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Syncytial Cytoplasmic Communication Invertebrates

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Annotation: *In this paper results of studies of cytoplasmic syncytial connections in the invertebrate nervous system are presented. It has been shown that in the nervous system, apart from chemical synapses and electrical membranous contacts, the third type of interneuronal communications exists — the cytoplasmic syncytial connection. Absolute criteria of syncytial connections were shown in light microscopy preparations and in tissue culture plexuses, as well as in electron microscopy investigations.*

Many years had passed since the time the neuronal theory was described and main provisions of reticularists were refuted. Now, nobody challenges the reasonability of the neuronal theory. However, exactly in the same way, the presence of original cytoplasmic fusion phenomena in the nervous system of various invertebrates is not challenged (Prosser, 1978). In literature, there also are accepted facts on the presence of the true cytoplasmic syncytial interneuronal connection in the nervous system. It is impossible to ignore the finding of the syncytial connection in molluscs, crustaceans, polychaetes, and other invertebrates (Young 1936, 1938, 1939; Nicol, Young, 1946; Nicol, 1948, Hagiwara, Morita, Naka, 1964; Günter, 1975; Sotnikov, Kamardin, Rybakova et al., 2009). All these studies, first and foremost, present absolute evidence of the principal existence of the interneuronal syncytium in the nervous system. For example, as described by J.Z. Young (1936), the giant axon of a mollusc (Loligo pealii), created by the syncytial fusion of the processes of many small neurons, became a favourite object of many electrophysiological experiments by famous researchers. Many fundamental discoveries in the area of neuromembrane biophysics were made using this syncytially created axon (Hodgkin, Huxley, 1939; Katz, 1968; Tasaki, 1971). Therewith, no one had any doubt that there is a single axon, i.e. the syncytia of many processes, not a bundle of independent axons of many neurons. J.Z. Young (1939) demonstrated syncytial "protoplasmic continuity" in the nervous system of other cephalopods as well. The author confirmed his morphological data by conducting electrophysiological experiments. Discovered by J.Z. Young (1936), the mode of creating the syncytial interneuronal connection by a fusion of various neuron processes (Fig. *1, a-e*) could be considered as fusion according to Young's principle. A syncytium is described also for adult shrimps Macrobrahium rosenbergii and Myxicola infundibulum (Fig. *1, f*) between giant neurons involved in avoidance behaviour (Friedlander, Levinthal, 1982), as well as in webworm Manduca sexta (Carr, Taghert, 1988). The multicellular or the syncytial form of giant fibres' creation (Fig. *1, f*) was found in annelids

and crustaceans (Nikol, Young, 1946; Nicol, 1948). Even partially successful attempts were made to join (fuse) peripherical and central stumps of the large, cut motor fibre of crustaceans (Bittner, 1973; Bouton, Bittner, 1981). After these studies were performed, there remained no doubt whatsoever no only that the syncytial interneuronal connection exists, but also that it can be created de novo in animals' nervous systems. This in no way disturbs the principal provision of the neuronal theory on cells' organization and synaptic interactions in the nervous system of most Metazoa. At the same time, the question remains why the presence of the cytoplasmic syncytial interneuronal connection has been so categorically denied since the present time by all neurologists.

With well-supported data on the presence of the interneuronal syncytial connection in invertebrates in situ, we considered it essential to reveal this form of connection in living neurons of a mollucs in cell culture. For the enzyme treatment of ganglia, a circum pharyngeal ring of mollusc Lymnaea stagnalis was placed in a 0.4% pronase solution. The culture medium was prepared on the base of the stock single medium RPMI-1640. The detailed method described is presented in the paper (Sotnikov, 2012).

