Counter-current transfer in reproductive biology

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Abstract

Heat and substances, including gases, steroids and peptide hormones, can pass from venous blood, interstitial fluid and lymph to the arterial blood; the process is called local counter-current transfer. It has been found in various reproductive organs in many animal species and in man: from the testis to the testis and epididymis; from the ovary to the ovary, tube and tubal corner of the uterus; from the tube and uterus to the ovary; from vagina to uterus; and even between brain blood vessels. Local transfer within the ovary has also been found. Local cooling that creates temperature gradients between organs or within an organ is one aspect of the transfer. Physiologically, the transfer also facilitates local feedback regulation of organ function in a process situated between general distribution of hormones through the systemic circulation and paracrine regulation. Counter-current transfer of drugs after local application opens up new possibilities for treatment.

Introduction

Counter-current transfer may be defined as a passive transfer of energy (heat) or substances from one solvent to a second solvent. The solvents may be flowing through closely connected tubes with walls impermeable to the solvent, but open for passage of either heat or the substance itself.

Counter-current transfer can be viewed as a means of local regulation of organ function. Temperature regulation is one example. Cooling of the arterial supply will result in a decrease in the temperature of the organ. An organ can be kept at a lower than body temperature (testis) or be able to maintain 37°C despite a high metabolic activity (brain). A second example concerns endocrine function such as transfer of testosterone from the testicular vein (where the concentration is 10 times greater than in the general circulation) to the testicular artery. The concentration of testosterone in the local arterial supply to all testicular and some epididymal tissues is therefore greater than that to the remainder of the body.

Hormonal regulation of body function is often categorised into two groups: the ‘real’ hormones that are distributed equally to all organs through the systemic circulation (classical endocrinology), and the paracrine effects between neighbouring cells that are based on local diffusion. Paracrine regulation works only over minute distances; substances will diffuse only fractions of a millimetre before they reach and transfer to capillary blood. We wish here to bring a third possibility into play: local counter-current transfer by means of a local increased arterial concentration will facilitate hormonal regulation within an organ through the locally increased concentrations of the regulatory substance(s). 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; an example is the interplay between ovary, Fallopian tube and uterus (see below). If it concerns small-organ blood vessels, the regulation will concern only those parts; an example of this is the ability of large ovarian follicles to maintain a temperature lower than that of the ovarian stroma (see below).

To set the stage: a 332-year-old drawing of the genital system in a woman clearly showed the ovarian artery in close connection with the utero-ovarian vein (De Graaf 1672; Jocelyn & Setchell 1972). The overall functional importance of this was neglected until the 1970s, when separation of the two sets of vessels (without interruption of the blood flow) resulted in a prolonged lifespan of the corpus luteum in sheep and cows (Ginther 1974, 1976).

Local counter-current transfer of heat and substances has been found in many animal species and demonstrated between many organs. The present article will review local transfer between the vessels of the reproductive organs of both males and females (Einer-Jensen 1988; Einer-Jensen et al. 1989). Although the brain is not viewed classically as a reproductive organ, transfer between the brain vessels will also be discussed.
Local transfer

A model system for counter-current transfer may be described in the following way. Two copper tubes are soldered together. Cold water is pumped through one, and hot water through the other – the inlets are at the opposite ends of the construction (counter-current). When the temperature is measured in the outlets from the tubes, the tube with a ‘cold water inlet’ produces warm water, and the tube with a ‘hot water inlet’ produces cool water (Schmidt-Nielsen 1972, 1981) (Fig. 1). In the present review, the model is described mainly as transfer from a vein to an artery. However, transfer from lymph to arterial blood, or from interstitial fluid to arterial blood, is also part of the full picture. The transfer system is primarily passive and does not need a specific transport system, but facilitated transport may be observed. A specific, local, active transport system has, to our knowledge, not been demonstrated to date. A simple approximate rule for counter-current transfer in reproduction is that transfer of heat is close to 100% effective, whereas only 10% of a gas is transferred, and only 1% of a larger substance.

