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Review Article

THE SUBCOMMISSURAL ORGAN, ITS PAST, PRESENT AND FUTURE PERSPECTIVE: A REVIEW

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SUMMARY

The subcommissural organ comprising modified ependyma, subependymal glial zone and a cellular hypendyma is located on the ventral aspect of the posterior commissure. In mid sagittal section, it can be divided into 4 subparts which extend from posterior commissure to recessus mesocoelicus forming roof of the cerebral aqueduct and III ventricle. Its tall columnar ciliated or pseudostratified ependyma abruptly changes into simple ventricular lining. Various forms of mucopolysaccharides, glycoproteins, neutral and Sudanophilic lipids, different enzymes show varying affinities towards the different structural components attributing indirectly to the functional significance of the organ. Scanning reveals a large number of cilia originating from apical spherical protrusions which intermix with those of others to form a network. Filaments along with RBCs and cellular debris form a rough irregular cord like Reissner's fibre towards the free ventricular surface. This is formed due to dynamic processes involving pre-packaging, packaging and unpackaging of secretory material, chemical modification and the hydrodynamic functions. This fibre seems to play role in cleansing of cerebrospinal fluid. Ultrastructure reveals well developed desmosomes in apical part of the ependymal cells and two types of nuclei on the basis of distribution of chromatin. The cytoplasm contains a uniform distribution of almost all the cell organelles and inclusion bodies. A specific arrangement of endoplasmic reticulum, Nebenkerne, in three forms especially toward supranuclear portion of the ependymal cells is a special feature.

Key words: Subcommissural organ, ependyma, subependymal glial zone, hypendyma, Reissner's fibre

The circumventricular organs (CVO) located at strategic locations within the ependymal wall of third and fourth ventricles possess modified ependyma and lack blood brain barrier except the subcommissural organ (SCO). These organs either secrete endocrines or their neuronal component regulates the hormonal stimuli. Recent study on the CVO reflects their involvement in immunopathogenesis of experimental autoimmune encephalomyelitis (Schulz and Engelhardt, 2005). The SCO has been currently a subject of great interest because of its enigmatic function even after a century of its discovery. An attempt has been made to compile the structural details and hypothetic functions of the organ in different species especially, the domestic animals which will form a basis for future strategies of neuro-endocrinologists and biotechnologists to explore the organ.

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HISTORY

The existence of typical tall and cylindrical ependymal cells on the lower surface of posterior commissure (PC) in mice (Stieda, 1870), reptiles, frogs and birds (Studnicka, 1900), first time led to consider this structure as an independent organ because of its structural and functional peculiarities especially significant role in fluid circulation in the cerebral ventricles in Ammocoetes (Dendy, 1902). These appeared as small depressions being covered by ciliated cylindrical cells called as "ciliated grooves". A similar type of tissue in *Amia calva* was called as typical cell tissue (Kappers, 1907). Marburg (1908) was first to report the tissue in humans.

The name, subcommissural organ, was adopted first time by Dendy and Nicholls (1910) who described it having composed of two strips made up of cylindrical epithelium. These strips joined to form a more or less pronounced fold in mouse, cat and chimpanzee. The organ is well

developed in the lower animals but rudimentary in man except the foetal period where it is highly developed. The organ is glandular in ox, pig and dog due to presence of ciliated cylindrical goblet like cells having amorphous material on their free surface (Bauer-Jokel, 1917). A close relationship exists between the SCO and pineal body because of regression of both organs in man during extra uterine life. The association of large pineal body with a small SCO concludes an inverse relationship between two in domestic animals except horse and dog (Marburg, 1920). Presence of similar type of cells (Pastori, 1927) and embryological association (Turkewitsch, 1936) between the two is another basis for correlation. The SCO of guinea-pig and man has been described as a tubular gland due to presence of drop like granular mass in columnar ependymal cells and on free ventricular surface of the organ (Pesonen, 1940, Reichold, 1942). The present review highlights the structural features of SCO in ox, horse, pig, dog (Talanti, 1958, 1959, Kumar *et al.*, 2007, 2008a, b), sheep, elk, llama (Talanti and Kivalo, 1960, Saggar *et al.*, 2000, 2002 a, b), reindeer (Talanti, 1966), camel (Afifi, 1964, Dellmann and Fahmy, 1966 a, Kumar *et al.*, 1999), buffalo (Dellmann and Fahmy, 1966 b, Ramkrishna and Saigal, 1985, 1986, 1987 a, b, Kumar *et al.*, 2006) and goat (Kumar, 1994, Kumar *et al.*, 1996, 1997 a, b, c, d, 1998, Kumar and Kumar, 2000, 2001).

