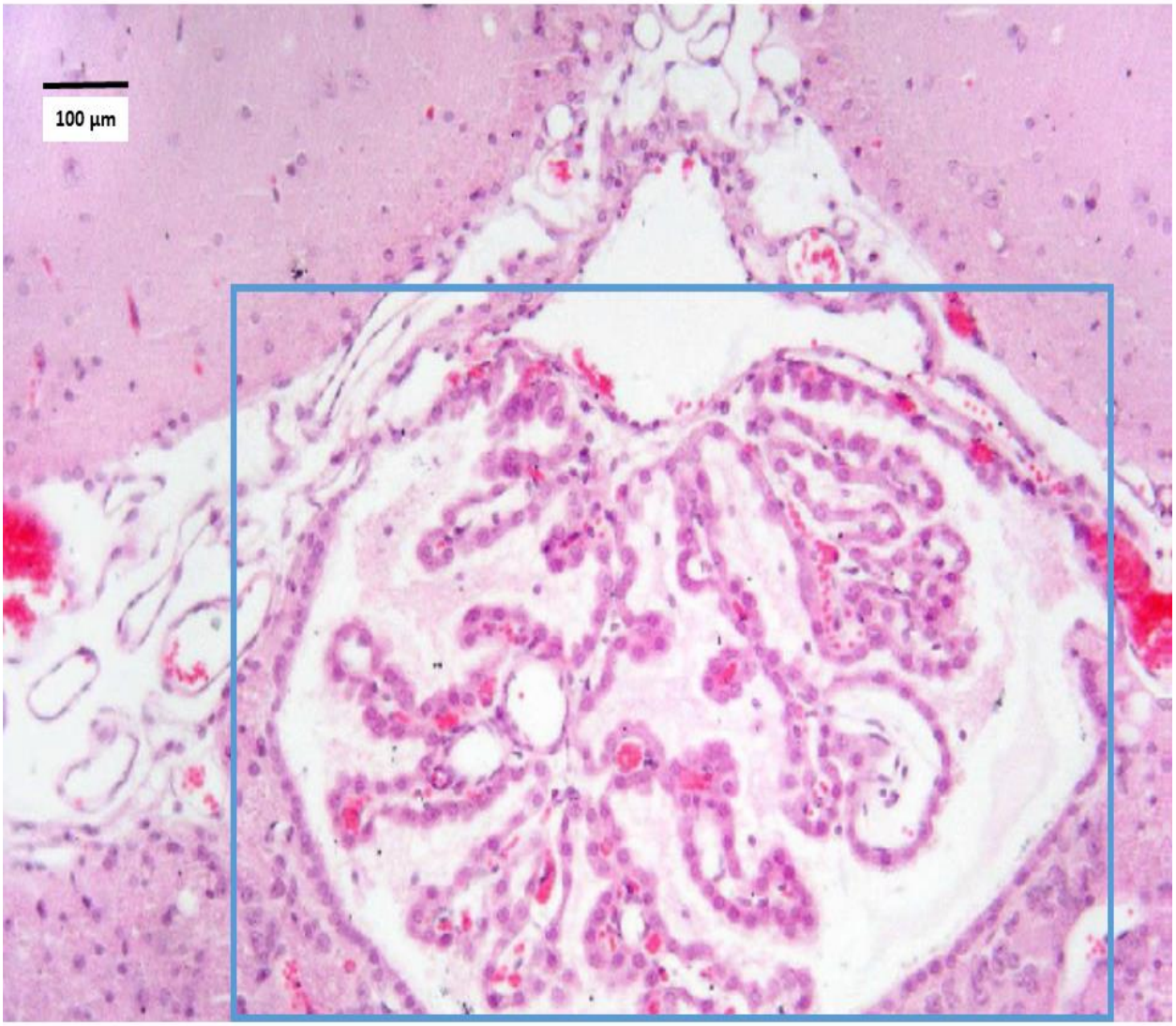
The peripheral counter-current transfer of heat, gases and soluble solid substances in different vascular complexes scattered throughout the mammalian body has been thoroughly characterized [1-5]. It has been well-established, in both the human and veterinary physiology, that there are anatomical locations for molecule exchange, which are integral to survival and basic homeostatic and reproductive functions, such as the process of $O_2/CO_2$ exchange in the lungs, renal filtration, heat and steroid transport in the pampiniform plexus, or the circulation of hormones in the utero-ovarian vasculature [1, 5-7]. Nearly three decades ago, the existence of cephalic sites for the counter-current transfer of biologically active substances was first reported [8].

