THE NEW ARMENIAN MEDICAL JOURNAL
Volume20 (2026), Issue 1 p.4-19

DOI: https://doi.org/10.56936/18290825-2026.20v.1-4

HOW EFFECTIVE IS OUR “UNIVERSAL” RECEPTOR SYSTEM?

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Received 17.12.2025 Accepted for printing 14.05.2026

Abstract

To what extent does the receptor mechanism reflect the pluripotent hormonal and mediator functions of secretory cells in vertebrate mammals? Even an analysis of relatively few, but quite informative literature sources indicates that existing concepts and hypotheses regarding receptor mechanisms require substantial correction.

In this context, the authors consider it appropriate to discuss several fundamental conceptual issues concerning future approaches to studying the functional activity of the receptor system in target cells throughout the organs and systems of our body.

In our body, the hormone-mediator functions of specialized target cells are likely not carried out by the specific binding of a single hormone and/or mediator to one receptor, but rather by the synchronous activity of several endogenous ligands acting on a single secretory cell. The existence of hybrid receptors in the human body supports the hypothesis that we have put forward. It is possible that the binding of one endogenous ligand may potentiate the entry of another ligand, which may already be recognized on the inner surface of the cell membrane and/or on the surface of the endoplasmic reticulum of the same target cell. Unfortunately, there is still no clear answer to this hypothesis. Is the synchronous activity within a single target cell ensured by strictly determined, evolutionarily conserved hormones and mediators, or does it follow a principle of selective “assembly” of multiple ligands?

Finally, the third important question: In cases where two or more ligands bind simultaneously to a single target cell, is the specific functional activity of each of them preserved, especially when these ligands are similar in their structural and functional characteristics?

It is also possible that under such conditions, many endogenous ligands acting simultaneously may have novel mediator and hormonal effects on the same target cell.

Unfortunately, our considerations have not been discussed by leading scientists studying receptor-mediated mechanisms in the human body.

Therefore, previously established theories, paradigms, and concepts concerning the formation and functioning of the receptor system of living cells require careful re-examination and, possibly, revision in light of the recommendations presented in this study.

Keywords: *receptor system, secretory cells, hybrid receptors, ligands, own interpretation*

Cite This Article as:

Zilfyan A.V., Avagyan S.A., Muradyan A.A. (2026). How effective is our “universal” receptor system?; The New Armenian Medical Journal, vol.20 (1), 4-19; DOI: https://doi.org/10.56936/18290825-2026.20v.1-4

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The human body contains numerous biologically active substances that function as hormones, mediators, or immunomodulators.

To this day, the dominating principle is that most endogenously active compounds have specific effects on particular target cells located in the internal organs of vertebrate mammals [*Nazarova F, Shakhzod A, 2023; Szyller H et al., 2024*].

Undoubtedly, every experienced researcher in the biological sciences may ask the following question: How many specific receptors must a single parenchymal and/or stromal cell possess to maintain its vital activity and to carry out its endocrine-secretory function, which ensures the integrative functioning of organs and systems at all levels?

The renowned immunologist and Nobel Prize laureate Frank Macfarlane Burnet confronted a conceptual dilemma that may be formulated as follows: If, in our organism, an evolutionarily formed receptor apparatus is clearly engaged at the levels of initiation, proliferation, and execution of immune reactions, how should we interpret the numerous facts in which the body encounters synthetic antigens against which no “immunological memory” exists?

The answer to this question was provided by Burnet with coauthors [*Burnet F, 1960; 1962; 1970*].

Currently, numerous studies explore various aspects of the formation and functioning of receptor mechanisms. However, these data are still insufficient to draw broad conclusions or establish relatively objective criteria for evaluating receptor mechanism functioning [*Poste G, Crooke S, 2013; Geng Y et al., 2016*].

In our view, the thesis that a single endogenously active compound acts on a single target cell exclusively through a receptor mechanism is rather unconvincing.

The same active cell may have multiple secretory functions through the synthesis of biologically active compounds. Therefore, it may be assumed that such a cell must be equipped with numerous specific receptors.

It is possible that endogenous biologically active factors exert their effects on the target cell via a competitive receptor mechanism [*Lee J et al., 2022*].