PRENATAL DEVELOPMENT

The SCO, a phylogenetically ancient and conserved structure, is one of the first brain structures to differentiate (Rodriguez *et al.*, 1998). The foetal SCO has been studied extensively in amphibians (Oksche, 1961, Naumann, 1986), chicken (Wingstrand, 1953, Ziegels, 1977, Schoebitz *et al.*, 1986, Naumann *et al.*, 1987, Karoumi *et al.*, 1990) and several mammalian species including the domestic animals (Talanti, 1959, Kohl and Linderer, 1973, Marcinkiewicz and Bouchaud, 1983, 1986, Meiniel *et al.*, 1990). The SCO secretory material is released in the ventricles first on 7th day of incubation as demonstrated by various histochemical methods. Reissner's fibre (RF) proper appears in the Sylvian aqueduct in 11 days old chick embryo. The cells of SCO start differentiating between 11-19 days of gestation in rat embryos. These cells showing secretory activity in 14 days old foetus have capacity for early synthesis of DNA. The complete differentiation of cells is accomplished during the first post-natal month in mouse and rats. The SCO cells of bovine foetus differentiate at the stage of 2nd intrauterine month (Meiniel *et al.*, 1990) and become functionally active at 3 months of gestation as evidenced by presence of secretory material which increases in amount up to 7th month comparable to the post-natal level (Talanti, 1959). The RF appears in the bovine foetus of 16-25 cm body length (Agduhr, 1922). A well developed SCO present in human foetus (Pesonen, 1940, Oksche, 1956, 1961, Wislocki and Roth, 1958, Olsson, 1958, Mollgard, 1972) starts regressing during post-natal life as only remnants of the SCO parenchyma are observed in adult human. The glycoproteinacious secretion of the SCO in human foetus is similar to that of other vertebrates except the protein backbone which appears to be different (Rodriguez *et al.*, 1990).

TOPOGRAPHY

The SCO present on the ventral surface of PC extends from anterior part of PC to recessus mesocoelicus occupying diencephalic and mesencephalic regions of the brain. It has been topographically divided into four parts viz: i) pars-supracommissuralis (PS), ii) pars-precommissuralis (PP), iii) pars-subcommissuralis (PU) and iv) pars-retrocommissuralis (PR) in man (Mollgard *et al.*, 1973), rat (Mitro and Palkovits, 1981), buffalo (Ramkrishna and Saigal, 1985), goat and sheep (Kumar *et al.*, 1997 c, Saggar *et al.*, 2000) and horse (Kumar *et al.*, 2007). An additional 5th part as ventro-lateral limbs extending ventral from a region between the PP and PU, forming the upper 1/7th of the lateral walls of III ventricle in buffalo (Ramkrishna and Saigal, 1985). Later, Kumar *et al.* (1997 c) in goat observed these limbs as ventral projections from horizontal strips of the SCO throughout the extent of the organ. The demarcation of the parts is

possible only in mid sagittal sections due to presence of recessus infrapinealis, recessus mesocoelicus and a groove toward the ventral surface of the ependyma. Whereas, the SCO in transverse sections just appears as a horizontal strip.

The PS extends from the cranio-dorsal aspect of the PC to its junction with pineal gland. The convex shaped PP is a caudal extension of PS up to the point of medial groove. The convex part of SCO with prominent ependymal folding extending from the caudal end of the PP to the opening of RM constitutes the PU. An arc shaped caudal continuation of PU forms PR which covers the caudal surface of PC and later continues for a short distance into the roof of the cerebral aqueduct under the commissure of rostral colliculus. Strongly convex shaped PU of the horse has prominent subparts which are not seen in other species (Kumar *et al.*, 2007). The maximum length of SCO in mid sagittal section is 1.0 mm in rat (Collins and Woollam, 1979), 4.69-5.70 mm in young and 6.2 mm in adult buffaloes, 2.3-8.7 mm in young male goats and 9.2 mm in horse (Kumar *et al.*, 2007). The maximum width is 0.5 mm in rat, 2.34-3.35 mm in young and 3.01 mm in adult buffaloes, 2.58 mm in young goats at the rostral part of the organ whereas 1.14-1.60 mm, 1.60 mm and 0.34 mm are the minimum values in the caudal portion of the organ in adult buffaloes and young goats, respectively (Ramkrishna and Saigal, 1985, Kumar *et al.*, 1997 c).

HISTOMORPHOLOGY

The SCO has two types of secretory cells being arranged into two distinct layers, an ependyma towards the free surface of ventricle and a hypendyma adjacent to PC in cattle and dog (Krabbe, 1925), domestic animals (Talanti, 1958), sheep, goat, elk, llama (Talanti and Kivalo, 1960), camel and water buffalo (Dellmann and Fahmy, 1966 a, b) and reindeer (Talanti, 1966). An additional subependymal glial zone consisting of glial tissue and blood capillaries sandwiched in between the two in buffalo (Ramkrishna and Saigal, 1986), goat and camel (Kumar *et al.*, 1997 b, Kumar *et al.*, 1999), sheep (Saggar *et al.*, 2002 b) and horse (Kumar and Timoney, 2008 a). In addition, a subhypendymal fibrous zone has been noticed only in the horses except areas where hypendymal cells penetrate the fasciculi of the posterior commissure (Kumar *et al.*, 2008 a). The degree of development of these cells population varies greatly among the members of vertebrate (Oksche, 1961).