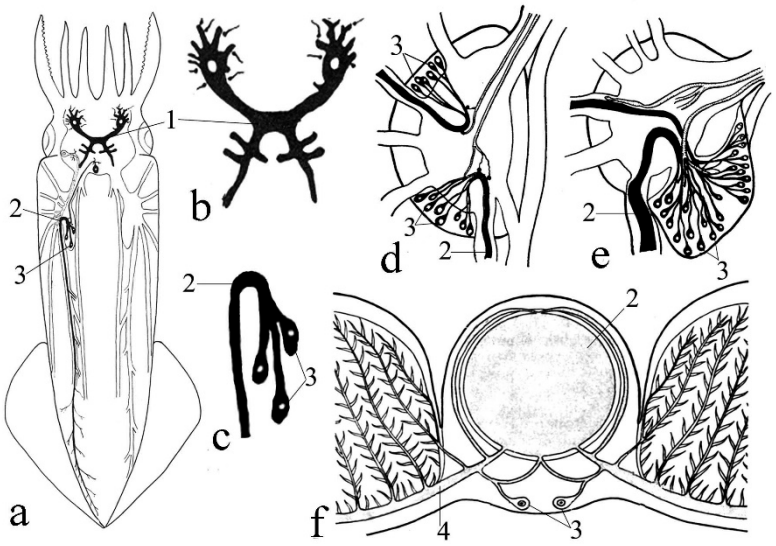

Fig. 1. Giant nerve fibers as an illustrative example of the syncytial cytoplasmic connection in the nervous system (schematic picture).
a – the total view of the Loligo syncytially connected neurons (from Young, 1936); b, c – enlarged details of a; b – syncytial connection of axons of two giant cells; c – neurosyncytium of axons fused in giant nerve fiber; d – fusion o processes of many neurons into the giant fiber in the cephalopod mollusc Sepia (from Young, 1939); e – the same in Loligo (from Young, 1939); f – giant fiber of *Myxicola infundibulum* formed by syncytial fusion of processes of many neurons (from Nicol, 1948); 1 – cytoplasmic anastomosis; 2 – formed giant axon; 3 – bodies of neurons forming giant axon; 4 – peripheral branch of giant axon.

The main advantage of the method of studies in vivo was the ability to study the structural kinetics of the culture and ability of the method to reveal structural modifications of a neuron over time. This method's advantage provided a way to develop special absolute criteria instrumental in proving the creation of syncytial.

connections in living neurons at light-optical level (Sotnikov, Malashko, Rybakova, 2006,

2012). Studies were performed using long (3-6 days) automated time-lapse microcinematography and computer analysis. To prove the creation of the cytoplasmic connection of neurons, criteria providing a means to differentiate process fusion from their junctions using the video investigations were used of living neurons kinetics. With that purpose as the theoretical justification (criterion of asyncytial connection), an inverted position was used of Waller's degeneration law. Surprisingly, Waller's degeneration concept, that in due time was the one of the important pieces of evidence supporting the absence of a syncytial connection in the nervous system, helped in revealing of syncytium. Since after cutting a nerve process from the neuron body (trophic centre) it shall degenerate, then if such a process does not degenerate after it is cut from its neuron's body, it means that it has a cytoplasmic connection with the body of another neuron (Bittner, 1973; Neumann, Coakley, Giordano-Santini et al., 2015). Such experiments are easy to conduct in tissue culture.

We were the first ones who suggested the new syncytial connection method between neurons revealing the use of light-optical observations of the structural process dynamics in a tissue culture. Figure *2* first demonstrates the establishment of "end-to-end" junctions between filopodia (*3*) lamellar cell processes *A* and *B*. Then, in 15 min. lamellas begin to contact with lamellas (*1, 2)* of neighbour cells *A, B* and the contour between them becomes invisible. We can presume that the processes of these cells have a syncytial connection, because in time a single intracytoplasmic cytoskeletal bundle is formed in them (Fig. *2, d-f, 4*) that, while not interrupting, passes from one lamella to other lamellas. Cell *A* appears to be bound with cell *B* via lamella *2* of cell *B* (Fig. *2, d, 4*).

However, this is not yet enough to prove a syncytial connection between these lamellar processes, but as it often occurs in primary cultures, cell *B* dies (Fig. *2, e, 5*) and its lamellar processes *2* and cytoskeletal bundle *4* remain intact at the same time. After losing its body (trophic centre), processes *2* of cell *B* are still not affected by Waller's degeneration, since in 100% of cases they appear with any neuron processes while separating from a body. In this case, they are preserved within 4 h up to the end of the examination. Moreover, in contracting they approximate cells *A* and *B* the distance between them is reduced by 9.2 % while the connecting anastomosis straightens out (Fig. *2, d-f*). It is possible only in the case the preserved viability process was able to obtain a new trophic centre, i.e. make a direct cytoplasmic syncytial connection with another cell.

