Chapter 2
Evolutionary Considerations of Neurotransmitters in Microbial, Plant, and Animal Cells

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2.1 Introduction

The "living" environment of a human includes microorganisms, plants, and animals as well as other human beings. The Relationship between them occurs via what is known as irritation events. The mechanism of irritability appears to have a common base in the form of chemical signals, chemicals which are uniform for every cell. Similar compounds likely to be found in living organisms include acetylcholine, dopamine, norepinephrine, epinephrine, serotonin, and histamine, collectively known as neurotransmitters, and have been found not only in animals (Boron and Boulpaep 2005), but also in plants (Roshchina 1991, 2001a; Murch 2006) and microorganisms (Hsu et al. 1986; Strakhovskaya et al. 1991; Lyte 1992; Oleskin et al. 1998a, b; Tsavkelova et al. 2006; Freestone and Lyte 2008). Thus, the presence of neurotransmitter compounds has been shown in organisms lacking a nervous system and even in unicellular organisms (Roshchina 1991, 2001a). Today, we have more and more evidence that neurotransmitters, which participate in synaptic neurotransmission, are multifunctional substances participating in developmental processes of microorganisms, plants, and animals. Moreover, their universal roles as signal and regulatory compounds are supported by studies that examine their role in and across biological kingdoms (Roshchina 1991, 2001a; Baluska et al. 2005, 2006a, b; Brenner et al. 2006). Any organism may release neurotransmitters, and due to these secretions (Roshchina and Roshchina 1993) the "living environment" influences every other inhabitant of biocenosis, determining relationships between organisms such as microorganism–microorganism, microorganism–plant, microorganism–animal, plant–animal, plant–plant, and animal–animal.

The universal character of their occurrence and similarity of functions at the cellular level should convince scientists to have doubt in the specific name "neurotransmitters" and exchange it, perhaps, for a more wider term such as "biomediators"

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to make it applicable to any living cell, not only organisms with nervous systems (Roshchina 1991, 2001a). The bioremediator concept permits us to imagine the evolutionary picture, where the neurotransmitter substances were participators of many different cellular processes, including non-synaptic systems of microorganisms and plants.

Non-nervous functions of the neurotransmitters (rather "biomediators" at the cellular level) are analyzed in this chapter, and their respective roles in the different evolutionary kingdoms are compared. This information gathered from species ranging from microorganisms to plants and animals may provide an insight into key problems in cellular endocrinology, and thereby has implications for understanding both health and disease causation. Such analysis can also undoubtedly provide useful perspectives to help guide the further development of the field of microbial endocrinology too.

2.2 Occurrence of Neurotransmitters in Living Organisms

2.2.1 Discoveries

Historical chronologies of the neurotransmitters' discoveries are represented in Table 2.1. The first neurotransmitters were the catecholamines found by the American scientist John Jacob Abel at the end of the nineteenth century in extracts from animal adrenal glands. During the years 1906–1914, the existence of neurotransmitter compounds were identified not only in animals, but also in fungal extracts which were used as medicinal preparations. The twentieth century was the epoch for the discovery of neurotransmitters, mainly by pharmacologists and animal physiologists related to medicine. The roles of the catecholamine compounds in plants and microorganisms became a subject of interest only after 50–70 years of the twentieth century. Pioneering studies included the investigations of Jaffe, Fluck, Riov, Stephenson, Rowatt, Girvin, and Marquardt (see references in monograph of Roshchina 2001a for more detail).

As can be seen from Table 2.2, the concentration range of the neurotransmitter compounds is similar for all three kingdoms of living organisms, although some organs and specialized cells of multicellular organisms may be enriched in these compounds. Over 40 years ago, Soviet physiologist Koshtoyantz (1963) presented a hypothesis that the neurotransmitters are peculiar to all animal cells independently of their position on the evolutionary tree; this view has been confirmed experimentally, and described in several monographs (Buznikov 1967, 1987, 1990) and review (Buznikov et al. 1996). The presence of the neurotransmitters in animals has now been confirmed for all taxa – from Protozoa to Mammalia. As for bacterial cells, no more than 10–12 species have so far been characterized as containing acetylcholine, catecholamines, and serotonin, although histamine has been found in most species of prokaryotes. The issue of mammalian-type hormones in microorganisms has also been considered (Lenard 1992).

Table 2.1 Discovery of neurotransmitters

Neurotransmitter	In microorganisms	In plants	In animals
Acetylcholine	Identified independently by Ewins and Dale (1914) in preparations of ergot spur fungus *Claviceps purpurea* in Great Britain and in bacteria *Pseudomonas fluorescens* (Chet et al. 1973)	In 1947 Emmelin and Feldberg found this substance in stinging trichomes and leaves of common nettle by biological method, based on muscle contraction	In 1921–1926 the presence of acetylcholine has been established in animals by Loewi and Navratil. But earlier, in 1906 student Reid Hunt (worked in USA laboratory of John J. Abel) discovered it in adrenal extracts of animals
Dopamine	Found in infusoria *Tetrahymena pyriformis* by Gundersen and Thompson (1985). Identified in bacterial and fungal microorganisms by Tsavkelova et al. (2000)	In 1944, found in *Hermidium alipes* by Buelow and Gisvold	Discovered in 1950–1952 by pharmacologists Arvid Carlsson, Nils-Åke Hillarp and von Euler in Sweeden
Norepinephrine (noradrenaline)	Identified in microorganisms by Tsavkelova et al. (2000)	In 1956–1958 found in banana fruits in Sweden laboratories organized by Waalkes and Udenfriend	Isolated from adrenal gland extracts of animals in 1897–1898 by John J. Abel
Epinephrine (adrenaline)		In 1972 found in leaves of banana *Musa* by Askar et al. (1972)	Isolated from adrenal gland extracts of animals in 1895 by Polish physiologist Napoleon Cybulski and in 1897 by American John J. Abel
Serotonin	Found in 1986 by Hsu with co-workers in many bacteria	Found in banana fruits (*Musa*) by Bowden et al. (1954)	Discovered by Erspamer in 1940 and Rapport et al. in 1948
Histamine	Found in ergot fungi *Claviceps purpurea* in 1910 by Barger, Dale and Kutscher	Observed in higher plants by Werle and Raub in 1948	In 1919 American John Jacob Abel isolated histamine from pituitary extract of animals

Sources: (Kruk and Pycock 1990; Roshchina 1991, 2001a; Kuklin and Conger 1995; Oleskin 2007; Kulma and Szopa 2007)

Table 2.2 Level of neurotransmitters in living organisms

	In microorganisms	In plants	In animals
Neurotransmitter	μg/g of fresh mass or * μmol/L or ** μg/billion of cells	μg/g of fresh mass	μg/g of fresh mass or * nM/L or ** nm/day
Acetylcholine	3.0–6.6	0.1–547	0.326–65200 (0.15–0.2 in brain)
Dopamine	0.45–2.13*	1–4000	<0.888*1214–2425**
Norepinephrine (noradrenaline)	0.21–1.87*	0.1–6,760	0.615–3.23*20–240**
Epinephrine (adrenaline)	No data	0.22–3833	1.9–2.46*30–80**
Serotonin	0.11–50,000**	0.0017–4000	0.21–0.96
Histamine	0.01–3.75	1 (1.34 – pain reaction for human)	0.5–100

Sources: (Fernstrom and Wurtman 1971; Kruk and Pycock 1990; Hsu et al. 1986; Roshchina 1991, 2001a; Oleskin et al. 1998a, b; Tsavkelova et al. 2000)

2.2.1.1 Acetylcholine

In animals, acetylcholine and/or the synthesizing enzyme choline acetyltransferase have been demonstrated in epithelial (airways, alimentary tract, urogenital tract, epidermis), mesothelial (pleura, pericardium), endothelial, muscle and immune cells, mainly in granulocytes, lymphocytes, macrophages, and mast cells (Wessler et al. 2001). Acetylcholine has also been found in Protozoa (Janakidevi et al. 1966a, b). Corrado et al. (2001) showed the synthesis of the molecular acetylcholine during the developmental cycle of *Paramecium primaurelia*. This neurotransmitter has a negative modulating effect on cellular conjugation. But in these unicellular organisms, the presence of functionally related nicotinic and muscarinic receptors and a lytic enzyme acetylcholinesterase has been established. Moreover, the authors could demonstrate (using immunocytochemical and histochemical methods) that the activity of enzyme choline acetyltransferase, which catalyzed acetylcholine synthesis, was located on the surface membrane of mating-competent cells and of mature, but not nonmating-competent *P. primaurelia* cells.

Acetylcholine has been well identified as a component of bacteria (its production was discovered in a strain of *Lactobacillus plantarum*) (Stephenson and Rowatt 1947; Rowatt 1948; Girvin and Stevenson 1954; Marquardt and Falk 1957; Marquardt and Spitznagel 1959). Cell free enzyme(s) participating in the acetylcholine synthesis were also first found in *L. plantarum* (Girvin and Stevenson 1954).