***Ependyma*:** The ependyma is lined by either tall ciliated columnar cells in rat, mouse, guinea-pig, hamster, ox, horse, pig, dog, sheep, goat, elk, llama and cow calf (Wislocki and Leduc, 1952, Talanti, 1958, Talanti and Kivalo, 1960, Isomaki *et al.*, 1965, Kohl, 1975, Mitro and Palkovits, 1981) or a modified tall columnar ciliated pseudostratified ependyma in camel, water buffalo (Dellmann and Fahmy, 1966 a, b, Kumar *et al.*, 1999), sheep (Barlow *et al.*, 1967, Saggar *et al.*, 2002 b), rat (Collins and Woollam, 1979), buffalo (Ramkrishna and Saigal, 1986), goat (Kumar *et al.*, 1997 b) and horse (Kumar and Timoney, 2008a). The folding of superficial layer and arrangement of ependymal cells into one or more layers make most interspecies differences. The folds and crypts like invaginations led to an increase in the surface area for secretory and absorptive functions. The ependymal thickness varies in different regions of the organ with their minimum and maximum values in PS and PU regions of the organ, respectively in buffalo and goat (Ramkrishna and Saigal, 1986, Kumar *et al.*, 1997 b). The modified ependyma of the organ abruptly changes to simple ventricular ependyma of III ventricle. The goblet cells with distended apical cytoplasm reported in domestic animals have been attributed due to unsatisfactory fixation of the tissues (Kolmer, 1921). The pseudostratified type ependyma contains different rows of nuclei particularly towards the base of ependyma in man, rat and domestic animals except water buffalo where only a few nuclei are present (Dellmann and Fahmy, 1966 b). The nuclei have been classified into round to oval shaped less basophilic type-I and darkly stained type-II of irregular shapes in goat, sheep (Kumar *et al.*, 1997 b, Saggar *et al.*, 2002 b) and horse (Kumar and Timoney, 2008a). The different types of nuclei represent varying functional stages of the cell types (Mollgard,

1972). The presence of cytoplasmic vacuolations in supra and infra nuclear portions of the cells indicates the occurrence of lipids. The fine cytoplasmic processes originating from basal part of the ependymal cells project into the subependymal glial zone where these processes either mix with glial processes or terminate at the periphery of small blood capillaries. The size of basal processes appears to be directly correlated with thickness of the hypendymal tissue layer. The ependymal cells contain fine granular eosinophilic cytoplasm with more activity towards ventricular surface and basal processes due to presence of an abundant smooth endoplasmic reticulum.

***Subependymal glial zone*:** This intermediate zone having mixed distribution of basal cytoplasmic processes, fine blood capillaries and small number of glial cells, extend throughout the extent of the SCO except at PR where it is less distinct (Ramkrishna and Saigal, 1986, Kumar *et al.*, 1997 b). However, it is acellular in superficial part and only a few small and large cells constitute the deeper part in camel (Afifi, 1964). The small sized round to oval shaped microglial cell possesses basophilic nucleus with eccentric nucleolus, whereas less populated microglial cell has large, vesicular and less basophilic nucleus with a clear nucleolus and scanty cytoplasm (Kumar *et al.*, 1997 b). The glial cells, considered as fibrous astrocytes (Leonieni, 1968), act as "a relay or end station" because of their significant role in the transport of substances from the CSF and blood vessels (Cammermeyer, 1965). The processes of these cells along with those of other cells form a meshwork entrapping vacuoles of different dimensions. The presence of large number of horizontally placed blood capillaries reflects the basal secretion (Kimble and Mollgard, 1973). These capillaries have been postulated as receptor areas for neurosecretory substance in functional connection with the hypophysis. This zone has been treated as part of hypendyma in other domestic animals.

Hypendyma: The term hypendyma was first time introduced by Krabbe (1925) in cattle and dog to the cellular area located below the ependymal cells of the SCO containing neuroglia elements, numerous blood capillaries, a few nerve fibers originating from PC and the cells having little protoplasm resembling to the glial cells. Later this term was adopted in other domestic animals. Hypendymal cells have been called to all those secretory cells of SCO which are not located within the ependyma (Oksche, 1961). The hypendymal cells classified in to type-I and type-II in goat show maximum numbers at the middle portion of the PU and frequently mix with pineal tissue and gray mater of the PC at PS and PR, respectively. Small sized microglial cells are mainly associated with blood capillaries whereas, the large sized macroglial cells tend to distribute toward the PC (Kumar *et al.*, 1997 b).

The aggregation of the cells in the form of cell cords with ducts and the linear arrangement of cell rows indicate the presence of tubular glands in ruminants except goat (Kumar *et al.*, 1997 b). Some of these ducts open on to the ependymal surface or into crypts formed by the ependyma except the buffalo (Ramkrishna and Saigal, 1986). Distended basal parts of these crypts suggest that these ducts are not extensions of the ependymal crypts. Moreover, the presence of ducts under the smooth ependymal surface and their deep penetration in between the fascicles of PC reflects the independent nature. It has also been postulated that rosettes made up of radially arranged cubical cells enclosing a small lumen around the recessus infrapinealis and the hypendyma of the SCO, may be due to the abstricture of the initially tubular structures in the epiphysis of camels (Talanti and Kivalo, 1960). The cylindrical ducts without characteristic internal cell lining occur in bovine foetus and are penetrated by the blood vessels (Turkewitsch, 1936). A more eosinophilic character and presence of granular mass in the parietal cells of the hypendymal ducts suggests secretory activity of the organ (Talanti, 1958). No functional significance could be assigned to tunnel like cavities present in bovine foetus, reindeer and goat (Talanti, 1959, 1966, Kumar *et al.*, 1997 b). The vacuolations in supranuclear portion of these hypendymal cell cords correspond to the sites of presence of lipids (Isomaki *et al.*, 1965).