However, the efficacy of retrograde transfer of hormones may be up to 12% under in vivo conditions and up to 30% under in vitro conditions (Krzymowski & Stefanczyk-Krzymska 2002, Stefanczyk-Krzymska et al. 2002). The physical distance separating the blood in the vein and corresponding artery is extremely large from a functional point of view. The thesis of such ‘long distance’ diffusion contradicts the statement ‘substances will diffuse only fractions of a millimetre before they reach and transfer to capillary blood’; either the postulate is not correct or additional mechanisms must exist in the blood vessels. The walls of blood vessels contain abundant vasa vasorum and capillaries. Their involvement in the transfer process has not been clarified to a satisfactory extent. Endothelial microvilli may also contribute by increasing the functional surface area (Zezula-Szpyra & Grzegorzewski 2000). There are indications that special functional arrangements do exist in the mesovarium and mesosalpinx (Stefanczyk-Krzymska & Krzymowski 2002); even morphological adaptations have been seen. In women, the uterine arterial wall is thinner in selected areas close to the vein (Bendz 1977), whereas in pigs the appearance of tuberculi several millimetres in diameter towards the lumen has been reported in the wall of the ovarian artery (Doboszynska 1986). The interstitial fluid and lymph also seem to be implicated. Both precollector and collector uterine lymphatics in pigs were covered and surrounded by a network of microvessels (Gawronska et al. 1997). The morphology of the vessels varied with the oestrous cycle (Zezula-Szpyra et al. 1997).

Many hormones are bound to plasma proteins during transport in the blood, and the bound fraction may reach 95–99% of the total concentration. It may take seconds, under in vivo conditions, to reach a steady state for the protein binding after a sudden addition of free hormone to blood (Einer-Jensen 1984, 1989). As approximately 90% of the testosterone in the testicular veins enters during the last passage through the testicular capillaries, a substantial fraction may still be unbound and available for transfer when it reaches the pampiniform plexus. The substance transferred from the vein blood must reach the arterial blood in its free form. Part of it will remain unbound when the arterial blood reaches the capillaries. The increase in the total hormone concentration may be only 10–50%, although this may mean a several-fold increase in the free fraction. This issue is not resolved.

Transfer of substances is influenced by molecular size, and by the solubility of the molecules in lipids (membrane penetration): large molecules are transferred less effectively than small molecules. There is probably not a sharp cut-off, rather a continuum. Transfer of substances of up to 3000 Da has been found (Schramm et al. 1986), whereas bovine albumin and red blood cells are not transferred. A lipophilic substance passes more quickly through cell walls and is therefore transferred more effectively than an almost identical hydrophilic substance (McCracken et al. 1984). Steroid hormones are about 250–300 Da and lipophilic; an effective transfer may thus be expected. Transfer of steroids connected with reproduction has been documented in both males and females; however, research concerning local transfer in the adrenal gland has been largely neglected. Nevertheless, local transfer of glucocorticoids within the adrenal has been suggested to be important for medullary production of adrenaline (Einer-Jensen & Carter 1995).

Transfer from testis to testis and to epididymis

Testis temperature has been found to be 1–2°C or more lower than body temperature (Harrison & Weiner 1949). A reduced temperature of the testicular arterial blood cools the testis; the venous blood is therefore also cooler than the body temperature. The venous blood cools the arterial, as a result of a special vascular arrangement (the highly coiled pampiniform plexus) in which the artery winds in and out through venous sinuses within the inguinal canal (Waites 1991; Setchell 1998) (Fig. 2). When the

Figure 1 Model of counter-current transfer of heat or a substance between two tubes.
venous blood leaves the plexus, the arterial blood has heated it and thus the central blood temperature remains unchanged. The low testicular temperature is initiated and maintained by a small heat loss through the relatively thin scrotal wall. The heat transfer system is very effective: under in vitro condition in which boar testes were perfused, its efficacy was close to 100% (Glad Sorensen et al. 1991). The loss of energy is thus small.

As demonstrated by the condition of cryptorchidism, which leads to destruction of the germinal epithelium, a reduced testis temperature is important for spermatogenesis. Sperm quality decreases if the testis temperature is too high (Mieusset et al. 1987, Dada et al. 2003). In boars, an increased testicular temperature was induced by microvascular interruption of the transfer: the origin of the testicular arterial blood was transferred to the femoral artery thus the pampiniform plexus bypassed. The testis temperature increased and spermatogenesis decreased, whereas production of testosterone was maintained (Myren & Einer-Jensen 1992). Varicocele (dilatation of the testicular veins) seems to disrupt the heat exchange mechanism and may induce infertility. Ligation of the dilated veins improves sperm quality (Matthews et al. 1998, Pasqualotto et al. 2003). Long-term cooling of the testes is reported to increase sperm quality in selected, infertile men. However, in addition to the time needed to induce the changes, one must wait 2 months for maturation of spermatozoa.