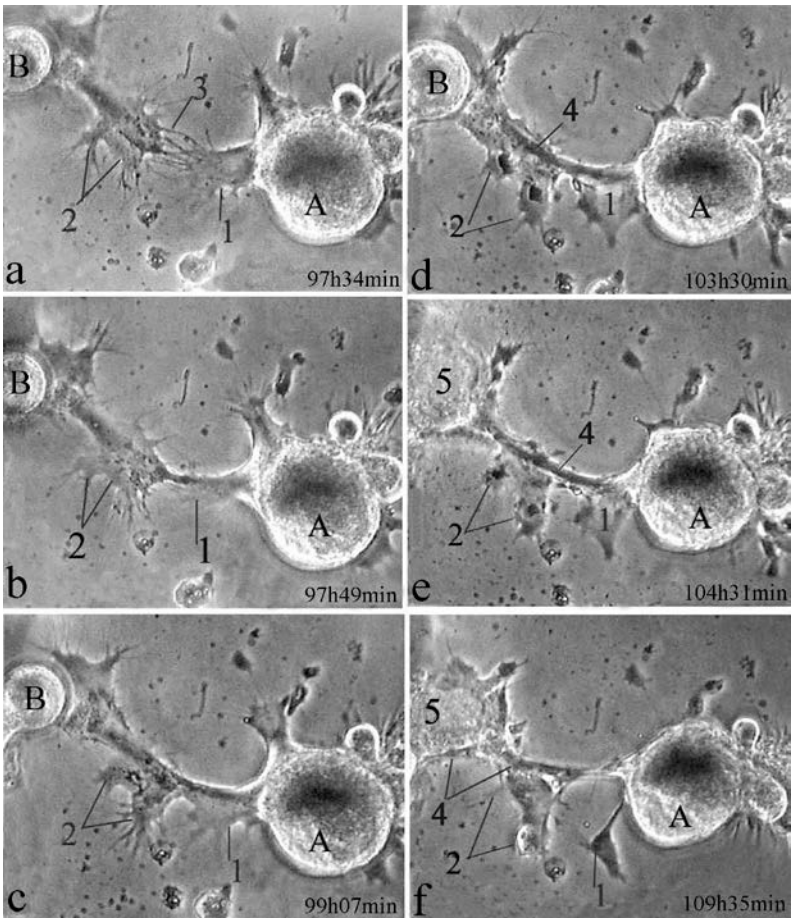

Fig. 2. Dynamics of formation of syncytial connection between neuronal processes of mollusc *Lymnaea stagnalis* in tissue culture.

a–e – stages of formation syncytium (time – from beginning of cultivation); A, B – neurons forming syncytium; 1 – process of neuron A; 2 – lamellar process of neuron B; 3 – connected filopodia of growth cones of cells A and B before fusion of their lamellar processes; 4 – the single formed cytoskeletal structure penetrating into lamellopodia of both cells; 5 – dead neuron. Supravital microscopy. Phase contrast. Obj. 40Ph, eyep. 10.