The primary focus of this mini-review is on the studies devoted to the molecular counter-current exchange systems in the cranial anatomy and physiology. Of particular interest are the choroid plexus and the cavernous sinus, and the yet incompletely defined therapeutic potential they may possess due to retrograde molecular transport and drug trafficking in the central nervous system (CNS). In addition, the putative downstream effects of these events on the metabolic and reproductive processes have also been briefly addressed. In general, the purpose of this mini-review was to carry out a comprehensive review of the published scientific literature in order to assess the current status of and to propose future research directives for the cranial counter-current exchange mechanisms in mammals. Perhaps our article will spark even greater interest in this area of biomedical research that may subsequently result in alternative hormone/drug administration techniques and therapeutic strategies.

## Choroid plexus blood-cerebrospinal fluid barrier (CPB-CSB) transfer

The choroid plexus is a network of blood vessels found within each of the four ventricles of the brain. It is derived from the pia mater and produces the cerebrospinal fluid [CSF; 9]. The CSF has many functions, which include providing the protective cushioning, maintaining the buoyancy of the brain and ensuring the constant removal of harmful metabolic waste products from the central nervous system [9]. The epithelium of the choroid plexuses plays a very important role in brain homeostasis since it acts as a mediatory structure between a vascularized stroma providing blood flow to the brain and CSF. In addition, these epithelial layers are characterized by an extensive network of microvilli and epithelial foldings, which greatly increase a surface area between CSF and the elaborate stroma capillary network (Figure 1). Therefore, it has been speculated that this interface may serve as a crucial structure governing molecular exchange in the brain [10]. Unlike the blood-brain barrier whose role in drug delivery to the brain has been thoroughly studied [11,12], until recently the choroid plexus has received relatively little attention [13]. Thyroxin ($T_4$) movement from blood to brain occurs at the basolateral side of the choroid plexuses as an alternative route to the blood brain via a carrier-mediated transport mechanism [13]. A study by Dzięgielewska et al. [14] examined the occurrence of the transport of proteins across the choroid plexus. Using labeled human and sheep plasma proteins in the sheep fetus experimental model, the authors found that significant amounts of proteins would readily transfer from blood to CSF in 60-day ovine fetuses; however, in the 85-day old fetus, both the levels of the proteins and their lifespan in CSF were significantly diminished. Chen et al. [15] further investigated the relationship between age and the functioning of the blood-CSF choroid plexus barrier in the sheep.

**Figure (1)**: The choroid plexus in the third ventricle of rat brain stained with hematoxylin-eosin (section thickness of 5-10 μm). The choroid plexuses consist of a folded sheet of simple cuboidal epithelium that surrounds a matrix of highly vascular connective tissue 'floating' in the cerebrospinal fluid in brain ventricles




Although the steady-state mRNA levels for insulin-like growth factor II (IGF-II) in the choroid plexus of young adult (1-2 years old) and older (7-10 years of age) sheep did not vary, IGF-II concentrations in CSF were markedly decreased in older animals. Collectively, these findings indicate that an intensive molecular transport mechanism does indeed exist in the choroid plexus during pre-natal and early post-natal stages, and that it presents itself as selective in nature or gradually declines as the somatic development progresses. In spite of those observations, the choroid plexus has never been relegated as a bystander structure for the molecular exchange mechanisms in the adult brain. An experiment carried out by Ghersi-Egea et al. [16] illustrates the

therapeutic potential of the choroid plexus-mediated blood-CSF barrier exchange system. Radioactively labeled sucrose administered via an intraventricular injection was tracked to follow its distribution throughout the brain in the rat. The flow of CSF transported at different rates into the ventricles as well as the ependymal tissues, the pia arteries and arterioles, and the perivascular space was described.

The observations made were supportive of the notion that the choroid plexus interface might participate in drug delivery to induce site-specific therapeutic effects in the difficult to reach regions of the brain. This putative role of the choroid plexus was later confirmed in a study by Thomas and Segal [17] who evaluated the transport of an anti-HIV agent to the brain; the ability of the drug 2', 3'-didehydro-3'-deoxythymidine (D4T) to gain access to the guinea-pig brain via the blood-brain barrier or blood-CSF barrier was investigated in order to devise the most effective strategy for clinical applications of the drug. The D4T was incapable of traversing the blood-brain barrier but relatively high penetration rates were noted via the blood-CSF barrier due to enhanced permeability of the choroid plexus blood-CSF interface. In addition to valuable therapeutic implications, the studies mentioned in the last two paragraphs alluded to the feasible crucial involvement of the blood-CSF choroid plexus interface in physiological regulatory processes in the brain.