Pesonen (1940) was the first to report on the rich vascularization of the SCO which was later confirmed in other domestic animals

(Bargmann and Schiebler, 1952, Wislocki and Leduc, 1952). A close association between blood capillaries, hypendymal and glial cells indicates an active transport mechanism of secretory substances in domestic animals. A dense network of hypendymal capillaries extends in the ependymal layer (Duvernoy and Koritke, 1964). Thus, the SCO has been compared with hypophyseal region due to presence of neurosecretory substance in the lumen of blood capillaries and its transportation through capillaries under neurohormonal control (Landau, 1960). Small nerve fibers in hypendyma and large longitudinally oriented nerve bundles close to the PC are present in domestic animals. These nerve fibers have their origin from bipolar cell ganglion at the rostral end of the SCO close to pineal gland in human foetus (Mollgard, and Muller, 1973) and from PC in domestic animals (Talanti, 1958). However, the origin of these fibers is difficult to establish due to their tortuous course. An additional distinct nerve fiber tract extends along mid sagittal plane from PS to PR in the hypendyma close to PC. A chemical synapse is formed by small group of axons around the hypendymal blood capillaries in rabbit (Kimble and Mollgard, 1973). Neurons in the form of pericommissural ganglion cells have been reported to be present in deeper part of the hypendyma (Yamada *et al.*, 1957, Isomaki *et al.*, 1965). In addition, a subhypendymal fibrous zone is also present in the areas where hypendymal cells do not penetrate the fasciculi of PC (Kumar and Timoney, 2008 a).

HISTOCHEMISTRY

The histochemistry reveals the presence of glycoproteins, neutral mucopolysaccharides-protein complexes, mucoproteins, glycoproteins and lipids in cytoplasm of different cell layers of the SCO in different species. The periodic acid Schiff's (PAS) reaction is present in the form of uniformly distributed fine granules in supra and infra nuclear cytoplasm of the ependymal, hypendymal and glial cells with its comparatively more activity towards the intercellular junctions, basal cytoplasmic processes and blood capillaries in domestic animals (Bargmann and Schiebler, 1952, Talanti, 1958, Barlow *et al.*, 1967, Leonieni, 1968, Nesic and Babic, 1979, Ramkrishna and Saigal, 1987, Kumar *et al.*, 1996), rodents (Wislocki and Leduc, 1952) and human foetus (Mollgard, 1972). The material is amorphous towards the ventricular surface and condensed along the luminal border of the hypendymal ducts. The diastase and maltase digestion does not affect activity in rodents and sheep (Talanti, 1958, Wislocki and Leduc, 1952, Barlow *et al.*, 1967) whereas it results in decreased PAS activity in human, buffalo and goat indicating the presence of glycogen along with other mucopolysaccharides. The presence of glycogen in neuroglia cells suggests its role in mediation of nutrition from blood vessels to nervous tissue proper (Shimizu and Kumamoto, 1952). A close relationship of glial cells processes with blood capillaries indicates the role of glycogen as a transportation media for the secretory material synthesized in the ependymal or hypendymal cells. More concentration of glycogen towards free and basal surfaces of ependyma led the SCO as an active metabolic organ in relation to absorption and detoxification of CSF (Sterba, 1969). The secretory material also contains chondroitin-4 and/or 6-sulphates, sialoglycoproteins towards the ependyma and hyaluronic acid around the vasculature (Mollgard, 1972). Faint metachromasia with toluidine blue in goat (Kumar *et al.*, 1996) reflects the occurrence of sulphated mucopolysaccharides, however, it is absent in rodents (Wislocki and Leduc, 1952). Molecular and functional features evidence that SCO spondin, a novel relative of the thrombospondin family, may be involved in neuronal development by modulating cell aggregative mechanisms (Gobron *et al.*, 1996).

Sudanophilic and neutral lipid droplets concentrate mainly towards the basal portion of the ependyma and moderately in hypendyma (Wislocki and Leduc, 1952, Talanti, 1958, Mollgard *et al.*, 1973, Ramkrishna and Saigal, 1987 a, Kumar *et al.*, 1996) including the parietal cells of hypendymal ducts in ox (Talanti, 1958). These lipid droplets represent the phospholipids or other bound lipids like lipoproteins. The secretory material is of glyco-proteinaceous in nature in dog and cat (Bargmann and Schiebler,

1952), small rodents (Wislocki and Leduc, 1952), human (Oksche, 1956, Wislocki and Roth, 1958) and buffalo (Ramkrishna and Saigal, 1987 a). Its proteinaceous component contains cysteine, tyrosine, tryptophan and arginine in domestic animals (Talanti, 1958 and Leonieni, 1968), human foetus (Mollgard, 1972). Protein containing sulphydryl group in the cell may play role in the enzyme systems, cell division, permeability and hormone synthesis (Barron, 1951).