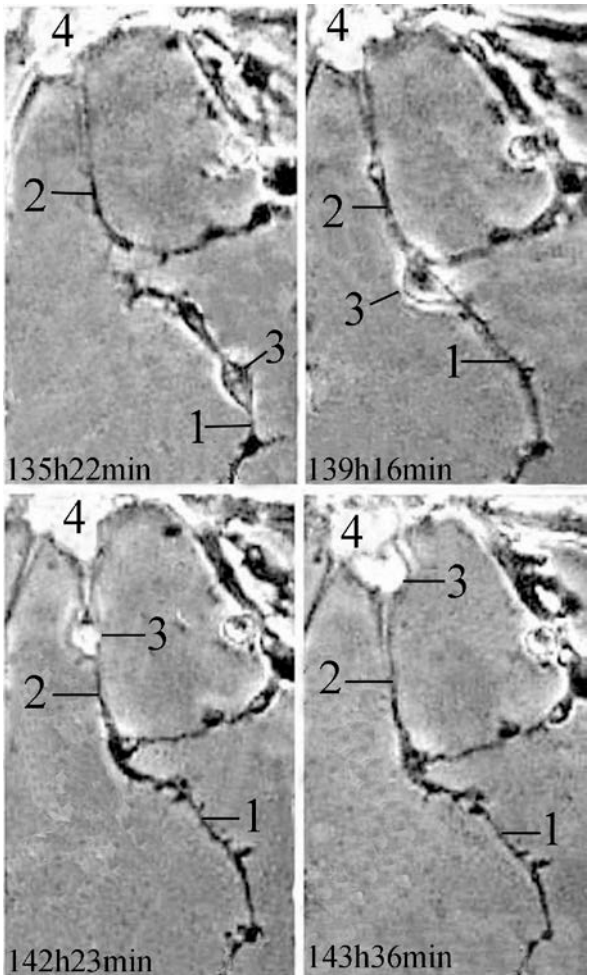

Fig. 3. Formation of syncytial connection between processes of two cells and translocation of cytoplasmic varicosity from one process to the other molluscs.
1 – process of the lower cell; 2 – process of the upper cell; 3 – varicosity translocated via the place of fusion of two processes; 4 – body of the upper cell. Tissue culture, computer time-lapse videoshooting. Time – from beginning of cultivation. Obj. 40Ph, eyep. 10.

In a formed plexus of tubular nerve processes in Fig. *3* it is shown that growing axon *1* makes contact with process *2* of another cell. Furthermore, in the microcimetography, the movement of varicosity cytoplasm *3* of process *1* into process *2* of cell *4* is observed (Fig. *3*) that confirms the creation of a syncytial connection between different cells with their processes' fusion. Whereby, the cytoplasmic varicosity *3* of process *1* slowly moves toward the combining point of processes *1* and *2* (Fig. *3*) in the course of 6 hours and 14 minutes and, overcoming it (Fig. *3, d*), flows from process *1* into process *2*. Then, this varicosity arrives at cell *4* (Fig. *3, e*) and is fused with it (Fig. *3*). The movement of the cytoplasmic varicosity from the process of one neuron into the process of another neuron is most likely only possible in the event of a syncytial connection of their neuroplasma. Such cytoplasmic varicosities' behavior, in our opinion, can be considered another criterion formed of a cytoplasmic syncytial connection of neurons *(Movements of local cytoplasmical thickenings along a fiber were observed in situ by P.A. Weiss (1969) and O.S. Sotnikov (2015); they associated this movement with neuroplasma flow).*

To provide strong evidence of the possibility of a syncytial connection between living neurons in a mollusc's tissue culture, it is necessary to obtain data not only in vitro, but studies must also be performed on syncytium possibility in the nervous system of other species of healthy invertebrates under natural conditions in situ. Meanwhile, it should be kept in mind that a syncytium in non-neuronal cells is created by perforation of membrane connections along with tight and gap junctions in the nervous system usually appear in early postnatal ontogenesis.

Observation of the effect of microvilli fusion and neuroid cell pseudopodia isolated from Gasser's ganglion neurinoma by G.P. Polyakova, N.V. Chudinovskaya, and L.I. Kondakova et al. (1983) has revealed membrane fusion in the form of tight junctions and gap junctions as the first stage of syncytium creation where the disorganization and destruction of membranes takes place. In other words, the tight junctions could be considered as one of the stages, the metastable structure according to Chizmadzhev Y.A., Pastushenko V.F. (1989) on how syncytium is formed. L. Cronier, J.C. Herve, S. Deleze et al. (1997) revealed that a gap junction's creation is always followed by trophoblast cell fusion in vitro. It is also shown in other cells (Zelenin, Kusch, Prudovsky, 1982; Zelenin, Bandrina, 1984), including neural cells (Ringerts, Savage, 1979). On the basis of numerous experimental data, a hypothesis was established of the membrane's fusion mechanism similarity during syncytium and membrane junction formation (Harris, Watkins, 1965)**.** The external cell membrane and cell membrane organelle fusion mechanism is presented in detail in many reviews (Orlov, Samosudova, Shungskaia, 1989; Mozhenok, Bulychev, Brown, 1990). As is already known, membrane fusion and syncytium creation is universal and is now already a well-studied cellular process. It is typical for many normally functioning non-neuronal cells. Also it appers in the event of pathology **(**Barski, Soricul, Cornefert, 1960; Mozhenok, Bulychev, Brown, 1990), during fertilization and in embryogenesis, while muscle fibres are being created (Nenashev, 1984; Orlov, Samosudova, Shungskaia, 1989; Shungskaia, Samosudova, Larin, 1988), when hybrid cells are artificially obtained (Zimmerman, Stopper, 1987), during the process of a tumour or the creation of giant multinuclear cells (symplasts), while substances are being transported by endocytosis, and during a mediator reuptake (Okada, Muragama, 1965; Tetzlaff, 1982). Constant fusion and movement are typical for the membranes of an endoplasmic reticulum (Zelenin, Bandrina, 1984), liposomes, and other organelles.