Research on the transfer of substances has concentrated on transfer of testosterone. Both intravenously injected radioactively labelled and endogenous testosterone are transferred in rat (Free & Jaffe 1975), pigs, sheep (Jacks & Setchell 1973), baboons (Einer-Jensen & Waites 1977) and man (Bayard et al. 1975). The transfer is fast, an increase in the arterial concentration being found within minutes after the start of an injection into the testicular vein. The difference between the total concentrations in the testicular artery and a peripheral artery represents a 10–100% increase, the range being influenced by the species, and the speed, solvent etc., used for the injection. However, the local difference in the free fraction may create a non-protein-bound testosterone concentration several times that of peripheral tissues (see above); the physiological impact could therefore be significant.

Peripheral administration of physiological doses of testosterone will, a priori, not influence the testicular concentration significantly, but induces a decrease in the endogenous production through a negative feedback effect on the pituitary secretion of follicle-stimulating hormone and luteinising hormone. Long-term administration of testosterone or anabolic steroids may therefore result in small and soft testes, although the peripheral need for androgenic hormones is covered. This will be a side effect of the male contraceptive ‘pill’, which is a mixture of androgenic and gestagenic substances. The transfer of testosterone is mainly based on blood-to-blood transfer; however, transfer from the testicular lymph to the arterial blood in boars was found to contribute significantly to the transfer (20–80% for the steroids tested), because of a high concentration in the slowly flowing lymph (Setchell et al. 1983).

It is a matter of debate whether the local transfer of heat or of hormones is the more important issue in the male system. Mammalian species (elephants) with abdominal testes have a rete and do breed successfully – and humans can reproduce above the replacement level under tropical conditions. Testis temperature in elephants is not known, whereas that of sea mammals may be lower than abdominal temperature as a result of cooling via the dorsal fin and associated vasculature (Rommel et al. 1992). Temperature in the abdominal testis has, to our knowledge, not been investigated. It is assumed that it is similar to the deep-body temperature. However, as the discussion below concerning ovarian follicular temperature indicates, this may be incorrect. It is our belief that local transfer of stimulating and regulatory hormones is as important as transfer of heat in order to obtain sensitive responses at a cellular level, especially when production of competent gametes is an objective.

The caput and part of the corpus epididymidis are supplied from the testicular artery, whereas the cauda and distal part of the corpus are supplied from the artery that follows the vas deferens. The exact border of the arterial supply may vary between species and still needs to be defined. The caput and (part of) the corpus temperature is therefore also less than the body temperature, which may decrease damage to spermatozoa during storage. This has been postulated to be important in species in which the males collect harems and the females have a short, synchronised oestrus in order to cover the short-time, high-demand for male gametes. Local transfer of testosterone will increase the hormonal supply through the artery to the caput (Einer-Jensen 1974). Androgen-binding protein in the rete testis fluid may therefore not be essential for local transfer to the caput. Although the discussion has
focused on testosterone, transfer of other steroids has also been documented. Transfer of other substances (e.g. peptides) has not yet been investigated satisfactorily.

In women, local transfer of heat has been found between vagina and urethra (see below). Transfer to the male urethra or prostate, or both, has apparently not been investigated. The possibility may be supported by investigations in conscious men. Documentation of transfer would indicate that rectal application of drugs (antibiotics, steroids or cytostatics) could induce a local high concentration in both the male urethra and the prostate gland. There is a dire need to improve treatment of prostate disease, which is a major problem and killer in mature and elderly men.