Circannual shifts between short- and long-day photoperiods, and their effects on metabolism and reproductive function continue to be a subject of rampant research in animal science [18-19]. Szczepkowska et al. [20] examined the effects of photic stimuli on the expression of tight junction proteins in the ewe's choroid plexus during alternating photoperiods; these tight junctions are responsible for creating a physical barrier that acts to decrease the blood-CSF interactions. Ovariectomized ewes were exposed to artificial long or short days for a total period of 3 months. It was found that only a short-day season, coinciding in sheep with the peak breeding activity, was associated with a significant reduction in the abundance of tight junction proteins, which then had a direct downstream effect on a lowered level of expression of several vital transmembrane and scaffolding proteins, including claudin-1 and afadin. A similar study conducted by Lagaraine et al. [21] confirmed that short-days significantly impinged on the expression of a wide range of tight junction-associated proteins, including occludin and zona occluding proteins (ZO-1 and ZO-2).

Additionally, Szczepkowska et al. [22] examined the effects of photoperiod on vascular endothelial growth factor (VEGF) receptor levels in the choroid plexus of ovariectomized ewes; the VEGF is a signal protein that stimulates angiogenesis and constitutes a part of the homeostatic system that restores the oxygen supply to tissues when blood circulation is inadequate or low. The VEGF also plays an important role in maintaining the normal microstructure of the choroid plexus. Data showed a significant increase in the populations of VEGF receptors KDR and NRP-1 in the short-day experimental group of ewes, indicating the possible role of VEGF in the photoperiod-dependent choroid plexus remodeling in this species. Those studies provided invaluable insights into the mechanisms and pathways that may control the structural integrity and function of the blood-CSF barrier of the choroid plexus. The fact that photoperiodic cues have been seen to alter choroid plexus permeability may pave the way to intriguing research directives. For example, it may be possible to increase the uptake of specific drugs at the choroid plexus level if its permeability is first enhanced by exposure to hormones mimicking photoperiodic changes or in combination with melatonin and/or its antagonists.

There is a great deal of evidence to suggest that the choroid plexus and its blood-CSF exchange barrier play an important role in the counter-current transfer of a wider

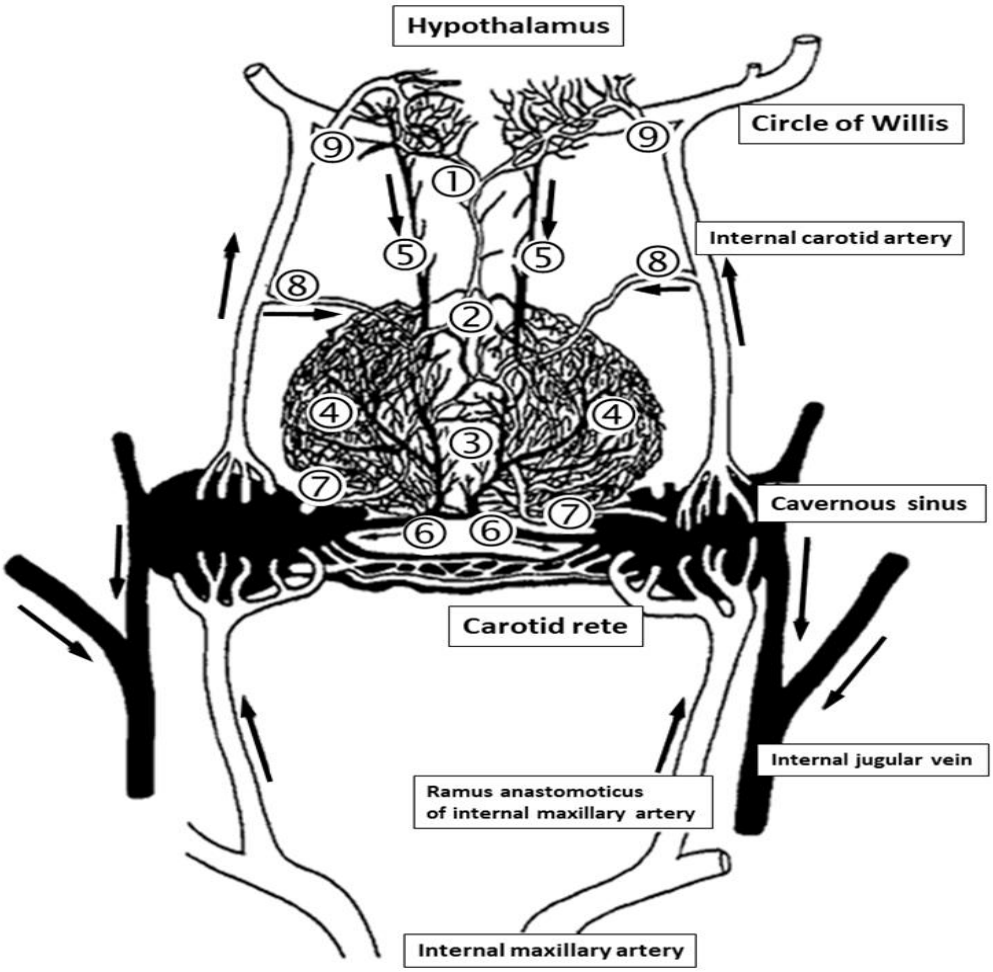
variety of substances than originally expected, ranging from amino-acid neurotransmitters to protein hormones [23]. One such example is leptin, which originates from adipose tissue and participates in the regulation of metabolism, reproductive processes and cognitive/adaptive function [24]. The binding sites for leptin are located in the specific regions of the hypothalamus and hypophysis, but its method of entry into the CNS was formerly unknown. Thanks to the work of Zlokovic et al. [25] it was determined that the transport of leptin to the CNS occurred via the blood-CSF barrier at the choroid plexus level and not the brain-blood barrier as previously assumed. This mode of leptin uptake is due mainly to the presence of high-affinity, fast-acting leptin transport mechanisms that effectively govern the exchange across the blood-CSF barrier and allow leptin to be carried by CSF to the hypothalamic and pituitary sites of action. Any failure in the proper functioning of these transporters is directly associated with the onset of leptin resistance [26]. The delivery of prolactin to the hypothalamus has also been regulated by the choroid plexus due to the site-specific overexpression of prolactin receptors that act to transport prolactin from the bloodstream to CSF [27]. The use of haloperidol (a dopamine antagonist) in a study by Mangurian et al. [28] resulted in a significant increase in prolactin uptake by the choroid plexus and this rise in choroid plexus prolactin concentrations was mirrored by a significant increase in CSF prolactin levels.