During membranes' fusion in the exocytosis of neuromediators and neurohormones, the same mechanisms of vesicle and neuron fusion along with their subsequent perforation takes place (Klein, 2005). Proteins SNARE, SNAP-25, and others controlling membranes' fusion are being studied during neuroexocytosis (Lu, Zhang, Menew et al., 2005; Flassoni, Jukerardi, Coco et al., 2005; Sorensen, 2005). The question is being discussed on whether a syncytial neuron connection required for a measles virus to be distributed between neurons or whether a membrane junction is sufficient (Card, Rinaman, Schwaber et al., 1990; Lawrence, Patterson, Gales et al., 2000). We first demonstrated that myelinisation is the process of the subsequent fusion of membrane parts of a Schwann cell to form their connections and their further combination into a giant junction (Sotnikov, 2008).

Since interneuronal avesicular junctions are common in the embryogenesis and postnatal ontogenesis of the nervous system during neurulation, regional differentiation, and migration

(Bogolepov, Yakovleva, Frumkina et al., 1986; Fulton, 1995), one can anticipate the appearance of syncytium signs during that time as well. As noted by A. Peters and M. Feldman (1973), in the 19-21-day embryons of ordinary rats there are often profiles of neural processes filled with vacuoles in the developing cortex. These axons feature partial neurolemma damage. As shown inside them in Fig. 19, such processes have often destroyed the membrane in the area of both contacting processes. Authors do not note that, but based on their preparations in the neuropile of growing dendrites, there are also syncytially bound, most likely dying, axons. The specified facts support the high potential of cells and many cell membrane structures to fuse. Undoubtedly, it is a common process in biology and it would be strange if it were absent from the nervous system.

In order to make the presence of a interneuronal syncytial cytoplasmic connection more convincing, we succeeded to target analyse preparations of osphradium for several species of molluscs using electronic microscopy (Sotnikov, Paramonova, Archakova, 2009). As an example, the osphradia were studied of Cryptonatica clausa, Viviparus sp., and Murex saxatilis. The isolated mollusc osphradia were fixed in 2.5% glutaric dialdehyde with a phosphate buffer of 0.1 mol/l, pH 7.3. After washing it out in a phosphate buffer of 0.1 mol/l, postfixation was performed in a 1.3% OsO_4 solution with a phosphate buffer of 0.1 mol/l, pH 7.4 in the course of 1 h. Then, the material was washed out again in a phosphate buffer of 0.1 mol/l, dried in ethanol, and filled with araldite (Sigma). Serial slices were stained by an uranyl acetate alcohol solution along with lead citrate by Reynolds.

The general structural basis of the mollusc's osphradium's integrative processes is of considerable interest. We studied interneuronal relations in an osphradium ganglion neuropile, in an osphradium axis, in a petalled nerve, in an osphradium nerve, and osphradium receptor cells. Typical axon-dendrite and axon-axon synapses, and peculiar axospiny synapses were revealed no different from similar vertebrate structures. Also, avesicular membrane junctions like a tight junction and gap junction were revealed as well (Kamardin, Nozdrachev, 2004; Sotnikov, Kamardin, Rybakova et al., 2009).

It was noted that in a ganglia, a nerve, a neuropile, and in the peripherical processes area of sensor cells there is no complete glial cover for single nerve processes and membranes of neighbour profiles are in close proximity (at a distance of about 20 nm). However, often in the area of neighbour structures, junctions appear accompanied by membrane fusion with the intercellular gap disappearng between them. The thickness of a pair of contacting membranes reduces almost by half. Such apposed axon profiles are dumbbell and eight-shaped (Fig. *4, a*). If the contacting membranes area is extended, the dumbbell form approximates to an "O" shape (Fig. *4, b*). Membranes of contacting profiles usually feature an inconstant and unusual structure: they lose contrast (Fig. *4, b*), thin (Fig. *4, a*), or, while blurring, invaginate into one of the profiles (Fig. *4, c*).