HISTOENZYMES

Acid phosphatase (ACP), a dephosphorylating enzyme, is localized throughout the ependymal cells and the blood capillaries and decreases towards the hypendyma in the SCO of rodents and domestic animals (Wislocki and Leduc, 1952, Kohl and Linderer, 1973, Kohl, 1975, Talanti, 1958, Kozlowski, 1969), buffalo (Ramkrishna and Saigal, 1987 b) and goat (Kumar *et al.*, 1997 a). Its activity in three types of lysosomal bodies especially type-II indicates the secretory phenomenon in sheep (Barlow *et al.*, 1967). However, the enzyme has been reported to be absent in the SCO of cat (Murphy and Wood, 1966). No definite physiological role can be assigned to this enzyme in the SCO except that it is present in the cells where more energy is required for maintenance of the cells themselves or the production of the specific secretory products of the cells (Leduc and Wislocki, 1952). The enzymic activity has also been correlated with transmembranic migration due to release of energy from phosphate bonds, granule formation, release or other secretory processes (Rosenberg and Wilbrandt, 1952, Smith, 1969). The presence of strong reaction in supranuclear region of ependymal cells supports the process of apical secretion in goat (Kumar *et al.*, 1997 a).

Alkaline phosphatase (AKP) enzyme has more affinity towards the basal portion of the ependyma, subependymal glial zone and blood capillaries of the SCO in domestic animals and human foetus indicating the SCO as a highly metabolic organ (Mollgard, 1972). The enzyme has been reported absent in dog and rodents (Bargmann and Schiebler, 1952, Leduc and Wislocki, 1952). Similarly, the absence of activity towards the ventricular surface of the ependyma in rat and goat reflects that the Reissner's fibre is free from this enzyme (Schutte, 1971, Kumar *et al.*, 1997a). This enzyme also plays a significant role in the process of absorption and transport across the membranes (Raekallio, 1970). A close relationship occurs between the sites of secretion and enzymic activity because of the action of enzyme on phosphomonoesters. A weak to strong glucose-6-phosphatase (GLP) activity in the form of diffuse fine granules mainly in the subependymal glial zone is involved in carbohydrate metabolism and release of glucose as glycogen (Kumar *et al.*, 1997 a). The enzymic activity in rodents has been attributed due to the hydrolysis of GLP by lysosomal ACP activity (Kohl, 1975). Non-specific esterases enzymes have the property to hydrolyse the esters of fatty acids except acetyl-choline. A weak to moderate reaction of these in the ependymal cells and hypendymal ducts exhibits their probable role at some stage of the lipid metabolism (Talanti, 1958, Wislocki and Leduc, 1952, Rechardt and Leonieni, 1972).

Acetyl-cholinesterase (ACH) enzyme is strongly present at the sites of nerve fiber tract, around blood vessels and hypendymal cell cords. The myelinated nerve fibres entering into cat SCO exhibits a significant activity (Murphy and Wood, 1966). Whereas, a sparse distribution of isolated nerve fibres in hypendyma and at the junction of hypendyma with the PC, presents scanty cholinergic nerve supply in goat (Kumar *et al.*, 1997 a). A strong reaction of glucose-6-phosphate dehydrogenase (GPDH) in rodents postulates the involvement of the organ in endocrine function ((DeLong and Balogh, 1965, Kohl, 1975). The enzyme produces ribosomal component of RNA through hexose monophosphate shunt which contributes for the synthesis of protein portion of the secretory substance (Diederen, 1970). The triphospho pyridine nucleotide generating system through hexose monophosphate shunt is essential for the synthetic functions of endocrine cells (Field *et al.*, 1960). The synthesis of steroid hormones, fatty acids and hydroxylation of steroid hormones

are other functions assigned to this enzyme.

Succinic dehydrogenase activity in the form of fine granules is distributed in the ependyma and hypendyma of rodents and domestic animals (Talanti, 1958, 1959, Barlow *et al.*, 1967, Kohl, 1975, Ramkrishna and Saigal, 1987 b, Kumar *et al.*, 1997 a) but absent in rats (Leduc and Wislocki, 1952, DeLong and Balogh, 1965). However, an increased activity of the enzyme during the development of rat has been correlated with increase in its metabolic activity (Kohl and Linderer, 1973). The increased distribution of enzyme in lower half of ependyma reflects a more distribution of mitochondria indicating it as a highly metabolic organ concerned with the cells own energy metabolism including citric acid cycle of Kreb's (Harman, 1950, Padykula, 1952, Kumar *et al.*, 1997 a). Similarly, the respiratory enzyme cytochrome oxidase in the form of distinct granules of uniform dimensions has more concentration at the basal portion of the ependyma and hypendyma suggesting more distribution of mitochondria and its effective role in anaerobic glycolysis (Kohl, 1975).