In general, competition for binding to a specific receptor on the surface of a target cell may be implemented through two principal mechanisms:

1. The enhancement of the synergistic effect of one endogenous compound on a cell by another. This mechanism is especially pronounced under pathological conditions.
2. The induction of a new effect in the target cell that differs from that produced by a previously competing ligand for the same receptor.

It is enough to give some examples of the pluripotent synthetic capabilities of lymphoid cells and of the key cellular component of the APUD system – tissue basophils. In this regard, it is worth referring to the statement of the Japanese investigator J. Kimoto regarding the multifaceted secretory function of lymphocytes. The author emphasized that human lymphocytes are capable of producing a broad spectrum of messenger ribonucleic acids (mRNA), followed by the synthesis of numerous biologically active substances, including adrenocorticotropic hormone, thyroid-stimulating hormone, enkephalins, prolactin, parathyroid hormone, interleukins, insulin, progesterone, immunoglobulins (IgG, IgM, IgE and IgA), gastrin, cholecystokinin and pancreozymin. According to the author, human cells, both somatic and embryonic, synthesize mRNA for many biologically active compounds. This basal or “illegal” transcription is very relevant to cellular life and is referred to as “the arrow of time within a single cell” [*Kimoto J, 1998; Frei A et al., 2012; Curk T et al., 2017*].

Over many years, tissue basophils were considered an important source of synthesis of such biologically active mediators as histamine, serotonin, glycosaminoglycans, prostaglandins, the slow-reacting substance of anaphylaxis, eosinophil chemotactic factor and neutrophil chemotactic factor.

Despite the wide range of endogenously active substances in tissue basophils – some of which were described by P. Ehrlich over 130 years ago, – new endogenously active factors have continued to be discovered [*Kay A., 2016*].

It is also noteworthy that numerous receptors have been identified on the surface of tissue basophils for various molecules, including acetylcholine, corticosteroids, corticotropin-releasing factor, adrenaline, parathyroid hormone, substance P, vasoactive intestinal peptide, adrenocorticotropic hormone (ACTH), somatotropin, endorphins, melatonin, leptin and others [*Theoharides T., 2017*].

Moreover, several researchers have reported convincing evidence for the synthesis of ACTH in tissue basophils [*Csaba G et al., 2006; Csaba G, Kovács P, 2009; Theoharides T, 2017*]. In tissue basophils, ACTH was detected both in the cytoplasm and within intracellular granules.

The first clear evidence supporting ACTH synthesis in tissue basophils is the detection of ACTH within their nuclei**.** The second piece of evidence is the identification of specific receptors for corticotropin-releasing factor on the surface of tissue basophils.

In our view, such selective activity of tissue basophils may be explained by their functional "gradation" into various subpopulations. Their functional activity in each specific organ where they operate is strictly aimed at supporting the particular functions assigned to these organs.

All these considerations allow us to reassess the functional significance of tissue basophils as an integral part of the APUD system in the human body.

In this context, to a certain extent, the pleiotropic synthetic potential of tissue basophils may be compared with the pleiotropic capacities of lymphoid cells in the human body. Thus, a similar "historical case" has already occurred in immunology and molecular biology, when lymphocytes (small lymphocytes) were previously described as monomorphic structures, but many years later were identified in a "new form" as subpopulations. Moreover, each lymphocyte subpopulation possesses its own strictly characteristic functional and secretory potential [*Deryugina E, James P, 2010; Zilfyan A et al., 2020*].

At present, special studies are being conducted that confirm the structural homology of numerous receptors that simultaneously participate in different intracorporeal systems of living organisms [*Noda M et al., 1983; Bhunia S, Saxena A, 2021*].

The observations of J.L. Marx (1987) are particularly noteworthy. He emphasized that "numerous proteins are structurally related even when the ligands that bind to them differ greatly in their chemical structure" [*Marx J, 1987; Marx N, 2004; Kellenberger E et al., 2008; Barelier S et al., 2011; Ruepp M et al., 2017; Marx D, Fleming K, 2021*]. Thus, the multidirectional functions of many receptors are characterized by homology in their chemical organization. For example, the primary structure of β-adrenergic receptors is largely similar to that of light-sensitive channel receptors, such as rhodopsin [*Dixon R et al., 1986*].