In the plant kingdom, acetylcholine is found in 65 species from 33 different families (Roshchina 1991, 2001a; Wessler et al. 2001; Murch 2006). Acetycholine was synthesized not only free, but also in a conjugated form as well, in particular

as conjugates of cholinic esters with plant auxins (Fluck et al. 2000). Acetylcholine is particularly abundant in secretory cells of common nettle stinging hairs, where its concentration reaches 10^{-1} M or 120–180 nmol/g of fresh mass. Together with the histamine contained in the secretion, acetylcholine may provoke a pain response and formation of blisters when the plant comes in contact with human skin.

Kawashima et al. (2007) have attempted to compare the concentration of the neurotransmitter acetylcholine in a wide variety of sources using the same experimental conditions, which involved a radioimmunoassay with high specificity and sensitivity (1 pg/tube). The authors measured the acetylcholine content in samples from the bacteria, archaea, and eucarya domains of the universal phylogenetic tree. The authors compared the concentrations in different groups of bacteria (*Bacillus subtilis*), archaea (*Thermococcus kodakaraensis* KOD1), fungi (shiitake mushroom and yeast), plants (bamboo shoot and fern), and animals (e.g., bloodworm and lugworm). The levels varied considerably, however, with the highest acetylcholine content detected in the top portion of bamboo shoot (2.9 µmol/g), which contained about 80 times of that found in rat brain. Various levels of acetylcholine-synthesizing activity were also detected in extracts from the cells tested, which contained a choline acetyltransferase-like enzyme (sensitive to bromoacetylcholine, a selective inhibitor of choline acetyltransferase). The enzyme activity was found in *T. kodakaraensis* KOD1 (15%), bamboo shoot (91%), shiitake mushroom (51%), bloodworm (91%), and lugworm (81%). Taken together, these findings demonstrate the ubiquitous expression of acetylcholine and acetylcholine-synthesizing activities among life forms without nervous systems, and support the notion that acetylcholine has been expressed and may be active as a local mediator and modulator of physiological functions since the early beginning of life.

2.2.1.2 Catecholamines

In unicellular organisms, biogenic amines are also synthesized. The large amounts of dopamine accumulated by cells of infusoria *Tetrahymena pyriformis* strain NT-1 and secreted into their growth medium were found to depend primarily upon an extracellular, non-enzymatic conversion of tyrosine to L-dihydroxyphenylalanine (Gundersen and Thompson 1985). Recently, the catecholamines norepinephrine and dopamine have been identified in microorganisms by high-performance liquid chromatography by Tsavkelova et al. (2000). Dopamine in concentrations 0.45–2.13 µmol/L was found in the biomass of bacteria *Bacillus cereus*, *B. mycoides*, *B. subtilis*, *Proteus vulgaris*, *Serratia marcescens*, *S. aureus*, and *E. coli*, but was absent in the fungi *Saccharomyces cerevisiae*, *Penicillum chrysogenum*, and *Zoogloea ramigera*. Norepinephrine was found (0.21–1.87 µmol/L) in the bacteria *B. mycoides*, *B. subtilis*, *P. vulgaris*, and *S. marcescens* as well as in fungi such as *S. cerevisiae* (0.21 µmol/L) and *P. chrysogenum* (21.1 µmol/L). It is especially interesting that in many cases, the content of catecholamines in microorganisms is higher than in animals, for example in human, blood norepinephrine is found about

0.04 μmol/L (Kruk and Pycock 1990). Moreover, it was demonstrated that bacteria, in particular *B. subtilis*, may release norepinephrine and dopamine out of the cell and, perhaps, by this way possibly participate in intercellular communication both in microorganism–microorganism and bacteria–host.

In plants, catecholamines have been found in 28 species of 18 plant families (Roshchina 1991, 2001a; Kuklin and Conger 1995; Kulma and Szopa 2007). The amount of dopamine found varies during plant development (Kamo and Mahlberg 1984), and sharply increases during stress (Swiedrych et al. 2004). Of particular note is the finding that increased amounts of dopamine (1–4 mg/g fresh mass) are found in flowers and fruits, in particular in Araceae species (Ponchet et al. 1982). This demonstrates the important role of the catecholamines as neurotransmitters in fertilization as well as in fruit and seed development.

2.2.1.3 Serotonin

Some microorganisms living within parasitic nematodes are also able to synthesize serotonin (Hsu et al. 1986). In the bacterial flora of the ascarid *Ascaris suum*, mainly facultative anaerobes (17 species) produced and excreted serotonin into the culture medium of up to 14.32–500.00 μg/g of fresh mass for *Corynebacterium* sp. (in the tissues of the helminth itself only 0.25 μg serotonin per g fresh mass). The concentration of serotonin, in terms of μg serotonin/10^9 cells for different cultures of microorganisms isolated from helminths is as follows: *Klebsiella pneumoniae* 8.15, *Aeromonas* 26.71, *Citrobacter* 0.58, *Corynebacterium sp.* 14.32–500.00, *Enterobacteria aggiomerans* 2.93, *Shigella* 1.04, *Achromobacter xylosoxidans* 1.66, *Chromobacterium* 3.67, *Achromobacter* 0.15, *Acinetobacter* 11.79, *Streptococcus* 37.52, *Listeria monocytogens* 4.71, and *E. coli* 3.33. Serotonin has also been found in the yeast *Candida guillermondii* and bacterium *Enterococcus faecalis* (Fraikin et al. 1989; Belenikina et al. 1991; Strakhovskaya et al. 1991, 1993). In 1998, Oleskin et al. also established the presence of serotonin in the phototrophic bacterium *Rhodospirillum rubrum* (1 μg/billion of cells ~3–12,500 μg/g of fresh mass) as well as in nonphototrophic bacteria *Streptococcus faecalis* and *E. coli* (50 and 3.3 μg/billion of cells, relatively). The inhibitor of tryptophan hydroxylase, *n*-chlorophenylalanine, affects the growth of the yeast *Candida guillermondii*, but not the development of the bacterium *E. coli*. This suggests that in the latter case, there is an alternative pathway to that found in animals (Oleskin et al. 1998a, b), which is peculiar (Roshchina 1991, 2001a) to plants: tryptophan ⇒ tryptamine ⇒ serotonin.

In plants, serotonin is found in 42 species of 20 plant families (Roshchina 1991, 2001a). Besides free serotonin, conjugated serotonins such as *N*-feruloylserotonin, *N*-(*p*-coumaroyl) serotonin, *N*-(*p*-coumaroyl) serotonin mono-β-D-glucopyranoside have been isolated from safflower *Carthamus tinctorius* L. seed. It should be noted that serotonin in animals (such as rats) may exist in complexes with heparin that prevents the aggregation of thrombocytes (Kondashevskaya et al. 1996).

2.2.1.4 Histamine

Histamine was first found in the ergot fungus *Claviceps purpurea* (Table 2.1), and subsequently in many bacterial and plant cells by Werle and coauthors (1948, 1949). Since then, it has also been observed in many types of foods as the result of microbial activity. Histamine is one of the biogenic amines formed mainly by microbial decarboxylation of amino acids in numerous foods, including fish, cheese, wine, and fermented products. A number of microorganisms can produce histamine. In particular, bacteria such as *Morganella morganii*, *Proteus* sp, and *Klebsiella* sp. are considered strong histamine formers in fish (Ekici and Coskun 2002; Ekici et al. 2006). Fernández et al. (2006) summarized the data on the histamine content as toxicant in food. Histamine poisoning is the most common food borne problem caused by biogenic amines. At non-toxic doses, this histamine can cause intolerance symptoms such as diarrhea, hypotension, headache, pruritus, and flushes. Just 75 mg of histamine, a quantity commonly present in normal meals, can induce symptoms in the majority. One separate problem concerns the histamine formed by microorganisms in animal pathogenesis. Gram-negative bacterial species such as *Branhamella catarrhalis*, *Haemophilus parainfluenzae*, and *Pseudomonas aeruginosa* have been demonstrated to synthesize clinically relevant amounts of histamine in vitro that implicate the bacterial production of histamine in situ as an additional damage factor in acute exacerbations of chronic bronchitis, cystic fibrosis, and pneumonia. Histamine may also increase the virulence of these bacterial species, unlike some Gram-positive species such as *Staphylococcus aureus* and *Streptococcus pneumoniae* (Devalia et al. 1989). Among "non-pathogenic" species, only the *Enterobacteriacae*, as a group, were found to form histamine in significant concentrations.

Significant amounts of histamine have also been observed in higher plants, initially by Werle and Raub in 1948, and subsequently described for 49 plant species belonging to 28 families ranging from basidiomycetes to angiosperms (Roshchina 1991, 2001a). Besides histamine itself, its derivatives *N*-acetylhistamine, *N*, *N*-dimethylhistamine, and feruloylhistamine are also found in plants. Especially high levels are observed in species of the family Urticaceae that could be one of the taxonomic classification signs. The Brazilian stinging shrub *Jatropha urens* (family Euphorbiaceae) contains 1,250 μg histamine per 1,000 hairs. The presence of histamine in stinging hairs is a protective mechanism that serves order to frighten off predatory animals by inducing burns, pain, and allergic reactions. Under stress conditions, a sharp increase of histamine is observed in plants, as in animals. Ekici and Coskun (2002) have determined the histamine content of some commercial vegetable pickles at the range of 16.54 and 74.91 mg/kg (average 30.73 mg/kg). The maximum value (74.91 mg/kg) was obtained from a sample of hot pepper pickles. The amount of histamine varies according to the phase of plant development. For example, in the marine red algae *Furcellaria lumbricalis* (Huds.) Lamour, the occurrence of histamine was from 60 to 500 μg/g fresh mass observed in both non-fertile fronds and sexual-expressed parts, in all regions of the thallus of male, female, and tetrasporophyte (Barwell 1979, 1989). The amount of histamine

(in μg/g fresh mass) in the male plant was 90–490 (sometimes up to 1,100), in the female plant 60–120, and in asexual tetra sporophyte 100–500. Especially enriched were the neurotransmitter cells of male plants, as the ramuli were approximately five times higher in histamine than female and asexual plants.