REISSNER'S FIBRE

Reissner's fibre (RF) was first time observed by Reissner (1860) as a thin string of extremely regular shape resembling the axis cylinder with characteristic high refringence and lying free within the central canal of *Petromyzon fluviatilis*. Later this structure was named RF after the name of Reissner (Kutschin, 1866). Stieda (1870) considered it as an artifact resulted due to coagulation of the contents of central canal by the fixing fluids, whereas, Studnicka (1900) regarded it as a secretory product of the ependyma in the central canal. The secretory ependymal cells of the SCO are highly specialized to secrete a specific glycoprotein called as SCO-spondin basally towards the posterior commissure and also apically towards free ventricular surface where these glycoproteins led to the formation of RF (Meiniel, 2007). An organic and functional connection between RF and SCO constitutes a nerve fibre having a role in transmission of optical reflexes (Sargent, 1900, 1901, 1904) and a mechanism controlling the motions especially the flexion of the body (Dendy and Nicholls, 1910). Reissner's Fibre acts as mechanoreceptor to indicate variations in CSF pressure through supraependymal nervous pathways to the choroid plexuses (Kolmer, 1921). The SCO-RF complex involved in CSF circulation led to absence of RF, aqueductal stenosis, increased CSF concentration of monoamines and a hydrocephalus due to primary and selective immuno-neutralization during fetal and early post-natal life (Perez-Figares *et al.*, 2001, Rodriguez and Yulis, 2001). A specific binding of radio labeled nor-epinephrine is a good evidence for its detoxifying function (Hess and Sterba, 1973). The major quantity of the secretions of the SCO ependymal cells is discharged in to the ventricular CSF. A part of this secretory material which is not soluble in CSF led to RF formation due to its condensation (Sterba, 1969). The RF extends cranio-caudally due to continuous shifting of released secretory material towards the caudal end where it gets accumulated in an amorphous loose mass called massa caudalis at the level of filum terminale (Leonhardt, 1980).

There is substantial evidence for distinguishing the different spatial and temporal stages for the CSF insoluble secretion released by the SCO (Rodriguez *et al.*, 1987). Thus, RF is regarded to be formed as a result of a dynamic process involving various mechanisms like a) shifting of the secretory material along the fibre structure, b) pre-packaging, packing, unpacking of the secretory molecules, c) chemical modification of the RF molecules at the distal end of the fibre, d) hydrodynamic factors having influence on the formation and the shape of the fibre (Rodriguez *et al.*, 1992). The ependymal secretory material capable of forming RF first aggregates in the form of a thin film at the top of microvilli and cilia of the ependymal cells which is regarded as pre-RF material (Rodriguez *et al.*, 1986, 1987, 1992) and can be demonstrated by histochemical staining methods (Wingstrand, 1953, Sterba *et al.*, 1967, Herrera and Rodriguez, 1990), by scanning and transmission electron-microscopy (Lindberg and Talanti, 1975, Weindl and Schinko, 1975). The appearance of pre-RF and RF at different stages of incubation in chick embryos (Schoebitz *et al.*, 1986) and tendency

of the pre-RF for early labeling to radio active precursors (Rodriguez *et al.*, 1990) also confirms the existence of this stage. The hypothesis is made that the secreted glycoproteins aggregates in the form of typical RF due to hydrodynamic factors of the CSF circulation (Olsson, 1958, Oksche, 1961). The mechanism of packaging of RF ingredients requires essential formation of disulfide bonds and could be related to the high content of cysteine in RF glycoproteins. Two forms of glycoproteins constitute bovine SCO proper whereas, the RF appeared to contain atleast six glycoproteins indicating a post release processing occurs during the pre-RF stage (Nualart *et al.*, 1991). The SEM reveals that filaments from ependymal cells along with RBCs and cellular debris gradually coalesce to form a rough, irregular cord like RF which may have the cleansing capacity in the CSF (Weindl and Schinko, 1975, Kumar *et al.*, 1998, 2008 b). The alignment of filaments in a particular direction reflects the morphogenetic significance of ciliary movements (Castenholz and Zoeltzer, 1980). The amorphous character and degree of tautness of RF suggests it other than a pathway along which substances such as peptides reach lower parts of the brain stem (Woollam and Collins, 1980). Ultra structurally RF possesses rough and smooth ER, a few Golgi bodies and electron dense inclusion bodies but the mitochondria and the nucleus are altogether absent (Kumar *et al.*, 1998, 2008 b). Well developed electron dense granules present close to Golgi complex also add to the RF by releasing their secretions (Hofer *et al.*, 1980).

SCANNING ELECTRON-MICROSCOPY

The scanning electron-microscopy (SEM) of the SCO presents round to oval shaped apical spherical protrusions (ASP) in the cat (Weindl and Joynt, 1972), cow (Lindberg and Talanti, 1975), rats (Collins and Woollam, 1979), goat (Kumar and Kumar, 2000), sheep (Saggar *et al.*, 2002 a) and buffalo (Kumar *et al.*, 2006). Most of these ASP give rise to a large number of cilia which intermix with those of adjacent cells and form a network. A few non-ciliated ASP have also been seen in goat, sheep and buffalo. The cilia are either absent or have a sparse distribution in rat and cat. The ASP possess small pores or holes on the outer surface. The occurrence of depression toward center of the protrusion possibly represents absorption as an additional functional capacity of the ependymal cells in the goat (Kumar and Kumar, 2000). However, these structures are covered with microvilli in rat (Collins and Woollam, 1979). Weindl and Joynt (1972) speculated that the protruded endings of the ependymal cells in feline SCO led to the secretory function whereas, Schechter and Weiner (1972) hypothesized that these endings represented a morphological correlate of an active secretory process supported by the presence of heterogeneous material between the protrusions in the buffalo calves, goat and cow (Lindberg and Talanti, 1975, Kumar and Kumar, 2000).