There is a well-known structural similarity among the receptors of several biologically active substances that function in various systems of the mammalian body. These include adrenergic, dopaminergic, and cholinergic receptors [*Venter J, Fraser C, 1983; 1984; Venter J, 1987; Shreeve S et al., 1985; Vickery R, von Zastrow M, 1999; Vallone D et al., 2000; Yarnitzky T et al., 2010*].

Certain resident bacteria and viruses pathogenic to humans compete for binding to specific receptors on particular cell populations that are responsible for the reception of many biologically active substances in mammalian organisms [*Finlay B, McFadden G, 2006; Almand E et al., 2017; Dawley C, Gibson K, 2019*].

Structural similarity has been observed between the reovirus receptor in mammalian cells and the β-adrenergic receptor in the tissues of small mammals [*Co M et al., 1985; Sawutz D et al., 1987; Li Q et al., 2022; Mammen M et al., 1998; Cichero E, Tonelli M, 2017*]. In the case of SARS-CoV-2, only a single antigen receptor has been identified: the S-spike protein, which mediates viral "adhesion" to the surface of target cells of the macroorganism [*Dejnirattisai W et al., 2021; Ubah O et al., 2021*]. At the same time, SARS-CoV-2 can also interact with a range of parenchymal cells expressing specific receptors for the angiotensin-converting enzyme [*Meinhardt J et al., 2024; Yang M et al., 2022; Vidoni C et al., 2022; Radovic S et al., 2023*].

Similar structural elements can be observed in cyclic adenosine monophosphate in mammals and in the eukaryotic species Dictyostelium discoideum (slime molds) [*Xie X et al., 2024*].

Chipens G.I. and co-authors suggested that "genes encoding the synthesis of many currently known hormones and mediators, as well as their receptors, originated early in evolution and have been partially preserved to this day in various species of primitive bacteria and other microorganisms" [*Chipens G, Veretennikova N, 1980, Chipens G et al., 1983*].

It is also worth noting that many hormones and other endogenous bioactive compounds in the body contain two components: a biologically active component and an immunoactive component [*Dufau M, Veldhuis J, 1987; Schaefer F et al., 1994*].

This structural organization forms the basis for the commercial production of specific antibodies to hormones and cytokines, which allows the determination of their levels in the body.

One possible mechanism of competition for receptor binding on a target cell may be explained by the immunoreactive fragment within the structure of competing hormones and mediators [*Smith C, O'Malley B, 2003; De Toni L et al., 2016*].

In certain cases, the immunoreactive fragments of two hormones or mediators may be structurally similar or even closely analogous. However, the responses of the same target cell are far from uniform or stereotypical, since they are mediated not so much by the immunoreactive fragments as by the biologically active сите [*Grody W et al., 1982; Murray T et al., 2005*].

How is it possible that the same cell (in our examples, tissue basophils and lymphocytes), with the ability to synthesize many different biologically active substances, contains such a wide variety of mRNAs? If such a situation exists, then, in our view, it is very difficult to imagine highly selective mechanisms that trigger the expression of a particular mRNA in a specific situation [*Ohtsuka S, Dalton S, 2008; Omole A, Fakoya A, 2018*].

To understand whether such a mechanism could function within a single pluripotent secretory cell, it is important to cite highly informative data indicating that the structural assembly of new intracellular biologically active substances occurs through stepwise mechanisms, and not even at the initial stages of activation of receptor-triggered mechanisms [Hirschi S et al., 2022].

According to the authors, possible mechanisms of receptor-mediated secretory activity may operate at the genetic level [Blalock J, Smith E, 1980; 1985; Moon T et al., 2014], exploring potential sources of specific biologically active substances, in which human lymphocytes and leukocytes were studied as possible sites of synthesis.

In order to elucidate the genetic mechanisms underlying the production of ACTH and endorphins in the context of human leukocyte interferon, researchers cloned interferon gene families in bacteria and determined their corresponding amino acid sequences [Maghnie M, 2013; Ali A et al., 2021]. Sequences characteristic of ACTH and endorphins were not detected in **α-interferon** molecules [Zilfyan A, 2020].

Therefore, the authors concluded that "in this particular case we are dealing with a post-transcriptional or post-translational addition to the indicated components — the products of γ-interferon genes".