2.2.2 Neurotransmitters as Toxicants

High concentrations of biogenic amines in foodstuffs and beverages can induce a range of toxicological effects (Fernández et al. 2006). Significant attention is needed to control the histamine levels in foods (Bodmer et al. 1999). Histamine poisoning is the most common food borne problem. Besides the compounds naturally found in vegetables and fruits as well as those formed as a result in the result of fermentation of cheese, wine, and sauerkraut, biogenic amines also play an essential role in the metabolism of the histamine-forming bacteria present in foods (Kung et al. 2007). Flushing of the face and neck are symptoms of histamine intoxication, followed by an intense, throbbing headache. Other symptoms include dizziness, itching, faintness, burning of the mouth and throat, and the inability to swallow. Taylor et al. (1978) reported that ingestion of 70–1,000 mg of histamine in a single meal is necessary to elicit any symptoms of toxicity. A level of histamine exceeding 10 mg/100 g of fresh weight is associated with poor product quality indicative of microbial spoilage, with levels of 200 mg histamine per kg of food product accepted as a toxic indicator for fish, and 10 mg/kg for wines, whereas for hot pepper pickles all values are below the level of 1,000 mg/kg. An average food content for histamine of approximately 30 mg/kg can be considered the minimal level for clinical symptoms of toxicity (Ekici and Coskun 2002). These toxicological problems are particularly severe in individuals who, for whatever reason, are deficient in diamine oxidase, the histamine-degrading enzyme. At non-toxic doses, histamine can cause intolerance symptoms such as diarrhea, hypotension, headache, pruritus, and flushes. Just 75 mg of histamine, a quantity commonly present in normal meals, can induce symptoms in the majority of healthy persons with no history of histamine intolerance.

The amount of neurotransmitters in cellular secretions can be increased following unfavorable stimuli, in particular the interactions with other organisms. Large amounts of dopamine are usually secreted by cells of infusoria *Tetrahymena pyriformis* into their growth medium (Gundersen and Thompson 1985). This release of dopamine is especially important during infection, when the animal or plant accumulates some of the neurotransmitters, from one side, and pathogens release neurotransmitters from another side (Romanovskaya and Popenenkova 1971). On northeastern Pacific coasts, the alga *Ulvaria obscura* produces large amounts of dopamine (van Alstyne et al. 2006). This organism, dominant in subtidal "green tide" blooms due to this antiherbivore defense, can be harmful to marine communities, fisheries, and aquaculture facilities because the alga presence is the cause of reduced feeding by echinoderms, mollusks, and arthropods.

Dopamine constituted an average of 4.4% of the alga's dry mass, and was responsible for the decreased feeding by sea urchins (*Strongylocentrotus droebachiensis*). Subsequent experiments demonstrated that dopamine also reduced the feeding rates of snails (*Littorina sitkana*) and isopods (*Idotea wosnesenskii*). This is the first experimental demonstration of a plant (algal) catecholamine functioning as a feeding deterrent.

2.2.3 Components of Cholinergic and Aminergic Systems

In microbial cells, components of cholinergic and aminergic systems similar to those found in mammalian cells, including the complete biosynthetic pathway required for their synthesis (relative synthetases) and their catabolism (cholinesterases, aminooxidases, and others), as well as functional analogs of cholino- and aminoreceptors are shown to be present.

2.2.3.1 Choline Acetyltransferase

The enzymes choline acetyltransferases or choline acetylases (EC 2.3.1.6) participate in the synthesis of acetylcholine from choline and acetic acid (Nachmansohn and Machado 1943). A cell free enzyme with "choline acetylase" activity was present in *Lactobacillus plantarum* (Girvin and Stevenson 1954). This enzyme activity has been also found in many plant species (Roshchina 1991, 2001a).

2.2.3.2 Cholinesterase

Enzymes which degrade acetylcholine to choline and acetic acid are named cholinesterases and were first found in 1937 by Loewi in the hearts of amphibia. The function of acetylcholinesterase at cholinergic synapses of animals is to terminate cholinergic neurotransmission (Augustinsson 1949). However, the enzyme is expressed in tissues that are not directly innervated by cholinergic nerves. Moreover, transient expression in the brain during embryogenesis suggests that acetylcholinesterase may function in the regulation of neurite outgrowth. Overexpression of cholinesterases has also been correlated with tumorigenesis and abnormal megakaryocytopoiesis (Small et al. 1996). Cholinesterase is also found in unicellular animal such as *Paramecium* (Corrado et al. 1999). An immunoblot analysis of the *Paramecium* enzyme revealed that the acetylcholinesterase had a molecular mass from 42 to 133 kDa, as reported for analogous enzyme isolated from higher organisms. Structural homologies between cholinesterases and the adhesion proteins indicate that cholinesterases could also function as cell–cell or cell–substrate adhesion molecules. Abnormal expression of cholinesterases of both types has been detected

around the amyloid plaques and neurofibrillary tangles in the brains of patients with Alzheimer's disease (Small et al. 1996).

As for microorganisms, Goldstein and Goldstein (1953) first described the production of cholinesterase by a strain of bacterium *Pseudomonas fluorescens* after the culture was grown with acetylcholine as the sole source of carbon. The *P. fluorescens* enzyme was inducible, mainly, by choline (not as a carbon substrate, but, perhaps, as a source of nitrogen) or by two- to threefold lesser degree by some choline esters: acetylcholine > propionylcholine = benzoylcholine > butyrylcholine > acetyl-β-methylcholine). Addition of glucose completely prevented the induction of *P. fluorescens* enzyme. The pH optimum for growth of the culture and cholinesterase activity was 7.0, although the culture growth was higher in alkaline medium, where spontaneous hydrolysis of acetylcholine is also maximal. The choline oxidase synthesis in the *P. fluorescens* has also been induced by choline. The cholinesterase of the bacterium may hydrolyze acetylcholine or propionylcholine, but to a lesser degree butyrylcholine, benzoylcholine, or acetyl-β-methylcholine. Like cholinesterase in animals, the enzyme activity in *P. fluorescens* was inhibited by neostigmine, with complete inactivation observed at high concentrations (10^{-3}–10^{-2} M) and only partly at the lower levels of 10^{-6} M. These levels of inhibition are similar to that observed in mammalian organ systems. Then, the *P. fluorescens* protein was isolated and characterized (Goldstein 1959; Searle and Goldstein 1957, 1962; Fitch 1963a, b). Moreover, the strains of the *P. fluorescens* tested preferred the acetylcholine for growth promotion over choline, glycerol, glucose, succinate, betaine, and serine (Fitch 1963a). The isolated cholinesterase was inhibited by neostigmine in smaller (1,000 times) concentration, than by physostigmine, but was not depressed by diisopropylfluorophosphate (Fitch 1963b). A bell-shaped substrate saturation curve was observed, and specific activity of the 115-times purified cholinesterase was 10.5 μmol/mg protein/min. The enzyme had the features both of true cholinesterase and acetylcholinesterase (Laing et al. 1967, 1969). Specific activity of the cholinesterase from *P. fluorescens* purified 40-fold by CM-50 Sephadex was up to 70 μmol/mg protein/min. The values of *Km* at pH 7.4 and 37°C were 1.4×10^{-5} M for acetylcholine and 2.0×10^{-5} M for propyonylcholine, respectively, while butyrylcholine and benzoylcholine were not hydrolysable at all. The purified enzyme was inhibited by organophosphorus compounds and neostigmine, but not by physostigmine.

Imshenetskii et al. (1974) showed that a large variety of microorganisms may decompose acetylcholine including 31 strains of bacteria (genera *Arthrobacter* and *Pseudomonas*) and two strains of fungi (from 194 strains studied) that live in soil. Around 100–200 mg of wet biomass of active microbial strains were able to decompose 15–30 μmol of acetylcholine during a 2 h incubation, with the most active strains (50 mg of wet biomass) able to degrade up to 10 μmol/min. This active soil strain was identified as *Arthrobacter simplex* var. *cholinesterasus* var.*nov*. The amount of the decomposed acetylcholine by this microbe was 30 times higher than in other strains (*Pseudomonas fluorescens* – 4 μM/h, *P. aerugenosa* – 1 μM/h), while *Arthrobacter simplex* var. *cholinesterasus*.var *nov*. had an activity of 300 μM/h. Actinomycetes (except two strains) and yeast had no significant cholinesterase activity.