TRANSMISSION ELECTRON-MICROSCOPY

Elucidation of ultrastructure of SCO has not been attempted in domestic animals except in young cattle (Isomaki *et al.*, 1965) and goat (Kumar, 1994). The tall columnar ependymal cells contain cytoplasmic organelles and inclusion bodies along with their nuclei at different heights. Thick club-or wedge-shaped apices of ependymal cells with undulating appearance and microvilli is a common feature. A few cells have uneven microvilli, the apices of which protrude in the form of round or oval modifications. Different profiles of cilia meant for secretory function in young bovine calf (Isomaki *et al.*, 1965) are reported absent or structurally less developed in highly differentiated ependymal cells of goat (Kumar and Kumar, 2000). Terminal bars (desmosomes) are well developed in the apical portion of the ependyma especially a zigzag pattern which highlights the inter-digitations between adjacent cells. The nuclei of most of the ependymal cells are irregular and a few show nuclear clefts along their longitudinal axis due to deep invagination of the nuclear membrane. The nuclei have been classified into two types on the basis of distribution of chromatin material and nuclear clefts. The most frequent type-I round

to oval nuclei have a uniform distribution of coarse condensed chromatin material with a tendency to accumulate in smaller clumps towards the inner nuclear membrane surface. The type-II nuclei of irregular shape with nuclear clefts are much fewer. Their chromatin material is regularly spaced in the form of condensed, irregular, polygonal aggregations at the inner surface of the nuclear membrane. In addition, a few large-sized clumps project from the periphery to the center of the nucleus. Both the types of nuclei possess spherical or oval centric/eccentric nucleoli. The modified chromatin nucleolus or chromoplast in the form of a large irregular structure having a less electron-dense granular material is mainly a feature of type-I nuclei.

The cytoplasmic organelles include centriole, microtubules, endoplasmic reticulum (ER), mitochondria and Golgi complex along with inclusion bodies. The presence of secretory droplets, vacuoles, small electron-dense bodies, osmiophilic asteroid droplets and large round spherical bodies indicates the secretory nature of these cells. The highly developed smooth ER of the ependymal cells forms a large membrane-bound labyrinthine structure towards the supranuclear portion of ependymal cells. Round or irregular sacs of smooth ER with dense homogeneous contents distend towards the apical portion of the cell. A high and low concentration of rough and smooth ER has been reported in rat (Collins and Woollam, 1979). The rate of protein synthesis in individual cisternae is relatively low, although the cell may display a high synthetic activity corresponding to the excessive number of rough endoplasmic reticulum (Alberts *et al.*, 1983).

A specialized arrangement of ER known as 'Nebenkerne' occurs in three forms in the supranuclear portion and occasionally adjacent to the ventricular surface of the ependymal cell (Kumar and Kumar, 2000). The first type has several concentric lamellae of ER tightly packed into spiral coils and some of these lay parallel with a regular inter-space. The lamellae extend at the periphery enclosing the large spaces with clumps of fine granulated condensed material. RNA granules are studded on the outer surface of the few lamellae. Round lipid droplets are either localized towards the centre of the lamellated coils or adjacent to the Nebenkerne. Free RNA granules are observed in the hyaloplasm of these lamellae. The second type of Nebenkerne has a less irregular arrangement of widely spaced coils bound by a thin membrane at the periphery. Its central and peripheral parts are expanded into sacs having granular mass and more electron-dense RNA particles. However, no material is present in the hyaloplasm of these lamellae. The third type of Nebenkerne is modified into a vacuolated form, comprising a meshwork of lamellae supported by vacuoles of different shapes and size. Homogeneous electron-dense fine-granulated particles are present in the lamellae. A few highly electron-dense bodies and lipid droplets are observed towards their proximity. A similar type of structure has been reported in the calf (Isomaki *et al.*, 1965) without subtypes. The mitochondria located at the neck of ASP are irregularly distributed in the rest of the cytoplasm, substantially increased concentration towards the basal processes. Lysosomes, Golgi complex and multi vesicular bodies with small hollow vesicles surrounded by thin membranes mainly occupies supranuclear position.