Transfer from ovary to ovary, Fallopian tube and to the tubal corner of uterus

Ginther’s group developed our understanding of the vascular anatomy, indicating the possible importance of the close connection between vessels in the female genital system (Ginther 1974, 1976). A similar anatomical pattern was found in women (Bendz 1977). Several groups also showed that surgical relocation of the vascular supply disrupted the oestrous cycle. As the ovarian artery supplies the tube and the tubal corner of the uterus, any substance transferred from the utero-ovarian vein or lymph to the ovarian blood will reach all these tissues (Fig. 3). Transfer of prostaglandin (PG) F2α was found between the utero-ovarian vein and the ovarian artery in sheep; the hormone had a luteolytic effect. Later, transfer was found of radioactively labelled inert gases (xenon-133, krypton-85), steroid hormones and peptides in several animal species (mice, pig, sheep, cow) and man (Einer-Jensen 1988, Einer-Jensen & Hunter 2000). As in the male, transfer occurs within seconds or minutes after the administration of almost all substances. PGF2α seems to form a special case, as the transfer was delayed for 20 min; this remains unexplained (McCacken et al. 1972). A difference between the endogenous concentrations of steroids in the ovarian arterial blood and systemic blood was also found (Hunter et al. 1983). Thus there seems to be little doubt that local counter-current transfer of regulatory substances underlies the normal function of the female reproductive system (Krzymowski 1992, Krymowski & Stefanczyk-Krymowska 2002). However, on the basis of our present knowledge, huge species differences exist. A ‘non-pregnant’ signal from the endometrium seems essential in domestic animals, whereas a ‘pregnant’ signal originating from interaction between the fertilised egg and tubal or endometrial tissues is essential in man. A more uniform model may appear when the question of an early pregnancy signal is clarified (see below).

Transfer facilitates exchange of information between different ovarian structures. Progesterone secreted by a corpus luteum may act to inhibit the growth of follicles in the same ovary more than that of follicles on the contralateral side (Fukuda et al. 1997). This might explain the tendency for ovulation to alternate between the two ovaries. This could be important, because contralateral selection of the dominant follicle in the succeeding cycle may favour early embryonic development (Fukuda et al. 1996). Local transfer must reach a certain level to have an impact. Conversely, if it were to become too effective, it might create two ovaries working independently of each other. Unfortunately, relevant information is limited. The most interesting aspect of local transfer seems to be communication between the ovary and the Fallopian tube and uterus (see below).

As with the testicular transfer, more than just simply veins and arteries are involved. Infusion of PGF2α into a local lymph vessel permitted transfer to the ovarian arterial blood (Heap et al. 1985). Even injection of a small depot of labelled hormones into the parametrial connecting tissue created an increased concentration in the ovarian arterial blood. Krzymowski and his co-workers described a portal system with two sets of serially connected capillaries in the parametrum (Stefanczyk-Krzywowska et al. 2002): the first set is connected with the large utero-ovarian veins, the other with the ovarian artery. This creates a very effective vein-to-artery transfer system. Similar arrangements have not yet been described in the blood vessels for any of the other systems reviewed in the present article. It would, however, be valuable to find a common principle facilitating the local transfer between the rather large vessels.

The ovarian artery forms an arcade with the uterine artery. The direction of the blood flow may, in theory, run in both directions through the shunt, as no valves will interfere. There is a general acceptance that the ovary and probably the Fallopian tube receive blood from

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**Figure 3** Model of counter-current transfer of heat or a substance from the blood in the utero-ovarian vein to the blood in the ovarian artery in a sheep. Transfer is also found between the vessels in the ovarian hilus. The ovarian artery supplies the Fallopian tube and the tubal part of the uterus.
the ovarian artery, whereas the uterus receives blood from the uterine artery (Fig. 4). The ‘border’ is probably close to the tuba—uterine corner; this will be elaborated on below. Special conditions (late pregnancy, thromboses) may act to change the direction of flow.

It may be deduced that substances produced in the ovary, released to the ovarian venous flow and transferred to the ovarian arterial blood will reach not only the ovary but also the Fallopian tube and possibly the tubal portion of the uterus. Preferential transfer of endogenous ovarian steroid hormones to the uterus has been demonstrated in women during both the follicular and luteal phases (Cicinelli et al. 2004b). Even ipsilateral transfer to uterine arterial blood close to the cervix has been found, in pigs (Stefanczyk-Krzymska et al. 1998). As the substances transferred include steroid and peptide hormones, it can be regarded as a one-sided (unilateral) regulation. Because many species, including man, are monovulatory, the inference here is that the functions of the ipsilateral organs are more ‘suitable and attractive’ for spermatozoa and later for the fertilised egg. Indeed, the spermatozoa may distribute preferentially to the tube on the ovulatory side, and the embryo tends to nidate on the ipsilateral uterine wall (Kunz et al. 1998).