More recently, the use of insulin-labeled autoradiography has revealed an extensive presence of insulin receptors in the rat choroid plexus [29]. Although the function of insulin receptors in the choroid plexus has not been fully elucidated yet, it can be deduced that they constitute a part of the receptor-transport system in the transfer of insulin to CSF or that the choroid plexus itself is the target for the CFS insulin [30-33]. Insulin concentrations in the brain are higher than in peripheral circulation due to hormone transfer from blood and de novo synthesis by the CNS neurons. Various physiological states affect the rate of insulin transport. It also varies among different brain regions (higher in the olfactory region, hypothalamus and cerebellum). These differences may determine the spectrum and timing of the central neurophysiological effects of insulin. Future investigations into these phenomena would form a novel and valid research avenue.

## Counter-current transfer of the perihypophyseal cavernous sinus-carotid rete system

Similar to the choroid plexus, the cavernous sinus was recognized as a site of molecular exchange in the cranial physiology in the early 1990's. A series of experiments conducted by and reviewed by Krzymowski et al. [34] was the first to establish the existence of a counter-current transfer system between the cavernous sinus (a vascularized area between the sphenoid and temporal bones in the cranium) and the carotid rete (a network of arterial blood vessels in the brain (Figure 2). Their topographic proximity had led the researchers to hypothesize that an exchange of biologically active substances between the two vascular compartments might be possible [35]. The carotid rete mirabile is actually situated "on route" of the venous blood flow, inside the cavernous sinus, and a large portion of blood effluent from the hypophysis, other parts of brain and the olfactory system passes through the perihypophyseal cavernous sinus to jugular veins [35]. Moreover, the left and right carotid rete are directly connected via the inter-carotid plexus and the left and right cavernous sinus are connected by the inter-cavernous sinus. Because of this unique arrangement, upon anatomical examinations the complex had appeared to form one vascular network and hence the supposition that it might facilitate the counter-current exchange was conceived.