The cholinesterase activity has also been found in lower groups of the plant kingdom: in extracts of Characeae algae *Nitella* by Dettbarn, in 1962 and mycelium of fungi *Physarium polycephalum* by Nakajima and Hatano in 1962, and then a series of classical papers of Jaffe and Fluck with coworkers in 1970–1975 were devoted to the observation of the enzyme in many plant species: ~118 terrestrial species and ten marine algae were identified as having cholinesterase activity (for more details see the relevant references in monographs Roshchina 1991, 2001a). The values of the enzyme activity (the substrate hydrolysis rate) in most higher plants is an average of 1–900 μmol/h/g fresh weight, depending on the plant species. It was specially shown that Bryophytes (mosses, liverworts and hornworts) demonstrate the maximal cholinesterase activity of up to 0.360 μmol/h/g fresh weight (Gupta et al. 2001). Thus, detection of cholinesterase activity could serve as an additional indicator of the acetylcholine presence. Recently, identification, purification, and cloning of maize acetylcholinesterase provided the first direct evidence of the enzyme formation in plants (Sagane et al. 2005). An especially important fact is that the acetylcholinesterase distribution in seedlings is sensitive to gravity, leading to asymmetry of the enzyme distribution (Momonoki 1997).

2.2.3.3 Enzymes of Biogenic Amine Metabolism

The biosynthetic pathway of biogenic amines includes decarboxylation and hydroxylation of corresponding amino acids, in particular phenylalanine for the catecholamines, tryptophan for serotonin, and histidine for histamine (Lawrence 2004). Phenylalanine, precursor of dopamine, norepinephrine and epinephrine, is first hydroxylated, transforming to tyrosine and then to dihydroxyphenylalanine (DOPA). These processes are catalyzed by phenylalanine hydroxylase or phenylalanine monoxidase and tyrosine hydroxylase or tyrosine-3-monoxidase. Dopamine, an immediate precursor of norepinephrine and epinephrine, arises from DOPA through decarboxylation by means of the enzyme decarboxylase dioxyphenylalanine and the decarboxylase of aromatic amino acids (EC 4.1.1.26). Another route of tyrosine transformation is via decarboxylation, when it transforms to tyramine, and then by hydroxylation with the participation of tyramine hydroxylase into dopamine, which is then oxidized to norepinephrine by the copper-containing enzyme β-hydroxylase 3, 4-dioxyphenylethylamine. Then, under the influence of the transmethylase of phenylethanolamines, the formation of epinephrine takes place.

In the catabolism of catecholamines, aminooxidases participate as a whole in oxidative deamination of the catecholamines to metanephrine, normetanephrine, vanillic aldehyde, dehydroxymandelic and vanillic acids. For microorganisms, this metabolism process has not yet been studied. In plants, diamineoxidases play the main role in catecholamine metabolism, unlike animals that use monoaminooxidases for this purpose (Roshchina 2001a). As for catecholamine-*O*-methyltransferases, they are present in all animal tissues, and especially active in nervous cells. In plants, the catecholamine-*O*-methyltransferases pathway is also possible because the last three compounds are ordinary products of plant metabolism (Kuklin and Conger 1995;

Roshchina 2001a; Kulma and Szopa 2007). Besides the above-mentioned ways of metabolism, catecholamines are oxidized by oxygen of air, forming oxidized products – red pigments aminochromes and black-brown pigments melanines which are polymers of indole (found both in plant and animals). The mechanism of oxidation per se is connected with the arising of superoxide radical – active oxygen $\dot{O}_2^-$ Blockade of oxidation of dopamine by superoxide dismutase confirms this possibility. Enzymatic oxidation of catecholamines to melanines by polyphenol oxidase has been also demonstrated (Roshchina 2001a). The above-mentioned enzymes are found only in animals and plants. There is little data for catecholamine oxidation of microorganisms, although monoaminooxidase activity in mycobacteria (Pershin and Nesvadba 1963) and *E. coli* (Takenaka et al. 1997) has been found.

Serotonin is synthesized in plants and animals from tryptophan formed by the shikimate pathway, which has also been proposed for microorganisms (Oleskin et al. 1998a, b; Oleskin 2007). This process proceeds by two pathways: either via 5-hydroxytryptophan or tryptamine formation, or the first step of serotonin biosynthesis via decarboxylation of tryptophan, which then transforms in plants to tryptamine by action of the enzyme tryptophan decarboxylase (EC 4.1.1.27), or by the dacarboxylation of aromatic amino acids (EC 4.1.1.26/27). Then, tryptamine is transformed to serotonin by hydroxylation with participation of the enzymes tryptamine-5-hydroxylase or L-tryptophan-5-hydrolylase (EC 1.14.16.4). Hydroxylation of tryptophan leads to the formation of 5-oxytryptophan in the presence of tryptophan-5-hydroxylase (EC1.14.16.4). At the next stage, 5-oxytryptophan is decarboxylated by the decarboxylase of aromatic acids to yield serotonin. Tryptamine 5-hydroxylase, which converts tryptamine into serotonin and common in animals, was also found as a soluble enzyme that had maximal activity in rice roots (Kang et al. 2007). The tissues of rice seedlings grown in the presence of tryptamine exhibited a dose-dependent increase in serotonin in parallel with enhanced enzyme activity. However, no significant increase in serotonin was observed in rice tissues grown in the presence of tryptophan, suggesting that tryptamine is a bottleneck intermediate substrate for serotonin synthesis. If we compare the enzymes from the different kingdoms, we can see more similarity. In particular, in the plant genus *Arabidopsis*, there is a homolog to part of a DNA binding complex corresponding to the animal tyrosine and tryptophan hydroxylases (Lu et al. 1992). Aminooxidases of biogenic amines may differ in microorganisms in relation to substrate specificity, in particular for the bacterium *Methanosarcina barkeri* and infusoria *Tetrahymena pyriformis* (Yagodina et al. 2000). Both studied enzymes can deaminate serotonin, but not histamine. The existence of one active center for substrate binding is supposed in the aminooxidase of the bacterium, while several centers are thought to exist in the infusoria.

For all living organisms, the biosynthesis pathway of histamine includes histidine decarboxylase which participates in the decarboxylation of histidine (Roshchina 2001a; Boron and Boulpaep 2005; Martín et al. 2005). The gene encoding histidine decarboxylase (*hdcA*) has been identified in different Gram-positive bacteria (Martín et al. 2005). Histidine decarboxylase used to be part of a cluster that

included a gene of unknown function (*hdcB*) and a histidine–histamine antiporter gene (*hdcC*) in *Pediococcus parvulus* 276 and *Lactobacillus hilgardii* 321 has been identified (Landete et al. 2005). Catabolism of histamine occurs also via methylation or acetylation in the presence of histamine-*N*-methyltransferase, or histamine-*N*-acetyltransferase, and genes cording of the enzymes have been found in bacteria, plants, and animals (Iyer et al. 2004).

2.2.3.4 Recognition of Neurotransmitters

The presence of neurotransmitters in cells is usually considered in the context of receptors to the compounds, according to concepts of neurotransmitter reception in animals. The main study methodology is based on pharmacological assays, where sensitivity to the neurotransmitter on cellular reaction is analyzed by the use of agonists and antagonists to the neurotransmitter. All perspectives on the issue for non-synaptic systems have a fundamental similarity to studies undertaken for the nerve cell.

For acetylcholine, there are two types of acetylcholine receptor – nicotinic (receptors respond to nicotine) and muscarinic (sensitive to muscarine). Corrado et al. (2001) showed the presence of functionally related nicotinic and muscarinic receptors and its lytic enzyme acetylcholinesterase in the unicellular animal *Paramecium primaurelia*. In plants, the presence of similar receptors has also been shown (Roshchina 2001a). Recently, it was established that muscarinic and nicotinic acetylcholine receptors are involved in the regulation of stomata function – the opening and closing movement – in the plants *Vicia faba* and *Pisum sativum* (Wang et al. 1998; Wang et al. 1999a, 2000). Leng et al. (2000) showed the regulation role of acetylcholine and its antagonists in inward rectified K^+ channels from *Vicia faba* guard cells. Location of the muscarinic receptor was shown in plasmatic membrane and chloroplast membranes (Meng et al. 2001), and cholinesterase activity was found in the cells (Wang et al. 1999b). The germination of plant microspores such as vegetative microspores of horsetail *Equisetum arvense* or pollen (generative microspores) of knight's star *Hippeastrum hybridum* was blocked by the antagonists of acetylcholine, which are linked with nicotinic cholinoreceptors and Na^+/K^+ ion channels (Roshchina and Vikhlyantsev 2009). The nicotinic cholinoreceptors were cyto-chemically identified in the single-cell amoebae *Dictyostelium discoideum*, slugs, and spores, however, the proteins immunologically related to the muscarinic receptors were not present in the spores (Amaroli et al. 2003). Interestingly, the nicotine and acetylcholine as the ligands of human nicotinic cholinoreceptors in culture of epithelial cells HEp-2 may stimulate the growth of *Chlamidia pneumoniae*. (Yamaguchi et al. 2003).