Within-ovary transfer

Transfer of heat in the utero-ovarian vein—ovarian artery complex has created some interest. Grinsted et al. (1980) found temperature gradients within different tissues of the rabbit ovary: large follicles were cooler than the ovarian stroma; the topic has been reviewed recently (Hunter 2003, Hunter & Einer-Jensen 2004). The temperature difference was confirmed in pigs, with measurements made during both laparotomy and laparoscopy (Hunter et al. 2000). Reduced temperature in mature Graafians follicles seems to demand two simultaneous processes: a heat-consuming process during water uptake in the expanding volume of follicular fluid (Luck et al. 2001), and a local heat transfer system between the follicular vessels (Fig. 4). Such local heat transfer has not yet been documented, but the vascular structures involved have been described (Macchiarelli et al. 1997, Hunter 2003).

No comprehensive physiological explanation has, to date, been offered for the reduced follicular temperature. We wish to point out a parallel situation found in the male gonad. Perhaps the decreased temperature is protecting against mutations in the germ cell line, so a decreased follicular temperature may be critical for the oocyte. However, an influence on enzymatic activity in the steroid biosynthetic pathway should not be overlooked. A third potential involvement could be in pathways to apoptosis, the decreased temperature affording protection against degenerative programmes in the various cell layers of maturing Graafian follicles (Hunter 2003).

![Figure 4: Model of counter-current transfer of heat or a substance between the blood vessels to and from a large follicle. Heat transfer maintains the low follicular temperature induced by endothermic heat-consuming processes in the follicular fluid. Transfer is also found between the vessels in the ovarian hilus.](image)

**Figure 4** Model of counter-current transfer of heat or a substance between the vessels in the ovarian hilus.

**Early pregnancy**

The main arterial flow to the uterus originates from the uterine artery, whereas the venous blood leaves only partly through the uterine vein (Fig. 3). Depending on the species, a small or large fraction leaves through the utero-ovarian vein. This creates a bypass for uterine substances with an impact on the ovary. The human corpus luteum seems to have a predefined cyclic lifespan of less than 2 weeks and the continuation of pregnancy is secured by a ‘pregnancy’ signal, seen as increasing concentrations of human chorionic gonadotrophin. In contrast, the oestrous cycle depends on a ‘non-pregnant’ signal in many domestic animals such as cow and sheep. If the uterus does not release a non-pregnant signal (a ‘luteolysin’), the corpus luteum will continue to secrete progesterone for months; the next oestrus and ovulation will therefore be delayed. The non-gravid signal was found to be PGF$_{2\alpha}$. Its correct action depends on local transfer between the utero-ovarian vein and the ovarian artery (McCracken et al. 1972). Production of progesterone from the corpus luteum will continue if the prostaglandin is ‘back-transferred’ to the uterus instead of reaching the ovary (Krzymowski et al. 1989).

An Australian group described an early pregnancy factor many years ago. It was present after ‘few hours’ in both women and several animal species. For a long time, it was difficult to reproduce the results outside the Australian continent, but early pregnancy factor is now a well-defined substance (Morton 1998, Schafer-Somi 2003). Modern molecular techniques open new pathways for the detection of an early pregnancy factor produced by the zygote in synergism with signal(s) amplified by cumulus and tubal cells (Hunter & Einer-Jensen 2003). During the next 10 years, early pregnancy signals will be characterised and assays developed for early diagnosis of pregnancy in several species. Factors may be species specific. The assay will be useful for early diagnosis of...
pregnancy after natural or in vitro fertilisation in man, and it will also have economic value in domestic farm animals.

**Vagina to uterus and urethra**

The vagina and rectum have been used for centuries for the administration of drugs. The French, in particular, continue to favour such routes. The main reason is either the fast and effective absorption or – if the substances are not absorbed – a local influence. Recent data obtained in gilts indicate that vaginal application of progesterone results in a rapid and semi-selective effect on the uterus (Einer-Jensen et al. 1993). The local transfer may be dependent on the stage of the cycle (Zhao & Einer-Jensen 1998).

The basis for this rather unexpected influence seems to be a local counter-current transfer from the vaginal vein blood to the uterine arterial blood, a ‘first pass effect’ (Fig. 5), (Cicinelli & de Ziegler 1999). The venous mesh created by the vaginal and rectal vein blood is in close contact with the uterine artery. The transfer must initially be based on the blood flow, because of the speed at which the transfer takes place (cooling within minutes); however, lymph vessels may well be involved.