It is possible that the synthesis of other biologically active substances in target cells, particularly in lymphocytes and tissue basophils, occurs at post-transcriptional or post-translational stages of secretory activity. At this stage, it is difficult to assess the validity of this hypothesis.

For many years, the dominant "membrane theory" of the living cell has emphasized the selective distribution of substances due to the permeability of the plasma membrane and its critical role in coordinating numerous cellular functions.

However, the molecular mechanisms responsible for transmembrane exchange of many metabolites remain insufficiently explored, especially those related to the selective permeability of cell membranes to specific biologically active substances and the structural-functional features of cytoplasmic membranes, particularly around the perimeter of a single cell [Chornyi S et al., 2021; Rudnik S, Damme M., 2021].

To this day, there is no doubt that the structural organization of the cell membrane serves as a "platform" for the distribution of the receptor apparatus on its surface.

At the same time, the literature cited in this article concerning receptor function and subsequent cellular responses - whether secretory, metabolic, or contractile - indicates that many aspects of this problem remain largely unexplored.

A key question is how a single target cell responds to at least two hormones simultaneously? Competition for receptor binding may occur, when prolactin and insulin-like growth factor-1 (IGF-1) act as ligands.

It can be hypothesized that:

1. Receptor-bound prolactin opens the "entry gates" for insulin-like growth factor-1, which, like prolactin, also binds to the same cell via its receptor mechanism. As a result, it is possible that the target cell's responses are selectively mediated primarily by insulin-like growth factor-1.
2. Prolactin, while facilitating insulin-like growth factor-1 receptor interaction on the inner surface of the cell membrane, may simultaneously exert its own biological effect on the target cell.

3. It is also possible that both hormones act on the same target cell sequentially, producing different secretory and/or metabolic responses.

If a similar mechanism of "synchronous" stepwise activity of two hormones applies to other somatic target cells of the human body, then the currently accepted idea that only one receptor specifically binds a ligand on the outer surface of the cell membrane may need to be reconsidered [*Jacobson K et al., 1992; Zhang B et al., 2020; Wu T et al., 2022; Wang Z et al., 2024*].

It is possible that not just two, but several receptors are involved in such a "symbiotic" interaction. One may assume that the inter-receptor relationships arising in this situation are highly complex, and it remains unclear how adequately target cells respond, in chronological sequence, to all receptor-mediated stimuli.

One specific hormone may facilitate the entry of one or more additional hormones into a target cell. These hormones may not only be selectively recognized by receptors on the inner surface of the cell membrane, but may also penetrate the cell by diffusion.

Moreover, in the human body the functions of many hormones and endogenous biologically active substances are realized through their "cooperation", when one group of hormones at the outer surface of the plasma membrane may facilitate the entry of another group of hormones into the cell. These hormones may then bind selectively to receptors located not on the outer surface, but on the inner surface of the membrane and on the endoplasmic reticulum of the same target cell.

Even if any of these hypothetical mechanisms occurs in the human body, we may need to revise our understanding of the functioning of the target cell receptor apparatus.

The insulin-like growth factor axis is currently a focus of detailed study [Barbiery B et al., 2003]. This axis involves multiple ligands – insulin, insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-2 (IGF-2), which function simultaneously as hormones and tissue growth factors [*Lee J et al., 2012*]. At physiological concentrations, insulin binds to insulin receptors (IR-A and IR-B), as well as to hybrid receptors composed of IR-A and IR-B subunits. Insulin-like growth factor-1 can bind to hybrid receptors IGF-1R + IR [*Belfiore A et al., 2003; 2009; 2017*].

IGF-2 binds not only to IGF-1R and IR-A receptors, but also to hybrid receptors IGF-1R + IR [*Frasca F et al., 1999*].

What is the biological purpose of hybrid receptors in the mammalian body?

Thus, the same specific receptor that binds a ligand "independently" can associate with another receptor. Such associations are referred to as "hybrid receptors" [*Chen W et al., 2005; Mancia F, 2008; Lamberts S, van Rossum E, 2004*].