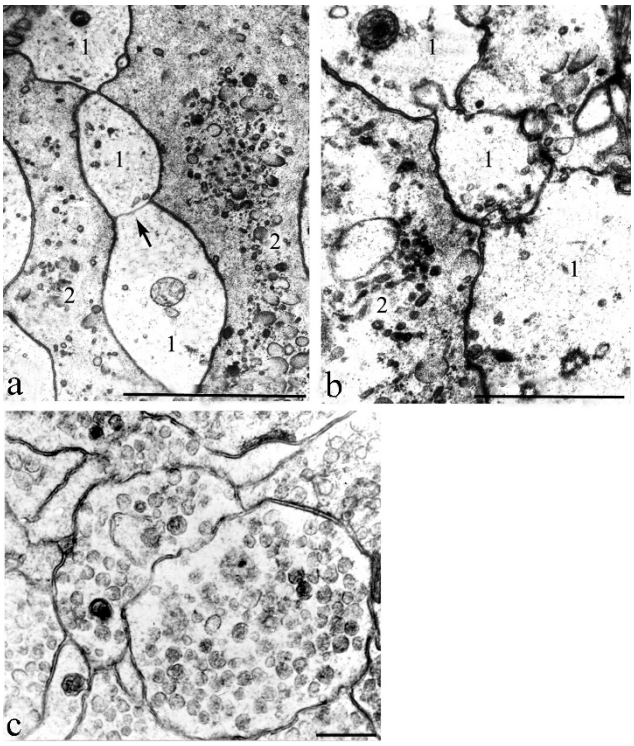

Fig. 4. Change of membranes in the area of contacts of neurites osfradium of molluscs. a – thinning of fused membranes of peripheral processes of receptor cells in the mollusc *Cryptonatica clausa* osphradia; b – the undulating surface of contacting presynapse membranes in neuropil of the osphradial ganglion Viviparus sp; c – loss of contrast and mutual invaginations of contact membranes of two adjacent receptor cells in the mollusc *Murex saxatilis* osphradia. Conversion of the 8-shaped into the O-shaped profiles; 1 – peripheral process of receptor cell; 2 – supporting cell; *asterisk* – thinning of fused membranes. Scale bar: a, c – 1 μm; b – 0.5 μm.

All of this provides evidence for the "metastable" state (under Chizmadzhev, Scherbakov, Cohen et al., 1995) of membranes in junction areas. In any case, in our preparations in the junction area of neighbour processes, their perforations, or even large cytoplasmic syncytial anastomoses, are often observed (Fig. *5*) up to the completion of the fusion of the processes (Fig. *5, d, e*). In the area of the osphradium axis in one preparation, we could reveal a group of syncytially bound dendrite profiles (Fig. *5, e*). And in this complex of associated dendrites, all stages of the syncytial connection's creation are observed from the membrane fusion's loosing contrast (two medium dendrites), prior perforation of fused contact membranes (two lower dendrites), and complete fusion of the processes (two upper dendrites).