In women, application of microionised progesterone in the vagina resulted in a doubling of concentration in the uterine arterial blood compared with peripheral arterial blood (Cicinelli et al. 1998). The progesterone concentration in endometrial cells was 10–20 times greater after vaginal administration compared with parenteral administration in doses resulting in identical peripheral plasma values (Cicinelli et al. 2000). The targeted impact may be to some extent explained as being based on local transfer from the vaginal lymph or vein blood to the uterine artery. However, as this concentration is only twice that of peripheral arterial blood, there must be an additional factor. The authors suggest this could be based on a delay of ‘some seconds’ in the binding of steroid to the plasma proteins in the uterine arterial blood (Einer-Jensen 1984, 1989). This creates a high concentration of unbound progesterone, which again explains the high uptake.

Our own experience is that, whenever and wherever hormones are transferred in the reproductive system, this will also be true of heat, and vice versa. Cooling of one organ, as a result of local transfer, results in cooling of the other organs supplied from the arteries involved in the transfer system. Cold saline can be used as a safe indicator ‘substance’. Cooling of the vagina in postmenstrual and fertile women resulted in a rapid cooling of the uterus and urethra, in addition to the distal 9 cm of the rectum. The tubal corner of the uterus was not cooled, indicating that the arterial supply originated from a different source, probably the ovarian artery. Using temperature probes with several points of measurement, it was found that the boundary was 1–2 cm from the tube (Einer-Jensen et al. 2001a). In younger women, the boundary moved during the menstrual cycle, probably because of the changes in oestrogen and progesterone production (Cicinelli et al. 2004a). The results support the theory of a unilateral influence on the tube from the ipsilateral ovary and even indicate that this influence involves part of the uterus. The local transfer to the urethra indicates that small doses of vaginal oestrogens, which will not induce general effects, may stimulate the urethra locally and reverse degenerative changes (Cicinelli et al. 2001). The site of vaginal administration may be crucial: administration close to the cervix seems to favour transfer to the uterus, whereas a ‘low’ vaginal position may favour transfer to the urethra (Cicinelli et al. 2003).

**Transfer in the head**

Hunting and hunted animals produce vast amounts of heat. Many of these animals, in addition to species living in a hot environment, may experience an increase in body temperature. The brain is the first organ to be damaged by high temperature. By way of protection, evolution has supported the development of a brain cooling system (Baker 1979). The respiratory air flow through the nasal cavities cools the nasal surface, partly through evaporation. The nasal venous blood is therefore cooler than deep-body temperature; it will cool the carotid blood through local transfer of heat (‘cold’) in the carotid artery–cavernous sinus complex (Fig. 6), and the cooled carotid blood will maintain the brain at a somewhat lower temperature than the rest of the body. The nasal ventilation is switched off — or, rather, bypassed — in individuals whose trachea has been intubated; nasal flushing with air then is able to decrease the temperature by 1–2 °C in a flow-dependent manner (Einer-Jensen & Khorooshi 2000, Einer-Jensen et al. 2001b). Such a mechanism may be present in man (Einer-Jensen et al. 2002). The cooling

![Figure 5](image_url) Model of counter-current transfer of heat or a substance between vaginal vein blood and uterine arterial blood in a woman. A similar transfer may take place from rectal vein blood (last 9 cm of rectum) to uterine arterial blood.
system seems to be autoregulated through a sphincter at the nasal outlet. Local contraction of the muscular venous wall will change the direction of flow from a ‘deep’ route via the frontal vein through the cavernous sinus to a superficial route via the facial vein, thus bypassing the heat transfer system.