Consequently, the main questions are:

1. What is the biological significance of the structural organization of the receptor apparatus in the form of hybrid receptor formation?
2. Are hybrid receptors a more universal structure for binding a specific ligand?
3. Are hybrid receptors polypotent and able to respond simultaneously to two or more ligands rather than to a single ligand?
4. How stable are the interactions between each ligand and its respective specific receptor individually, if the organism requires a mechanism of coordinated specific response based on receptor hybridization?
5. What mechanisms underlie the functioning of hybrid receptors, i.e., do they operate only through protein receptors located on the plasma membrane, or through receptors localized within the cytoplasm?It is also possible that two mechanisms operate simultaneously – one involving a receptor localized on the membrane and another on the surface of the endoplasmic reticulum within the same target cell.

In our point of, in addition to the insulin/insulin-like growth factor (IGF) axis, other hormones and mediators in the human body may also function through hybrid receptor mechanisms. It appears that hybrid receptor mechanisms are more advanced and effective than those that use only a single receptor binding to a specific ligand [*Soos M, 1990; Licitra E, Liu J, 1996*].

It is possible that a single ligand acting through hybrid receptors can produce multiple biologically active compounds, each affecting a different site.

On the other hand, hybrid receptors may provide a more reliable and complete response in cases where one of the component receptors becomes biologically impaired due to repeated exposure to ligands entering the cell [*Slaaby R et al., 2006; Turvey S et al., 2022*].

The role of aliphatic polyamines, particularly putrescine, is also highly significant in the mammalian body. These molecules operate at subcellular, cellular, and tissue levels in various integrative systems [*Schipper R et al., 2000; Kahana C, 2008; Avagyan S, Zilfyan A, 2019*]. Among their multiple functions, putrescine has a cardiostimulatory effect, which is reflected in a significant increase in the contractile activity of cardiomyocytes [*Passariello C, 2012*].

It is also noteworthy that the stimulatory activity of putrescine has been demonstrated in both *in vivo* and *in vitro* model systems [*Avagyan S et al., 2008; 2009; 2019*]. In both cases, a single application of putrescine at minimal concentrations comparable to those observed in the blood of intact laboratory animals and healthy humans was sufficient to produce a measurable cardiac stimulatory effect. Based on these findings, the authors proposed that the myocardial effect of putrescine is mediated via a receptor-dependent mechanism.

The study of Bordallo C. and co-authors showed that putrescine exerts its contractile effect by binding to β-adrenergic receptors on cardiomyocytes. Furthermore, the cardiostimulatory effect appears to be mediated through an increase in intracellular adenylate cyclase activity [*Bordallo C et al., 2008*].

Based on our research, we propose four possible putrescine-dependent receptor mechanisms operating at the myocardial membrane:

1. The same receptor apparatus might bind both catecholamines and putrescine. However, since the structural organization of putrescine differs significantly from catecholamines such as epinephrine and norepinephrine, it is unlikely that a β-adrenergic receptor can bind both ligands simultaneously on the surface membrane of cardiomyocytes.
2. Two receptors may function simultaneously on the myocardial membrane: one specifically binding catecholamines via β-adrenergic receptors, and the other binding putrescine.
3. Such a "symbiosis" of two potential receptors may operate on the principle of hybrid receptors, with catecholamines and putrescine acting as ligands.
4. It is possible that under extreme conditions, when catecholamine production in the adrenal glands is impaired, the contractile function of cardiomyocytes is largely maintained through putrescine receptor activation at their membrane.

In our opinion, such a principle of selective reception of various endogenous ligands by the same target cell may reflect the evolutionary "refinement" of adaptive mechanisms [*Kenakin T, 2003; Schupp M, Lazar M, 2010; Valant C et al., 2012*].

Our hypotheses require either verification, critical evaluation, or even rejection.

Serious limitations of the "membrane theory of the cell", along with many recently reported findings regarding receptor mechanisms, have led to the development of new hypotheses, concepts, and theories about the mechanisms of cellular function [*Höber R, 1946; Fan J et al., 2010; Das U, 2021*].

It is appropriate to present a summary of the "Physical Theory of the Living Cell" proposed by the American scientist Gilbert Ling, which challenges the currently accepted "membrane theory of the living cell".