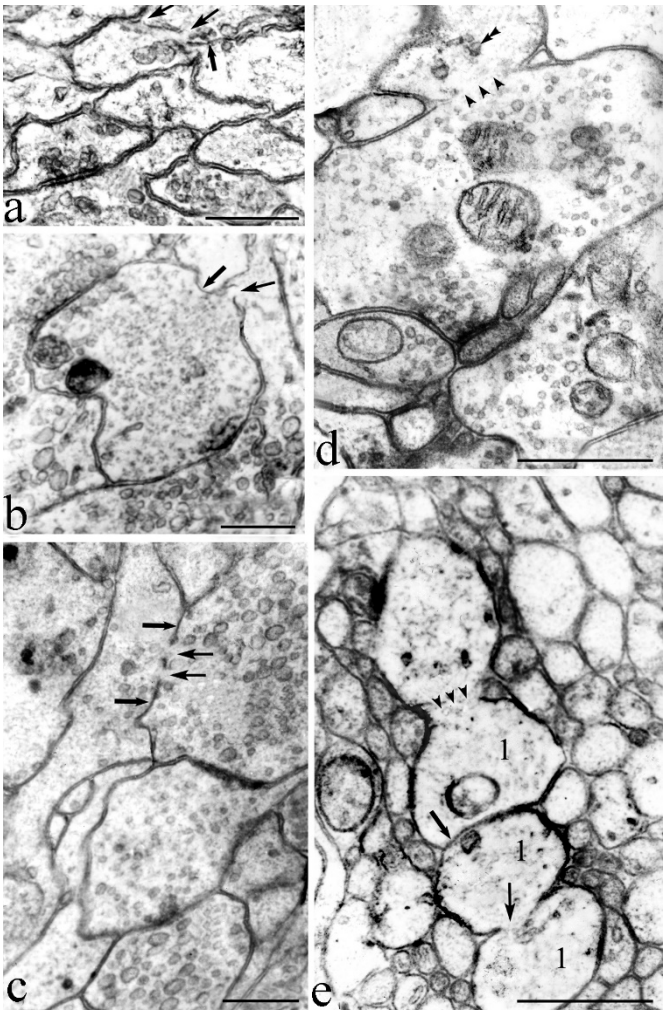

Fig. 5. Perforations of contact membranes (a–c) and extensive syncytial connection (d, e) of neurites molluscs.

a – perforation of contact of two processes and residual structures of perforated membranes in the pearl oyster osphradial nerve; b – perforation of contact membranes of nerve profiles in neuropil of the osphradial ganglion of Viviparus sp.; c – perforation of contact membranes between axons and residual membrane structures in the central area of the *Murex saxatilis* osphradial axis; d – fusion of two nerve profiles and residual structures in the nerve of the *Murex saxatilis* petal; e – fusion and perforation of contact membranes, of dendrite profiles (1) of the central area of the *Murex saxatilis* osphradial axis. *Thick arrow* – thinning of fused membranes; *thin arrow* – perforations of membrane contacts; *double arrow* – residual membrane structures in the area of perforation; *arrowhead* – boundary of fusion of syncytially connected profiles. Scale bar: a – 0.5 μm; b. d – 1 μm; c – 0.6 μm; e – 0.4 μm.

Therefore, the results of the studies in vivo and the electronic microscopy studies of normal mollusc neurons of several species ascertain the ability of neuron membranes to fuse creating perforations and an extensive cytoplasmic syncytial connection not distinguishing them from the cells of all other histological types.

The fact emerges that membranes' fusion and their perforations appear under two conditions: the absence of a glial sheath and the presence of tight and gap junction type intermembrane junctions *(At transmission microscopy these two different structures often look similar)*. As noted

above, the syncytially bound nerve fibres of an osphradium often have no glia and we studied neurons with intentionally removed glia in the tissue culture.

Therefore, we can presume that glia prevents the creation of syncytial connections in the nervous system. It appears exactly to explain the absence of the syncytial connection in the most regions of the nervous system of adult vertebrates. As known, invertebrates have low neuron process coverage with glia. Thus, their syncytial connections evidently were not incidental findings. As A.A. Zavarzin (1941) noted, the concepts of interneuronal syncytium have long since remained in the neurobiology of invertebrates and as shown by the data provided, it has expectedly existed until the present time. In literature there are actually many experimental factors accounting for the possibility of nerve processes and the fusion of neuron bodies.

For the time being, it is premature to speak in detail about the functional role of syncytial connections in the nervous system. However, we can make the following preliminary assumptions. Since, according to the data of certain authors, electro-permeable membrane junctions are historically older than chemical synapse junctions (Shapovalov, Shiryaev, 1987; Shapovalov, 1997) and syncytial perforations in all cells are created specifically on the basis of electrically permeable junctions by membrane fusion (Nenashev, 1984), then we can presume that the syncytial cytoplasmic connection is one of the oldest mechanisms of cell communication in the nervous system. Even in the imaginal disc of invertebrates: insects, nemertines, echinoderms, the progenitor cells of all cells, and neuroblasts, there are numerous large intercellular perforations. An assumption was even made that all cells of imaginal discs are bound syncytially and constitute an integral membrane system.

Despite its primitiveness, the connection has all the abilities of a interneuronal connection via electrical couplings (Kusano, Grundfest, 1965) and even includes some advantages. For example, in the presence of certain syncytial connections between giant multineuronal axons creating a cyclic connection, the local trauma of one of them will not cause death or blockade of the nervous system (Nicol, 1948). This phenomenon could be considered as an important adaptation and such frequent identification of syncytial anastomoses in invertebrates nervous system as the third natural mode of interneuronal communication.

Therefor, on the basis of the analysed materials, we can confidently affirm that invertebrates have a syncytial cytoplasmic connection and it plays a significant role in these animals' life activities. It would be strange and oppose all principles of evolutionary biology to argue that such a type of interneuronal connection is typical and important only for invertebrates, while in vertebrates not observed at all.

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