Electron-dense round bodies are present in the supra- and subnuclear portions of the ependymal cells. Fewer electron-dense bodies resemble secretory granules of proteinaceous nature. Osmiophilc droplets or bodies are classified into three types based on their morphology. Type-I are asteroid osmiophilic droplets having a highly osmiophilic character. Type-II is characterized by homogeneously distributed, less electron-dense content surrounded by an outer smooth covering and a close association with Nebenkerne and large, round osmiophilic bodies. However, these types of smaller bodies are studded with osmiophilic granules and have a beaded appearance that highlight the outer membrane. Type-III consists of round osmiophilic bodies where inner structures have electron-dense osmiophilic inclusions and peripheral lipid globules. Cytoplasmic inclusions have been reported in the SCO secretion. The pale and dense inclusions are derived directly from rough ER, by-passing

the Golgi apparatus. However, it has been postulated that the initial synthesis of material starts in the rough ER, followed by the addition of carbohydrates and packaging of the secretory product in the Golgi complex (Schmidt and D'Agostino, 1966, Sterba *et al.*, 1967, Diederen, 1970). The protoplasmic basal processes of the ependymal cells terminate in the pericapillary space. An enormous increase in population of mitochondria is observed as compared to the apical portion. The Nebenkerne and inclusion bodies are present in almost all forms as already described.

Polygonal shaped hypendymal cells have been classified into two types on the basis of nuclear morphology and chromatin distribution in bovine and caprine (Isomaki *et al.*, 1965, Kumar and Kumar, 2001). Irregular shaped nuclei of type-I cells have electron-dense nucleolus, chromoplast and small aggregates of chromatin material. Type-II cells nuclei contain larger nuclear clefts and evenly spaced highly electron-dense chromatin clumps towards the inner nuclear membrane. Its large sized nucleolus is highly electron-dense having nucleolonemal strands demarcating pars-amorpha. Morphological differentiation of nuclei reflects variation in the metabolic activity of the cells. Type-I cells have been reported in a stage of resting whereas type-II cells are at a stage of lively functional activity (Isomaki *et al.*, 1965). Cytoplasm of the hypendymal cells possesses ER in the form of a highly specialized structure constituting a large membrane bound system with the predominance of rough ER. The smooth ER in the form of round or irregular shaped tubules or sacs has dense homogeneous content and sometimes tended to conflow forming the larger secretory droplets. Nebenkerne, a characteristic arrangement of ER, are distributed as described in the ependymal cells. Golgi complex is uniformly distributed with a more tendency towards Nebenkerne. Mitochondria and three types of osmiophilic bodies are observed as seen in the ependymal cells (Isomaki *et al.*, 1965, Kumar and Kumar, 2000, 2001). The protoplasmic and fibrous processes of hypendymal cells intermingle with those of other cells and glial cells. The processes contain few mitochondria, small sacs of ER and fine granular material in areas adjacent to pericapillary basement membrane whereas, fibrous processes contain bulk of microfilaments which follow parallel and slightly wavy course. The micro and macro glia cells, scanty in number are distributed amongst the hypendymal cells. The microglia cells have round to oval nuclei and less electron-dense cytoplasm with sparse distribution of Golgi, mitochondria and a more distribution of lysosomes, microfilaments and electron-dense bodies. The macroglia cell contains elongated and indented nucleus. The other cytoplasmic features are similar to those of macroglia cells. Large cavities without a cell lining are traversed by processes of hypendymal cells in cattle and goat (Olsson, 1958, Isomaki *et al.*, 1965, Kumar and Kumar, 2001). These cavities are often distended and lead to folding of the superficial ependyma in cattle (Isomaki *et al.*, 1965). A group of cells packed by junctional complexes form rosettes like structure with a very small lumen in the rat (Rodriguez *et al.*, 1992) and with a very large cavity in bovine SCO (Olsson, 1958, Isomaki *et al.*, 1965). A large pericapillary space is observed between capillary endothelial basement membrane and hypendymal cells. This arrangement is generally indicative of a leaky blood brain barrier (Brightman *et al.*, 1970). Pores are present in capillary wall at regular intervals in the form of fenestrations bridged by thin diaphragm like arrangement. The diaphragms are supposed to be formed by a fusion of two adjacent membranes followed by progressive elimination of some layers of these membranes. A non-fenestrated tight endothelium formed a barrier for tracer injected intravascularly (Weindl and Joynt, 1972) constituting an efficient blood brain barrier. Collagen fibres are present in perivascular space of blood capillaries. The presence of long spacing collagen could result due to release of secretory glycoproteins of the SCO as *in-vitro* formation of this collagen may be induced by adding glycoproteins to collagen solutions. Their presence also reflects a special type of ependymo-vascular interaction which may lead to a local decrease in the efficiency of blood brain barrier (Schwink and Wetzstein, 1966). Pericytes are observed in close contact with the capillary

outer wall. Irregular myelinated nerve bundles occur in the deeper part of the hypendyma close to posterior commissure (Isomaki *et al.*, 1965, Kumar and Kumar, 2001). A few synapses also occur in between neural elements, protoplasmic glia cells and hypendymal cells.

A large number of experiments have been conducted on the SCO of different species keeping in view the varying functional hypothesis but no definitive role could be ascribed to it. A combine approach of recent molecular and biotechnological techniques along with the ultrastructure may lead to unveil some unexplored features of the organ. This paper will prove a boon to neuro-endocrinologists and biotechnologists to provide a structural and correlative functional basis of the SCO to formulate future strategies.

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