The receptors for biogenic amines, peculiar to highly organized animals, are known as dopamine receptors, adrenoreceptors, and serotonin and histamine receptors. The similar receptors were observed in bacteria (Lyte and Ernst 1993; Freestone et al. 2007) and in plant cells (see monographs Roshchina 1991, 2001a). Alpha and beta adrenergic-like receptors may be involved in catecholamine-induced growth of Gram-negative bacteria (Lyte and Ernst 1993). In particular, Freestone et al. (2007)

showed the blockade of catecholamine-induced growth of *E. coli*, *Salmonella enterica*, and *Yersinia enterocolitica* by adrenergic and dopaminergic receptor antagonists. In plants, adrenoreceptors participate in cytoplasm movement, ion permeability, and membrane potential, in flowering of *Lemna paucicostata*, photophosphorylation, as well as the seed and pollen germination (Roshchina 1991, 2001a; Baburina et al. 2000; Kulma and Szopa 2007). Serotonin- and histamine-sensitive receptors in plants regulate the seed, pollen, and vegetative microspores germination (Roshchina 1991, 2001a, 2004, 2005a). Shmukler et al. (2007) discussed earlier hypotheses of protosynapse for low-organized animals and embryos of high-organized animals, where the distribution of membrane serotonin receptors is restricted to the period of blastomer formation during cleavage and localized in the area of interblastomer contact. The hypothesis was based on their experiments, where the membrane currents of the *Paracentrotus lividus* early embryos have been registered after local application of serotonin drugs with special micropipette. Receptors of neurotransmitters may be linked with ion channels. Moreover, some domains of the ion channels appear to be common with the cytoskeleton, in particular with actin (Cantiello 1997), and so the received chemosignal is likely to spread to the organelles via actomyosin filaments (Roshchina 2005a, 2006a, b).

2.3 Common View on the Neurotransmitter (Biomediator) Functions

The presence of neurotransmitters in any organism leads us to the problem of information transmission within and between the living cells as a whole. Like the genetic code, having a common base in all living organisms in a form of the sequence and combination of several purine and pyrimidine bases, the mechanism of irritability appears to have a common base in the form of chemical signals uniform for every cell. The compounds acetylcholine and biogenic amines named neurotransmitters, besides having specialized mediator function in organisms with nervous systems, also play other roles, not only in animals, but also in microorganisms and plants. From this position, one could call the compounds rather "biomediators," than "neurotransmitters" or "neuromediators" (Roshchina 1989, 1991).

2.3.1 Functions of Neurotransmitters on Different Evolutionary Steps

The function of compounds named neurotransmitters originates from simple chemotaxis and chemosignaling of microbial cells and leads to intercellular communication (Fig. 2.1). The so-called neurotransmitters may regulate (as hormones) growth and development of other unicellular organisms, and be attractants or repellents for them. In higher concentrations the same substances also play a defense role (for saving or

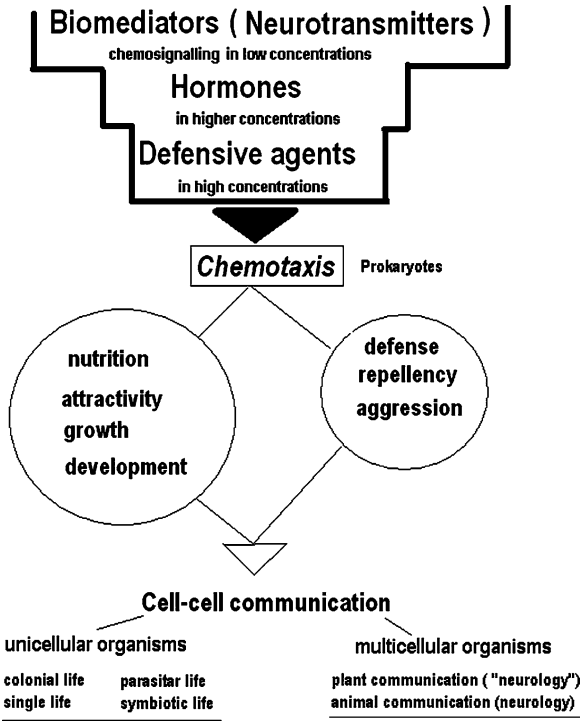

Fig. 2.1 The scheme of the evolution in the neurotransmitter (biomediator) function

aggression) or, in some cases, serve as an origin of cultural food. The following step in evolution includes the development of colonial relations (parasitar or symbiotic) and then the formation of multicellular organisms that forms more specialized function of biomediators in the irritation transfer along the multicellular system. This evolution way leads us to the concept of neurology, not only for animals, but also for plants (Baluska et al. 2005; Brenner et al. 2006; Murch 2006).

In Table 2.3, we compare the main functions of the neurotransmitters in all kingdoms. The realization of the irritation impulse transfer into a cell from the surface or between compartments of the cell occurs with the participation of neurotransmitters, and on cellular level the compounds may induce different reactions. Neurotransmitters are stored in secretory vesicles, and then can be liberated within cell or out. Primary reaction to acetylcholine is often a change in membrane permeability for ions, while other reactions for both the neurotransmitter and biogenic amines are connected with the systems of secondary messengers – cyclic nucleotides, Ca^{2+}, inositol-3-phosphate, etc.

First of all, the neurotransmitter functioning as chemosignal (the neurotransmitter is released from one cell and percepted by another) occurs in certain structural forms – the chink forming between cells or between organelles within cell. We can usually see the chink between plasmic membranes of any contacted cells such as

Table 2.3 The established functions of neurotransmitters in living organisms

Neurotransmitter	Microorganisms	Plants	Animals
Acetylcholine	Regulation of motility	Regulation of membrane permeability and other cellular reactions up to growth and development in many plant species	Regulation of cell proliferation, growth and morphogenesis. The carriage of nerve impulses across the synaptic chink, from one *neuron* to another of impulses across the "motor plate," from a neuron to a muscle cell, where it generates muscle contractions
Dopamine	Stimulation of gram negative and gram positive bacterial growth and virulence	Regulation of many cellular processes from growth and development to defense reactions	Decreases peripheral vascular resistance, increases pulse pressure and mean arterial pressure. The positive chronotropic effect produces a small increase in heart rate as well. Important for forming memories. In embryos of Vertebrata and lower animals may regulate development
Norepinephrine (adrenaline)	Bacterial growth stimulation	Regulation of many cellular processes from growth and development to defense reactions	Increases peripheral vascular resistance, pulse pressure and mean arterial pressure as well as stimulates of the thrombocytes' aggregation
Epinephrine (adrenaline)	Bacterial growth stimulation	Regulation of many cellular processes from ion permeability, growth and development to defense reactions	Induced vasodilation (mainly in skeletal muscle) and vasoconstriction (especially skin and viscera)
Serotonin	Stimulation of growth of culture and cellular aggregation bacteria *Streptococcus faecalis*, yeast *Candida guillermondii*, *E. coli* K-12 and *Rhodospirillum rubrum*. Regulation of membrane potential	Regulation of growth and development of many plant cells	Control of appetite, sleep, memory and learning, temperature regulation, mood, behavior (including sexual and hallucinogenic), vascular function, muscle contraction, endocrine regulation, and depression. In embryos of Vertebrata and lower animals may regulate development

Histamine	Stimulation of cultural growth and cellular aggregation of *E. coli* K-12	Regulation of the growth and development at stress	Involves in many allergic reactions and increases permeability of capillaries, arterial pressure is decreased, but increases intracranial pressure that causes headache, smooth musculature of lungs is reduced, causing suffocation, causes the expansion of vessels and the reddening of the skin, the swelling of clothStimulation of the secretion of gastric juice, saliva (digestive hormone)

Sources: (Anuchin et al. 2007, 2008; Buznikov 1967, 1987, 1990 Faust and Doetsch 1971; Burton et al. 2002; Freestone et al. 2007; Lyte and Ernst 1992, 1993; Lyte et al. 1997; Oleskin et al. 1998a, b; Oleskin 2007; Roshchina 1991, 2001a; Strakhovskaya et al. 1993)

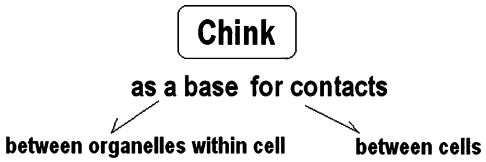

Fig. 2.2 Structure where the neurotransmitters action is possible

the membranes of unicellular contacting organisms and synaptic membranes of cells in organisms with a nervous system (Roshchina 1991, 2001a, b; Buznikov et al. 1996; Shmukler et al. 2007). As seen in the scheme presented in Fig. 2.2, at any membrane contacts, either time-changed or constant, chinks may be formed. There are chinks between endoplasmic reticulum and organelles within cells, or between different cells. Today, constant or temporary chinks between cells or within the cell are considered a necessary structural form for the chemosignal transfer.

As can be seen from Table 2.3, common cellular effects of neurotransmitters in any type of living kingdom cell are the changes in membrane permeability (short-time effects) and the regulation of growth and development (long-time effects). Regulatory function of the neurotransmitters appears to be an ancient function, relating processes occurring both within a cell and the environmental unicellular populations. The secretion that contains neurotransmitters is released out of any cell and may contact with other cells at chemotaxis. The cell, which receives similar chemosignals, responds primarily by the changes in ion permeability and the formation of action potential, and then with various metabolic and growth reactions. Some other aspects and details will be described below.