As already stated, transfer of heat and substances seems to take place simultaneously; thus transfer of substances in the carotid artery–cavernous sinus complex may also be expected. Transfer of steroid and peptide hormones, and of pheromones, has been found in several animal species (e.g. rat, rabbit, sheep, pig) under both in vivo and in vitro conditions. Using an isolated perfused head model, transfer to the carotid blood was demonstrated after infusion of the pig pheromone androstenol (Stefanczyk-Krzyzmowska et al. 2000), oxytocin (Grzegorzewski et al. 1995), and luteinising hormone-releasing hormone (Grzegorzewski et al. 1997) into the infraorbital vein. The advantage of the isolated, perfused head is the lack of recirculation through the general vascular system. In anaesthetised rats, 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. Radiolabelled substances were applied in the nasal cavities. A head:heart ratio greater than 1.00 indicated that tritiated water, tyrosine and propanol were transferred locally in the circulatory system to the head and brain tissue is (relatively) increased after infusion into the infraorbital vein, one must expect that substances released from the brain cells to the blood will also be transferred locally to the brain arterial blood. Such an increased concentration will have an impact on the brain cells, and represent a semi-specific stimulation or inhibition of function. This is not a traditional feedback system, nor a paracrine signalling, but represents a third possibility, of humoral communication. Because this field of research is new, its importance is unknown – which is not to say that it is unimportant.

**Physiological and pharmacological significance**

Physiological and pharmacological evaluations have been included in individual sections above; a general overview is attempted here. Local counter-current transfer of endogenous messenger substances has been reviewed in many reproductive organs (including the brain), and documented in other non-reproductive organ systems. Nature does not play games; there must be a reason, a physiological function, associated with local transfer.

Transfer of heat is one very special function. Protection from life-threatening cooling or overheating is obviously important; the physiological reason for local cooling of the testis and large follicles remains open for discussion. Cooling of the brain by the respiratory air flow may save life under conditions of extreme exposure. Brain damage as a result of lack of cooling may occur in man; fever or brain trauma may induce brain hyperthermia. Intensive care patients routinely undergo tracheal intubation; surprisingly, the potential life-saving or damage-diminishing effect of simple nasal air flushing in selected patients suffering from hyperthermia has not been investigated, for example by using catheters that would measure pressure and temperature simultaneously (Einer-Jensen et al. 2002). The number of patients damaged unnecessarily is therefore unknown.

In our opinion, we have been discussing a ‘semi-local’ system of hormonal regulation. The mechanism is positioned between the distribution of regulatory substances through the general circulation and paracrine regulation between neighbouring cells. The system may be regarded as ‘organ feedback regulation’: substances secreted by one cell type will return to other cell types in the organ. As shown with oestradiol, hormones may regulate the efficacy of the system itself. One brain centre will communicate, through the vascular system, with other centres. The impact will not be as specific as distribution through neural pathways; it is, rather, a matter of generation of tension gradients.

Sometimes more than one organ is involved. The testis will communicate locally with the ipsilateral caput and corpus epididymidis. Similarly, the ovary will both send and receive messages from the ipsilateral tube. Even part of the uterus may be involved in the system. The local communication is probably important for regulation of sperm and egg transport and macromolecular aspects of tubal secretions, including passage of early luteotrophic signals.
Regulation through local transfer is semi-specific, as only part of the substances secreted will be transferred. There will always remain a basal concentration in the general circulation. Evaluation of the importance of the local transfer systems is therefore more difficult than models with a ‘yes–no’ regulation. Such evaluation should keep some of the future generation of scientists usefully occupied for some time.

Pharmacologists should also show an interest in the possibilities of using local application to achieve semi-specific targeting of drugs. Vaginal application of steroids will induce greater concentrations in arterial blood to the uterus or urethra than in other arteries. Vaginal application also opens a possible therapeutic approach through which local treatment of genital cancer could be possible. The organs would receive a ‘greater than the peripheral’ concentration of the cytostatic substance, and the regional lymph glands would be targeted through the lymph. Low-molecular lipophilic substances should be selected for an initial trial.

Nasal application of drugs has, like vaginal application, been used for general treatment because of the high resorptive capacity. However, nasal application may have a special place in the treatment of brain diseases, by increasing the concentration of the drug in the carotid blood to a value greater than that in peripheral blood. This could be true for hormones, psychopharmacological or vasoactive drugs (treatment of migraine). Nasal sprays containing gonadotrophin-releasing hormone may primarily be using the brain counter-current system to reach the central structures. The local effect of this hormone appears not to have been discussed, and the efficiency of the transfer system merits investigation. The influence of the stage of cycle on potential transfer would seem an important aspect. The area has scarcely been explored in clinical trials, but should be part of a drug documentation programme.

A final word: it is time to accept that a ‘normal’ arterial concentration of a hormone or a drug depends on the precise site from which the sample is obtained. Hormone concentrations in a sample obtained from the ovarian artery on one side may be different from a sample collected from the contralateral side or from a peripheral artery.

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