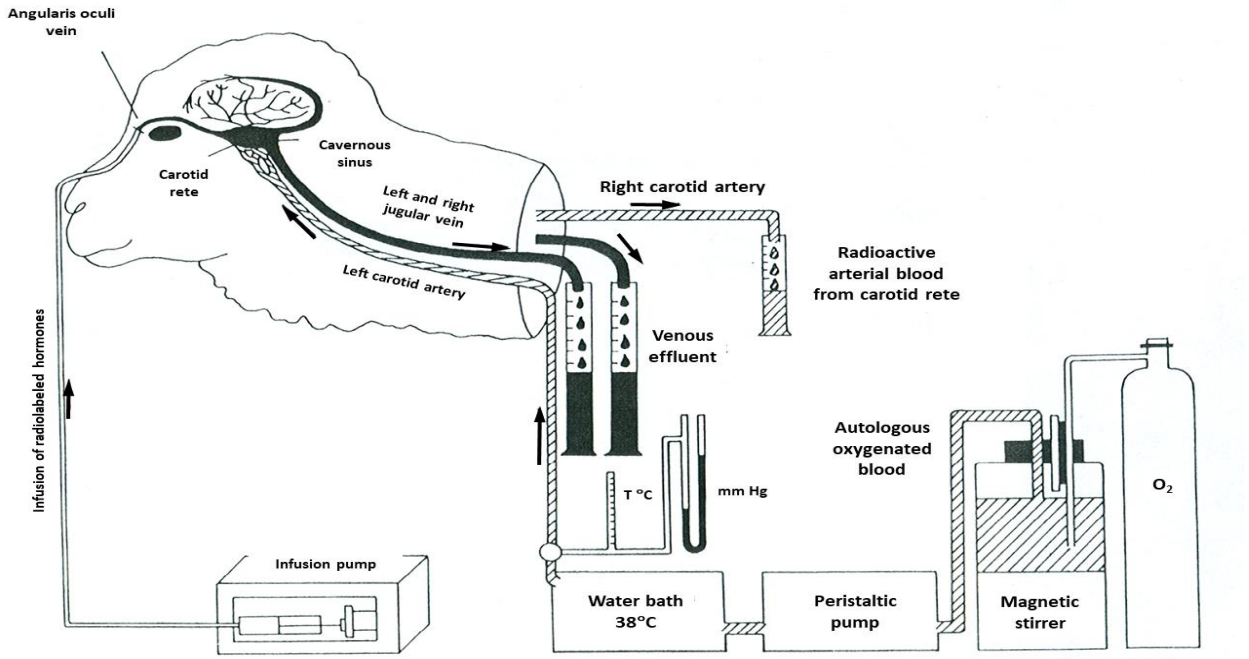
**Figure (2)**: A basic schematic of the cavernous sinus-carotid rete complex and associated vascular networks. Consecutive numbers denote: ① infundibulum, ② infundibular stem, ③ infundibular processes, ④ adenohypophysis, ⑤ long portal veins, ⑥ inferior hypophyseal veins, ⑦ inferior hypophyseal arteries, ⑧ middle hypophyseal arteries, and ⑨ superior hypophyseal arteries. Modified from original conference materials by Krzymowski et al [35]




The results of pilot studies on the cranial counter-current exchange in rabbits by Krzymowski et al. [36] were originally presented during the XV Annual Congress of the Polish Physiological Society in Cracow, Poland (20-23 September 1990). Subsequently, using a population of ewes and gilts, different radiolabeled hormones including progesterone, luteinizing hormone releasing hormone, oxytocin, and β-endorphin were introduced into the cavernous sinuses and their levels measured simultaneously within the carotid rete blood effluent (Figure 3).

In all experiments and specimens examined, there were significantly elevated levels of the aforementioned hormones confirming that a powerful counter-current transfer system for the exchange of steroid hormones and neuropeptides at the base of brain did indeed exist in mammalian species. Those early publications sparked the interest and evidently merited further investigations, and so a study published by Grzegorzewski et al. [37] employed a very similar experimental design in an attempt to identify other hormones that are prone to recycling by this pathway.

**Figure (3)**: A diagram illustrating the experimental approach (i.e., isolated head model) to assessing the occurrence of the counter-current transfer of hormones in the cavernous sinus-carotid rete complex in sheep. Animals were euthanized and exsanguinated, and the heads perfused with autologous blood were used to demonstrate the inter-vascular passage of radiolabeled hormones administered via the ocular vein. Modified from original conference materials by Krzymowski et al. [30, 32]




The authors once again used a radiolabeled hormone, oxytocin, administered into the cavernous sinus via the angular oculi veins for a total duration of 5 min. Furthermore, they analyzed the outcome of the experiment in the gilts allocated to various groups according to the discrete stage of the estrous cycle. It was found that almost all gilts on days 1-3 and days 12-13 of the estrous cycle studied (metestrus and mid-diestrus, respectively) had measureable levels of the transferable radiolabeled oxytocin whereas the gilts on days 4-11 (early diestrus) and from day 14 to the next ovulation (proestrus and estrus) had no recordable levels of oxytocin transferred. Therefore, it would appear that the transport of oxytocin along this pathway strongly depends on the stage of the estrous cycle or endocrine milieu of animals. Several years later, another study was published by Grzegorzewski et al. [38] in which the counter-current exchange of radiolabeled luteinizing hormone-releasing hormone (LHRH) at various stages of the pigs' estrous cycle was examined. The findings of that study were in a very close agreement with those obtained during their previous work, with a significant spike in LHRH transfer occurring in gilts on days 1-2 and 12 to 14 of the estrous cycle. However, the specific underlying mechanisms whereby the stage of the ovarian cycle and associated endocrine changes can impinge on the incidence and/or a rate of the counter-current exchange within the cavernous sinus-carotid rete vascular system remain unknown.