2.3.1.1 Functions in Microorganisms

The first report, showing acetylcholine production in bacterium strains, was from *L. plantarum* and. *L. odontolyticus* (Stephenson and Rowatt 1947). Approximately 5 μg acetylcholine/mg dry wt. cells/h was formed if the bacteria were grown both in vegetable juice and washed cells. Acetylcholine can be also used as substrate for microorganisms, and regulates their development in special conditions (Imshenetskii et al. 1974). Its regulation of motility peculiar to photosynthesing bacteria *Rhodospirillum rubrum* and *Thiospirillum jenenese* has also been shown (Faust and Doetsch 1971).

Catecholamines can regulate the growth of Gram-negative bacteria, including *E. coli* (where concentration dependent specificity was observed with response to norepinephrine ››› epinephrine > dopamine), *Y. enterocolitica* and *P.s aeruginosa* (Lyte and Ernst 1992; Freestone et al. 1999). Dopamine also stimulates the cultural growth of *E. coli*, *Y. enterocolica*, *S. enterica*, *S. epidermidis*, etc., and the cellular aggregation and formation of colonies of *E. coli* and *S. epidermidis* (Lyte and Ernst

1993; Neal et al. 2001; Freestone et al. 2007; Anuchin et al. 2007, 2008). Similar effects on Gram-negative bacteria *E. coli, S. enterica* and *Y. enterocolitica* were observed for norepinephrine (Lyte and Ernst 1992, 1993; Lyte et al. 1997; Freestone et al. 1999, 2007; Burton et al. 2002) and on *E .coli* for epinephrine (Anuchin et al. 2007; Freestone et al. 2007). Serotonin stimulated cultural growth and cellular aggregation of bacterial species, including *Streptococcus faecalis*, the yeast *Candida guillermondii*, (Strakhovskaya et al. 1993), *E. coli* K-12 and *Rhodospirillum rubrum* at concentrations of 2×10^{-7}–2×10^{-5} M (Oleskin et al. 1998a, b; Anuchin et al. 2007, 2008). Moreover, histamine showed similar effects on *E. coli* (Anuchin et al. 2007, 2008). Serotonin at 10^{-6}–10^{-5} M concentrations also inhibited light-dependent membrane potential generation in *Rsp. rubrum*, but in the myxobacterium *Polyangium* sp. serotonin stimulates cell aggregation and myxospore formation (Oleskin et al. 1998a, b). At concentrations near 20 μM, serotonin inhibits cell aggregation and microbial culture growth and photo-dependent membrane potential of the bacterium *Rsp. rubrum*. At micromolar amounts, the effects presumably result from the specific action of serotonin as an intercellular communication agent accelerating and possibly synchronizing the development of the microbial cell population. According to Oleskin et al. (1998a, b), the growth stimulation of microorganisms by serotonin over a millimolar to micromolar range has been demonstrated in prokaryotes, both Gram-positive including *Streptococcus faecalis* (Strakhovskaya et al. 1993) and Gram-negative bacteria including *E. coli* and *Rsp. rubrum* (Oleskin et al. 1998a, b). In some cases, such as that for *Bacillus brevis*, the degree of growth stimulation achieves 100% of control. Freestone et al. (2008a, b) showed that catecholamine stress hormones can significantly increase the growth of a wide range of gram negative and gram positive bacteria. Using a novel two-fluorophore chemotaxis assay, it was found that *E. coli* is attracted to epinephrine and norepinephrine (and also increased the bacterial motility and biofilm formation), while it is repelled by indole (Bansal et al. 2007). Moreover, epinephrine/norepinephrine upregulated the expression of genes involved in surface colonization and virulence, while exposure to indole decreased their expression (Bansal et al. 2007). Histamine synthesis by respiratory tract microorganisms: was also observed, and its possible role in pathogenicity considered (Devalia et al. 1989).

Much attention has also been given to the role of colonial organization and intercellular communication in parasite/commensal/symbiont-multicellular host organism systems. Data from the literature on the ability of microorganisms to form plant hormones (biogenic amines) have been reviewed by Tsavkelova et al. (2006), who discuss the *Rhodospirillum rubrum* pathways whereby the biogenic amines are metabolized, and their effects on the development and activity (physiological and biochemical) of the microorganisms are considered. The role as hormones and hormone-like substances is in the formation of association-type (microorganism-host) interactions. The review by Oleskin et al. (2000) suggested that the integrity and coherence of microbial populations (colonies, biofilms, etc.) be viewed as peculiar so-called "super-organisms," which are thought to have become multicellular organisms during the course of evolution. This included such relevant phenomena as apoptosis, bacterial altruism, quorum effects, collective differentiation

of microbial cells, and the formation of population-level structures such as an extracellular matrix. Emphasis can also be placed on the channels in colonies and agents of intercellular communication in microbial populations. The involvement of a large number of evolutionarily conserved communicational facilities and patterns of intercellular interactions can therefore be underscored. Moreover, an interesting fact is the 5-hydroxytryptophan conversion to serotonin under UV-irradiation (Fraikin et al. 1989). This neurotransmitter may serve as a protector for microorganisms in similar unfavorable conditions. For example, dinoflagellates (a large group of flagellate protists contained in marine plankton) and green algae *Gonyaulax polyedra* synthesize the protector melatonin, using serotonin as a precursor (Balzer et al. 1993). Circadian rhythms of indoleamines in the dinoflagellate *Gonyaulax polyedra* and persistence of melatonin rhythm in constant darkness, have a relationship to 5-methoxytryptamine.

2.3.1.2 Function in Plants

In plants, neurotransmitters demonstrate a high biological activity, playing a role as chemosignals, regulators of membrane permeability, growth and development regulators, etc. (Roshchina (1991, 2001a). Some examples will be considered below.

A signaling role of acetylcholine is well seen as the participation in plant root-shoot signal transduction (Wang et al. 2003b; Baluska et al. 2004, 2005; Brenner et al. 2006). Acetylcholine causes rooting in leaf explants of in vitro raised tomato (*Lycopersicon esculentum* Miller) seedlings (Bamel et al. 2007). Contractile effects of acetylcholine connected with membrane ion permeability were also observed in the regulation of the stomata function – the opening and closing movement in plants such as *Vicia faba* and *Pisum sativum* (Wang et al. 1998, 1999a, 2000). It was established that muscarinic and nicotinic acetylcholine receptors are involved in the event. A regulatory role for acetylcholine and its antagonists in inward rectified K^+ channels from guard cells protoplasts from leaf stomata of *Vicia faba* was found (Leng et al. 2000). Ca^{2+} and Ca-related systems were found to participate in acetylcholine-regulated signal transduction during stomata opening and closing (Wang et al. 2003a; Meng et al. 2004). A chloride channel in the tonoplast (vacuolar membrane) of *Chara corallina* also responds to acetylcholine (Gong and Bisson 2002). Electric processes participate in the electrical signaling, memory and rapid closure of the carnivorous plant *Dionaea muscipula* Ellis (Venus flytrap), and acetylcholine is thought to include in the phenomenon (Volkov et al. 2009).

Acetylcholine and cholinergic system play essential roles in plant fertilization and breeding. For example, lower activities of acetylcholinesterase and choline acetyltransferase in pistils (Tezuka et al. 2007) or in pollen (Kovaleva and Roshchina 1997) were associated with self-incompatibility. A role for acetylcholine can be proposed as dealt with phytochrome and photoreceptor in the growth regulation as well. Wisniewska and Tretyn 2003). There is a connection between some fungal infections (in particular for the *Fusarium* fungi) and the accumulation of plant growth regulators,

gibberellic acid, and auxins. Acetylcholine and antibody against acetylcholinesterase may inhibit biosynthesis of gibberellic acid, one of the main growth hormones (Beri and Gupta 2007). The enzyme may also be included in choline-auxin relations that affected plant growth processes. Direct evidence for the hydrolysis of choline-auxin or indole acetylcholine conjugates by pea cholinesterase has been demonstrated by some authors (Ballal et al. 1993; Bozso et al. 1995; Fluck et al. 2000).

A defense function for catecholamines in the plant cell has also been considered in the literature (Roshchina 1991, 2001a; Szopa et al. 2001; Kulma and Szopa 2007). Increased dopamine content in some algae, in particular *Ulvaria obscura,* has led to the consideration of the neurotransmitter as a feeding deterrent (van Alstyne et al. 2006). This is a novel ecological role for a catecholamine. The confirmation of dopamine production acting as defense mechanism against grazers was done from experiments with isopods, snails, and sea urchin eating the agar-based foods contained exogenous dopamine. Damaged algae were also found to release a water-soluble reddish-black substance (dopachrome) that inhibits the development of brown algal embryos, reduced the rates of macroalgal and epiphyte growth and caused increase mortality in oyster larvae (Nelson et al. 2003). Further, serotonin itself (Roshchina 2001a) and its derivatives, such as melatonin (Posmyk and Janas 2009), may also play a protectory role as antioxidants in various plants.

2.3.1.3 Functions in Animals

Currently, we have information about cellular functions for all animal organisms, including those which lack a nervous system and specialized functions peculiar to multicellular organisms with nervous system. First are related to the growth (similar with microbial and plant systems) and morphogenetic reactions. According to modern concepts, acetylcholine and serotonin may play a morphogenetic role in animals – from lower to higher ones (Buznikov 1990; Buznikov et al. 1996; Lauder and Schambra 1999).

The specialized function of neurochemical compounds concerned with the transmission of signals from one neuron to the next across synapses has been considered almost exclusively for neuronal systems as described in classical animal physiology. Neurotransmitters are also found at the axon endings of motor neurons, where they stimulate the muscle fibers to contract. The first of the neurotransmitters to be studied, acetylcholine, transfers nerve impulses from one neuron to another, where it propagates nerve impulses in the receiving neuron, or from a neuron to a muscle cell, where it generates muscle contractions. Moreover, genetic defects of acetylcholine signaling promote protein degradation in muscle cells (Szewczyk et al. 2000). It is obviously important to have proper nervous system and muscle functioning. In the adult nervous system, neurotransmitters mediate cellular communication within neuronal circuits. In developing tissues and primitive organisms, neurotransmitters subserve growth regulatory and morphogenetic functions as regulators of embryogenesis (Buznikov 2007). They regulate growth, differentiation, and plasticity of developing central nervous system neurons. Cellular effects of

acetylcholine in animals may also be related to pathogenesis of diseases such as acute and chronic inflammation, local and systemic infection, dementia, atherosclerosis, and finally cancer (Wessler et al. 2001).

2.3.1.4 Possible Evolution of Neurotransmitter Reception

Since neurotransmitters are found in all living organisms – from unicellular to multicellular ones, Christophersen (1991) has described their possible evolution in terms of the molecular structure of neurotransmitters and adaptive variance in their metabolism, like that known for hormone receptors (Csaba 1980). The similarity of domains in signal receptors (Berman et al. 1991) was seen to compare with the physicochemical properties of signal receptor domains as the basis for sequence comparison. Christophersen (1991) advanced the hypothesis that all metabolites, even minor ones, are expressed as a result of stimuli and are directed against or support actions of receptor-based systems that reflect the evolution of receptors. For example, there is a similarity in some domains of rhodopsin, bacteriorhodopsin, and neurotransmitter receptors (Pertseva 1989, 1990a, b; Fryxell and Meyerowitz 1991). Recently, transgenic technique has permitted the expression of the human dopamine receptor in the potato *Solanum tuberosum* (Skirycz et al. 2005). A blockade of catecholamine-induced growth by adrenergic and dopaminergic receptor antagonists has been also observed for *E. coli* O157:H7, *S. enterica* and *Y. enterocolitica* (Freestone et al. 2007) The similarity and universality of basic endocrine mechanisms of the living world are shown in the examples of the development of receptor-based mechanisms of protozoa and invertebrates (Csaba and Muller 1996). First of all, there are conservative parts or domains in modern cholino- or aminoreceptor, which are also found in prokaryotes and had no changed in the evolution (Pertseva 1989, 1990a, b). Homology of some bacterial proteins (from *Mycobacterium smegmatis*, *Corynebacterium glutamicum*, and *Halobacterium salinarum*) to mammalian neurotransmitter transporters (for example vesicular monoamine transporter) was observed as well (Vardy et al. 2005). Today, molecular evolution of the nicotinic acetylcholine receptor has also been confirmed by the multigene family in excitable cells of highly organized animals (Le Novere and Changeux 1995).

2.3.2 Participation of Neurotransmitters in Chemical Relations Between Organisms

2.3.2.1 Microorganism–Microorganism Relations

Communication between microorganisms through their secretions (extracellular products released) enriched in hormones or neuromediators is proposed in many reports (Kaprelyants and Kell 1996; Kaprelyants et al. 1999; Oleskin et al. 2000;

Kagarlitskii et al. 2003; Oleskin and Kirovskaya 2006; Oleskin 2007). Neurotransmitters participate in the communication with each other for growth, in particular serotonin as an intercellular communication agent accelerating and possibly synchronizing development of the microbial cells. Exogenous serotonin stimulates the growth of yeast *Candida guillermondii*, and the Gram-positive bacterium *Streptococcus faecalis* at low concentration near 10^{-7} M added with a periodicity of 2 h (Strakhovskaya et al. 1993). Photoactivation of the synthesis of endogenous serotonin in cells exposed to UV light at 280–360 nm led to the photostimulation of the same cultivated cells in lag-phase (Strakhovskaya et al. 1991; Belenikina et al. 1991). Exogenous serotonin at 2×10^{-7}–10^{-5} M also accelerates culture growth and induces cell aggregation in *E. coli* and *R. rubrum* (Oleskin et al. 1998a, b). Moreover, dopamine and norepinephrine stimulate the growth of *E. coli*, *S. enterica*, *Y. enterocolitica*, and the staphylococci as well as the yeast *Saccharomyces cerevisiae* (Neal et al. 2001; Kagarlitskii et al. 2003; Oleskin and Kirovskaya 2006; Freestone et al. 2007).

2.3.2.2 Microorganism–Plant Relations

The communications of plant–microorganisms or plant–fungi via neurotransmitters is still a relatively unexplored field. Although the presence of the compounds is documented for some fungi and rhizobial bacteria (Roshchina 2001a), we can only speculate that there is a role for microbial-produced hormones in plant physiology. However, recently Ishihara et al. (2008) found that the rice pathogenic infection by fungi *Bipolaris oryzae* (the formation of brown spots on the leaves) leads to the enhanced serotonin production as a defensive response. In the defensive mechanism, the tryptophan pathway is involved as well. The pathway enzymes of rice have been characterized (Kang et al. 2007).

2.3.2.3 Microorganism–Animal Relations

Microorganisms may live within an animal organism and have simple symbiotic or parasitic relationships with their host. The example of non-parasitic cooperation can be found in the marine sponge that used acetylcholine and its hydrolyzing enzyme acetylcholinesterase of the associated bacterium *Arthrobacter ilicis* (Mohapatra and Bapujr 1998). The clinical aspect suggested by microorganism–animal interactions based on hormones is understandably of special interest. Evans with co-workers first reported in 1948 that catecholamines such as epinephrine were able to enhance bacterial infections. Presently, we know that they may stimulate the growth of Gram-negative bacteria (Lyte and Ernst 1992, 1993). The concept of "microbial endocrinology", in which pathogens are considered to exploit the host effector's molecules as environmental signals promoting growth and virulence factor deployment, has been proposed (Lyte 1992; Lyte and Ernst 1993, Freestone et al. 2008a, b). Cells of bacteria and fungi release neurotransmitters (for example norepinephrine and dopamine) out into the matrix of cellular cover as shown, in particular the bacterium *Bacillus subtilis*, and with the compounds participate in intercellular

communication (Oleskin et al. 2000). Matrix contained biopolymers permit low-molecular neurotransmitters to diffuse among the colonial population. In this case, the compounds serve as chemosignals or information agents of short-radius activity. The formulation of the hypothesis regarding the microbial recognition of catecholamines produced during periods of stress as a potential mechanism by which bacteria can utilize the host's environment to initiate pathogenic process was formulated in 1992 (Lyte 1992; Lyte and Ernst 1993) and developed (Lyte et al. 1996; Lyte and Bailey 1997; Freestone et al. 2008 a,b) showed that norepinephrine stimulates the growth of low inocula of commensal and pathogenic *E. coli* in a minimal medium supplemented with serum. Norepinephrine also forms a complex with transferrin-bound iron in blood or serum, and Freestone et al. (1999, 2000) demonstrated that norepinephrine supplies iron for bacterial growth in the presence of transferrin or lactoferrin. Utilization of iron-catecholamine complexes involving ferric reductase activity has also been found for *Listeria monocytogenes* (Coulanges et al. 1997).

Other examples are changes in the blood and tissue histamine content in rabbits when sensitized with streptococci combined with heart muscle extract (Kozlov 1972) or as well in those of serotonin and histamine in the organs infected with bacterium *Bacterium prodigious.* The review of Freestone et al. (2008a) reveals that responsiveness to human stress neurohormones is widespread in the microbial world and relates to the new concept of microbial endocrinology.

2.3.2.4 Plant–Plant Relations

In the relationships between different plant species, neurotransmitters may play a role of attractant or repellent for normal coexistence (Roshchina 1991, 2001a). Plant microspores such as vegetative microspores of horse-tail *Equisetum arvense* from Cryptogam (spore-bearing) plants or various generative microspores (pollens) from Phanerogams (seed-bearing) plants are unicellular structures containing acetylcholine, catecholamines and histamine (Roshchina 2001a) and are the specific objects of microbiology having medicinal areas of the interests (Roshchina 2006b), acting as drugs or allergenous agents. An especially significant role of neurotransmitter compounds is seen in the pollen–pollen interaction named pollen allelopathy and pollen–pistil relations during pollination that regulate fertilization of certain plant species (Roshchina 2001b, 2007, 2008). Catecholamines stimulate the microspores germination (Roshchina 2001a, 2004, 2009). Fungi and other microorganisms living within many plant cells also appear to release neurotransmitters that act as plant growth regulators. We may only speculate on the biological significance of these observations as yet.