The only attempt so far to address this question appears to be a study undertaken by Skipor et al. [39]. The existence of human chorionic gonadotropin (hCG)/luteinizing hormone (LH) receptors throughout the body, including the brain blood vessels and several non-gonadal tissues, has been vastly documented [40,41]. Consequently, it was inferred that the cavernous sinus-carotid rete complex might also contain these receptors and administered radiolabeled gonadotropin-releasing hormone (GnRH) concurrently with hCG into the cavernous sinus of ewes in order to study the influence of gonadotropin on the counter-current exchange within this complex. Interestingly, in animals pre-treated with estradiol benzoate, the transfer of GnRH from the venous cavernous sinus to the arterial carotid rete was inhibited by hCG, whereas the ewes without the estradiol benzoate priming exhibited the normal level of hormonal exchange. Using mRNA expression analyses and immunohistochemistry of isolated cavernous sinus-carotid rete vasculature, they confirmed the presence of GnRH and LH receptors and thus concluded that both gonadoliberin and LH could modulate the activity of this exchange system. Although these findings provide an additional insight into the estrus-specific activity of the cavernous sinus-carotid rete counter-current transfer, they nonetheless fail to clarify the exact regulatory mechanism(s) of the hormonal exchange between these vascular structures.

### Nasal administration and the brain-specific counter-current transfer

Nasal drug administration for systemic effects has been practiced since ancient times (e.g., tobacco products, vaporized herbal extracts and other medicinal plant preparations). In the 1990's, however, the nasal cavity and its vascular network have also emerged as a subject of interest in the investigation of the cranial counter-current exchange. In 2000, a study by Einer-Jensen and Larsen [42] set out to evaluate the efficacy of a nasal route of drug administration. Nasal administration of tyrosine and propanol in anesthetized rats was followed by a rapid and immense uptake of those substances via a local exchange between the nasal venous and cerebral arterial blood. Encouraged by these preliminary data, Einer-Jensen and Larsen [43] conducted another study in which nasal administration of diazepam resulted in a greater concentration of the drug in the brain arterial blood than in the systemic circulation. Subsequently, however, the interest evoked by these early results proved unsustainable, at least for some drugs, as another study carried out once again by Einer-Jensen et al. [44] that focused on anti-migraine drugs found no preferential efficacy of drug accumulation in the brain upon their nasal administration. In spite of those inconsistencies, a study designed by Skipor et al. [45] and following the exact same line of reasoning as earlier attempts by Einer-Jensen and Larsen examined the effectiveness of nasal administration of steroid hormones. A significant increase (5-fold rise over 20-25 min) in progesterone concentrations in the head compared to the heart/peripheral circulation was observed after the nasal application of a gestagen in pigs. Even though the nasal route of administration and ensuing counter-current transfer of various drugs and hormones to the central nervous system have only been vaguely researched, they show promise for the development of divergent treatments with brain-specific effects, and hence merit further studies.

## Conclusions

Even though cephalic sites for the molecular counter-current transfer described in this mini-review hold irrefutable potential for experimental work and clinical applications, they have received very little investment, innovation or advancement in recent years. Earlier studies concerning this subject matter serve as a proof of concept but no clinical trials or assessment of downstream effects have been attempted. The

available literature indicates a more integral and widespread role that the cranial counter-current exchange may govern in mammalian physiology and reproduction than originally thought. This field of research still holds legitimate therapeutic potential and hence it may deserve to become a subject of reinvigorated attention.