2.3.2.5 Plant–Animal Relations

Participation of neurotransmitters in plant–animal relations has been evidently shown for dopamine (van Alstyne et al. 2006). This is dangerous for marine communities,

fisheries, and aquaculture facilities due to similar antiherbivore defense that is the cause of reduced feeding by echinoderms, molluscs, and arthropods (see above in Sect. 2.1.2). Role of neurotransmitters excreted in the plant–animal relations is "terra incognita" as yet.

2.3.2.6 Animal–Animal Relations

Neurosecretion utilizes mechanisms common to all eukaryotic membrane transport, and the process should be a model of the secretion as a whole (Bajjalieh and Scheller 1995). The role of neurotransmitters in the contacts with other organisms may be seen from the effects of the secretions released. For instance, large amounts of dopamine are secreted by cells of infusoria *Tetrahymena pyriformis* into their growth medium (Gundersen and Thompson 1985). Secretions from cones of *Drosophila* contain acetylcholine (Yao et al. 2000), and dopamine and norepinephrine are found in the salivary glands and brain of the tick *Boophilus microplus* (Megaw and Robertson 1974). Exogenous neurotransmitters such as dopamine and serotonin may act as both growth stimulators or as defense agents (Boucek and Alvarez 1970; Yamamoto et al. 1999).

2.3.2.7 Biomediator Role of Neurotransmitters

Non-neurotransmitter functions of the compounds known as neurotransmitters are especially important in the relationships of bacteria and fungi with plants and animals. It appears to be a significant factor in nature. Based on our present knowledge, one could imagine neurotransmitters rather as biomediators that via cellular secretions participate in cell–cell communications in biocenosis, i.e., a group of interacting organisms that live in a particular habitat and form a self-regulating ecological community (Fig. 2.3). We think that information about intracellular location of the compounds and their release within any cell as well as

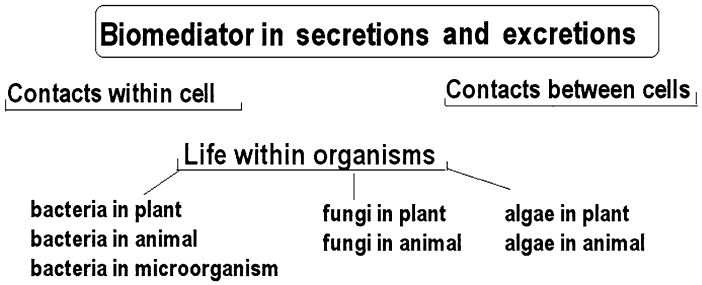

Fig. 2.3 Possible relationships with participation of biomediators

their effects on the cellular organelles could be useful in the study of cell endocrinology. The role of acetylcholine and biogenic amines as intracellular regulators has been confirmed for sea animals (Buznikov 1990; Buznikov et al. 1996) and some plants (Roshchina 1989, 1990a, b, 1991, 2006a, b). A special case is related to the life of microorganisms within host cell of animal or plant. The release of neurotransmitters should occur within and out the guest cell (independently parasitar or not). A universal (biomediator) role of neurotransmitters may be a subject of future investigations.

2.4 Use of Microorganisms and Medicinal Plants Enriched in Neurotransmitters

2.4.1 Microbial Neurotransmitters

Stress stimulates the formation and releasing of biogenic amines, in particular epinephrine, a hormone produced during stress that affects heart rate, blood circulation and other functions of the body. Microorganisms possess the ability to recognize hormones within the host and utilize them to adapt to their surroundings. Norepinephrine and epinephrine, which are released during human stress responses, may act as environmental cues to alter the growth of individual microbes. The growth stimulation of 43 oral bacteria by norepinephrine and epinephrine was found (Roberts et al. 2002), especially for *Actinomyces naeslundii*, *A.s gerenscseriae*, *Eikenella corrodens*, and *Campylobacter gracilis*, and suggest that stress that induces changes in local catecholamine levels in the mouth may play a significant role in the etiology and pathogenesis of periodontal disease. The bacteria-induced enhanced level of the compounds may be recommended as a valuable diagnostic test in medical practice.

Chemical reactions performed by microorganisms have been used as a modern tool in chemistry. In work of Boaventura et al. (2004), the ability of the fungi *Beauveria bassiana* and *Aspergillus niger* to modify the chemical structure of indole compounds was studied. *B. bassiana* was able to transform 3-indolylacetonitrile into 3-methylindole, while *A. niger* transformed tryptamine into 5-hydroxyindole-3-acetamide. These fungi were able to perform both reduction and oxidation of the indole compounds fed, the oxidation occurring with improved levels of oxygen uptake. The synthetic use of microorganisms to perform reactions in the indole nucleus of serotonin is of industrial interest as a way to synthesize active indole derivatives and this area has attracted great attention. According to Heller et al. (2004), serotonin also enhances the activity of membrane-sensitive drug amphotericin B against *A. fumigatus* in vitro. Thus, the combination of known drugs with biogenic amines may lead to the promotion of medicinal effects.

2.4.2 Plant Neurotransmitters

Plants may be suitable for medicine as a source of neurotransmitters and antineurotransmitter drugs or as a polygon for testing of the neurotransmitters and antineurotransmitter compounds as well as model system to study in cell endocrinology.

Neurotransmitters themselves can serve as an active matter of pharmacologically valuable plants. Examples of such plants are published earlier (Roshchina 2001a). Among them are recommendations for practical medicine regarding acetylcholine-enriched food and medicinal species, for example *Digitalis ferruginea* and *Urtica dioica*, catecholamine-enriched *Musa* sp. (Roshchina 2001a), serotonin-enriched *Hippophae rhamnoides*, *Juglans nigra*, and *J. regia* (Bell and Jansen 1971; Badria 2002). Useful features of medicinal plants enriched in neurotransmitters are likely connected with the formation of non-hazard complexes with neurotransmitters such as conjugates of auxins (Ballal et al. 1993; Bozso et al. 1995; Fluck et al. 2000) or phenol–histamine (Hikino et al. 1983). Possession of acetylcholine receptor binding activity is peculiar to many medicinal plants used to improve failing human memory (Wake et al. 2000; Luedtke et al. 2003). Antineurotransmitter natural compounds may also be used in medicine. Agonists or antagonists of neurotransmitters as well as anticholinesterase compounds, mainly alkaloids (Schmeller et al. 1997) or terpenoids (Atta-ur-Rahman et al. 2001), occur in pharmacologically valuable plant material and are effective against diseases from ancient time (Roshchina 2001a). For example, the alkaloids berberine, palmatine, and sanguinarine (inhibitors of cholinesterases, choline acetyltransferase or some receptors) are toxic to insects and vertebrates and inhibit the multiplication of bacteria, fungi, and viruses (Schmeller et al. 1997).

Model systems of plants may also be used for a drug testing. New approaches to the testing of neurotransmitter and antineurotransmitter compounds may be the plant biosensors found among sensitive microobjects, in particular plant microspores such as vegetative horse tail microspores or the generative male microspores named pollen (Roshchina 2004, 2006a, b, 2007). Biosensors are analytical systems, which contain sensitive biological elements and detectors. Intact plant cells are a possible biosensor, having a natural structure that determines their high activity and stability (Roshchina 2006a, b; Budantsev and Roshchina 2004, 2007). Changes in the germination and autofluorescence of unicellular microspores of plants as well as their cholinesterase activity were considered possible biosensor reactions (Roshchina 2005a, b). They could serve as biosensors for medicinal drugs such as known agonists and antagonists of neurotransmitters, instead of animals with the necessity of their vivisection.

Plants appear to be model systems for cell endocrinology. Unicellular plant systems such as the above-mentioned microspores are also suitable models for cellular endocrinology considered in any cell of both unicellular and multicellular organisms. It is a way to an understanding of neurotransmitter occurrence in organelles and different compartments that is based on the concept of universal mechanisms in intracellular chemical signaling from plasmalemma to organelles (Buznikov 1990; Roshchina 1989, 1990a).

The study of neurotransmitter function and location within a cell could be done with fluorescent compounds from microbial and plant cells that bind with the receptors or enzyme of neurotransmitter metabolism (Roshchina 2008). For example, the fluorescent antineurotransmitters *d*-tubocurarine, muscarine (Roshchina 2005a, b, 2008), and some Bodipy derivatives of neurotransmitters (Roshchina et al. 2003; Roshchina 2008) are used as fluorescent natural dyes and markers because they bind with cellular receptors.

2.5 Conclusion

Examination of the compounds known as neurotransmitters or biomediators reveals a similarity in their main functions at the cellular level for all living organisms. These compounds change the membrane ion permeability, electrical characteristics of the cells and in final we see the integral response of the cell or organism as a whole – stimulation or inhibition of growth and development. Neurotransmitters regulate their own metabolic processes within a cell and the relationships (allelopathy) between neighbors with biocenosis, may serve as attractants or repellents as well as oxidative agents (biogenic amines). Interactions between microorganism–microorganism, microorganism–animal (human) and microorganism–plant play essential roles in the environment, and thus neurotransmitter compounds should be considered universal agents of irritation in this living relationship. We should know that our understanding of these relationships is small and that we are just at the beginning. However, the recognition of such relationships is increasingly changing the medical and pharmacological perspectives regarding the non-nervous functions of the neurotransmitters.

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