## References


1. Piiper J (1982) Respiratory gas exchange at lungs, gills and tissues: Mechanisms and adjustments. J Exp Biol; 100: 5-22.
2. Jodal M, Lundgren O (1986) Countercurrent Mechanisms in the Mammalian Gastrointestinal Tract. Gastroenterology; 91(1): 225-241.
3. Job Faber J, Thornburg KL, Binder ND (1992) Physiology of Placental Transfer in Mammals. Amer Zool; 32(2): 343-354.
4. Einer-Jensen N, Hunter R (2005) Counter-current transfer in reproductive biology. Reproduction; 129(1): 9-18.
5. Tabęcka-Łonczyńska A, Gilun P, Stefańczyk-Krzymowska S, et al. (2014) Local transfer of testosterone and aromatase activity in the spermatic cord in wild boar/pig hybrids in short-daylight and long-daylight periods. Reprod Biol; 14(4): 282-288.
6. Gottschalk CW, Mylle M (1958) Evidence that the mammalian nephron functions as a countercurrent multiplier system. Science; 128(3324): 594.
7. Maina JN (2002) Structure, function and evolution of the gas exchangers: comparative perspectives. J Anat; 201(4): 281-304.
8. Krzymowski T, Skipor J, Grzegorzewski W (1992) Cavernous sinus and carotid rete of sheep and sows as a possible place for countercurrent exchange of some neuropeptides and steroid hormones. Anim Repro Sci; 29(3): 225-240.
9. Strazielle N, Ghersi-Egea JF (2000) Choroid plexus in the central nervous system: biology and physiopathology. J Neuropathol Exp Neurol; 59(7): 561-574.
10. Keep RF, Jones HC (1990) A morphometric study on the development of the lateral ventricle choroid plexus, choroid plexus capillaries and ventricular ependyma in the rat. Brain Res Dev Brain Res; 56(1): 47-53.
11. Cordon-Cardo C, O'brien JP, Casals D, et al. (1989) Multidrug-resistance gene (P-glycoprotein) is expressed by endothelial cells at blood-brain barrier sites. Proc Natl Acad Sci USA; 86(2): 695-698.
12. Schinkel AH, Smit JJ, Van Tellingen O, et al. (1994) Disruption of the mouse mdr1a P-glycoprotein gene leads to a deficiency in the blood-brain barrier and to increased sensitivity to drugs. Cell; 77(4): 491-502.
13. Zibara K, El Zein N, Sabra M, et al. (2017) Thyroxine (T4) Transfer from Blood to Cerebrospinal Fluid in Sheep Isolated Perfused Choroid Plexus: Role of Multidrug Resistance-Associated Proteins and Organic Anion Transporting Polypeptides. Front Neurol; 8: 214.
14. Dzięgielewska KM, Evans CA, Malinowska DH, et al.(1980) Blood-cerebrospinal fluid transfer of plasma proteins during fetal development in the sheep. J Physiol; 300: 457-465.
15. Chen RL, Kassem N, Redzic ZB, et al. (2009) Age-related changes in choroid plexus and blood-cerebrospinal fluid barrier function in the sheep. Exp Gerontol; 44 (4): 289-296.
16. Ghersi-Egea JF, Finnegan W, Chen JL, et al. (1996) Rapid distribution of intraventricularly administered sucrose into cerebrospinal fluid cisterns via subarachnoid velae in rat. Neuroscience; 75(4): 1271-1288.
17. Thomas SA, Segal MB (1998) The transport of the anti-HIV drug, 2',3'-didehydro-3'-deoxythymidine (D4T), across the blood-brain and blood-cerebrospinal fluid barriers. Br J Pharmacol; 125(1): 49-54.
18. Gluckman PD, Breier BH, Davis SR (1987) Physiology of the somatotropic axis with particular reference to the ruminant. J Dairy Sci; 70(2): 442-466.
19. Kirsz K, Zieba DA (2012) A review on the

effect of the photoperiod and melatonin on interactions between ghrelin and serotonin. Gen Comp Endocrinol; 179(2): 248-253.
20. Szczepkowska A, Lagaraine C, Robert V, et al. (2013) Effect of a two-week treatment with a low dose of 2,2'4,4',5,5'-hexachlorobiphenyl (PCB153) on tight junction protein expression in ovine choroid plexus during long and short photoperiods. Neurotoxicol Teratol; 37: 63-67.
21. Lagaraine C, Skipor J, Szczepkowska A, et al. (2011) Tight junction proteins vary in the choroid plexus of ewes according to photoperiod. Brain Res; 1(1393): 44-51.
22. Szczepkowska A, Wąsowska B, Gilun PD, et al. (2012) Pattern of expression of vascular endothelial growth factor and its receptors in the ovine choroid plexus during long and short photoperiods. Cell Tissue Res; 350(1): 157-166.
23. Skipor J, Thiery JC (2008) The choroid plexus-cerebrospinal fluid system: undervaluated pathway of neuroendocrine signaling into the brain. Acta Neurobiol Exp (Wars); 68(3):414-428.
24. Zięba DA, Amstalden M, Morton S, et al. (2003) Effects of leptin on basal and GHRH-stimulated GH secretion from the bovine adenohypophysis are dependent upon nutritional status. J Endocrinol; 178(1): 83-89.
25. Zlokovic BV, Jovanovic S, Miao W, et al. (2000) Differential regulation of leptin transport by the choroid plexus and blood-brain barrier and high affinity transport systems for entry into hypothalamus and across the blood-cerebrospinal fluid barrier. Endocrinology; 141(4): 1434-1441.
26. Caro JF, Kolaczynski JW, Nyce MR, et al. (1996) Decreased cerebrospinal-fluid/serum leptin ratio in obesity: a possible mechanism for leptin resistance. Lancet; 348(9021): 159-161.
27. Hirai J, Nishita M, Nakao N, et al. (2013) Regulation of prolactin receptor gene expression in the rat choroid plexus via transcriptional activation of multiple first exons during postnatal development and lactation. Exp Anim; 62(1): 49-56.
28. Mangurian LP, Walsh RJ, Posner BI (1992) Prolactin enhancement of its own uptake at the choroid plexus. Endocrinology; 131(2): 698-702.
29. Baskin DG, Brewitt B, Davidson DA, et al. (1986) Quantitative autoradiographic evidence for insulin receptors in the choroid plexus of the rat brain. Diabetes;35(2): 246-249.
30. Plum L, Schubert M, Brüning JC (2005) The role of insulin receptor signaling in the brain. Trends Endocrinol Metab; 16(2): 59-65.
31. Bondareva VM, Chistyakova OV (2007) Insulin and insulin-receptor signaling in the brain. Neurochem J; 1(3): 176-187.
32. Chiu SL, Cline HT. (2010) Insulin receptor signaling in the development of neuronal structure and function. Neural Dev; 5(7).
33. Yanagita T, Nemoto T, Satoh S, et al. (2013) Neuronal Insulin Receptor Signaling: A Potential Target for the Treatment of Cognitive and Mood Disorders, Mood Disorders, Prof. Nese Kocabasoglu (Ed.), ISBN: 978-953-51-0959-4, InTech, DOI: 10.5772/54389
34. Krzymowski T. (1992) New pathways in animal reproductive physiology: Frontiers and perspectives. J Physiol Pharmacol; 43(1): 5-19.
35. Skipor J, Grzegorzewski W, Wąsowska B, et al. (1997) Counter-current transfer of beta-endorphin in the perihypophyseal cavernous sinus-carotid rete vascular complex of sheep. Exp Clin Endocrinol Diabetes; 105(5): 308-313.
36. Krzymowski T, Bartlewski P, Skipor J, et al. (1990) Counter current transfer of hormones from venous into arterials blood vessels at the base of brain in rabbit. Acta Physiol Pol Suppl; 34: 172-173.
37. Grzegorzewski W, Skipor J, Wąsowska B, et al. (1995) Counter current transfer of oxytocin from the venous blood of the perihypophyseal cavernous sinus to the arterial blood of carotid rete supplying

the hypophysis and brain depends on the phase of the estrous cycle in pigs. Biol Reprod; 52(1): 139-144.

38. Grzegorzewski WJ, Skipor J, Wąsowska B, et al. (1997) Countercurrent transfer of 125I-LHRH in the perihypophyseal cavernous sinus-carotid rete vascular complex, demonstrated on isolated pig heads perfused with autologous blood. Domest Anim Endocrinol; 14(3): 149-160.
39. Skipor J, Bao S, Grzegorzewski W, et al. (1999) The inhibitory effect of hCG on counter current transfer of GnRH and the presence of LH/hCG receptors in the perihypophyseal cavernous sinus-carotid rete vascular complex of ewes. Theriogenology; 51(5): 899-910.
40. Reshef E, Lei ZM, Rao CV, et al. (1990) The presence of gonadotropin receptors in nonpregnant human uterus, human placenta, fetal membranes, and decidua. J Clin Endocrinol Metab; 70(2): 421-430.
41. Lei ZM, Rao CV, Kornyei JL, et al. (1993) Novel expression of human chorionic gonadotropin/luteinizing hormone receptor gene in brain. Endocrinology;132(5): 2262-2270.
42. Einer-Jensen N, Larsen L (2000) Transfer of tritiated water, tyrosine, and propanol from the nasal cavity to cranial arterial blood in rats. Exp Brain Res; 130(2): 216-220.
43. Einer-Jensen N, Larsen L (2000) Local transfer of diazepam, but not of cocaine, from the nasal cavities to the brain arterial blood in rats. Pharmacol Toxicol; 87(6): 276-278.
44. Einer-Jensen N, Larsen L, Deprez S, et al. (2001) Intranasal absorption of sumatriptan and naratriptan: no evidence of local transfer from the nasal cavities to the brain arterial blood in male rats. Biopharm Drug Dispos; 22(5): 213-219.
45. Skipor J, Grzegorzewski W, Einer-Jensen N, et al. (2003) Local vascular pathway for progesterone transfer to the brain after nasal administration in gilts. Reprod Biol; 3(2): 143-159.