The "Association-Induction Theory" by Gilbert Ling is based on two earlier concepts introduced by the same author: the "Fixed Charge System" and the "Theory of the Multilayer Organization of Polarized Cell Water". According to these concepts, Ling established new static and associative criteria for the physiological functions of the cell. The "Association-Induction Theory" also characterizes the dynamic, inductive properties of living cells [*Ling G 1982; 1984*].

According to the "Association-Induction Theory", it is not lipids but highly polarized and structured water that forms a continuous barrier at the cell surface. Thus, the cell surface is presented not by a protein-lipid membrane, but by surface-oriented proteins along the inner perimeter of the cell, which polarize and structure cytoplasmic water into multilayered formations.

Such multilayered formations cover the cell with a continuous layer. Surface proteins, through their β- and γ-carboxyl polar and nonpolar groups, along with water, form a selectively diffusive barrier that regulates the exchange of water, nonelectrolytes, and other substances between the cell and its environment.

The authors of the present publication do not consider it necessary to undertake a critical analysis of the main provisions of this theory. However, they strongly recommend specialists to familiarize themselves with Gilbert Ling's "Physical Theory of the Living Cell," which was also published in Russia [*Ling G, 1988; 2008, 2014*].

A more detailed description of the development stages of the "Association-Induction Theory of the Cell" can be found in a series of publications by G. Ling issued between 1981 and 2008.

As is known, the membrane theory of the cell is based on its known properties:

- ➢The distribution of substances between the cell and its environment.
- ➢The regulation of cell volume.
- ➢Membrane permeability.
- ➢Electrical potentials.

Membrane-dependent processes, particularly those mediated by protein structures that facilitate ligand–receptor interactions, play a crucial role in maintaining these fundamental cellular properties [*Song X et al., 2012; Müller M et al., 2019; Jiang Y et al., 2012*].

In vertebrate mammals, two relatively autonomous mechanisms of receptor activity have been identified. The first is ligand–receptor interaction occurring at the cell membrane. The second is triggered by the entry of a ligand (either bound to or released from a surface-localized receptor) into the cell, where it exerts its effects by binding to receptors located in the cytoplasm and/or the nucleolus of the same target cell [*Ling G, 1982; 1984; Takara K et al., 2010; Du R et al., 2023; Zheng S et al., 2023; Zhang W et al., 2023*].

In this context, an important question still lacks a clear answer, despite advances in biochemistry and molecular biology.

What are we talking about? Are these two independent, relatively ancient receptor processes formed during evolution, or are they two receptor processes that developed in stages during evolution and which are relatively more recent, already providing more complex functional responses to target cells as they acquire new secretory-modulatory functions?

Receptor proteins are constantly synthesized in the nucleoli and, after complex interactions with transfer and messenger RNA, are released into the cytoplasm. Further formation, maturation, and transport of cellular receptors occur in the granular endoplasmic reticulum, utilizing energy sourced from the mitochondria surrounding the Golgi complex.

What occurs periodically, and within a relatively short time frame, not only during the formation of intracellular receptor processes but also in maintaining the viability of the target cell itself?

It appears that every time a secretory-mediator target cell receives a signal and encounters an endogenously active ligand that is periodically generated within the body, it starts synthesizing new receptors. These receptors bind to their ligand, following synthesis in the nucleolus, interaction with both messenger and matrix RNAs, subsequent differentiation and accumulation in the endoplasmic reticulum, and, in specific circumstances, translocation to the cell membrane. This continuous binding of intracytoplasmic and nucleolar receptors with endogenously active ligands entering the cell may result in a functional overload of the intracellular structures of the receptor apparatus over a relatively short period of time.

Let us review certain aspects of the receptor apparatus within the cell membrane.

Currently, it is widely accepted that some proteins, which lose activity and are subsequently degraded as a result of ligand–receptor interactions, are continuously replaced by new ones.

This mechanism of "self-renewal" of the receptor apparatus on the cell membrane operates not only under pathological conditions but also plays a crucial role in the physiological functioning of the body's integrative systems.

However, the conclusion that this "adaptive" mechanism truly requires the continual production of new receptors to replace those that are degraded under persistent ligand stimulation is very questionable. It is well known that the processes of physiological self-renewal of cell populations, and even the structures within a single cell, are far from unlimited. It is unlikely that the same target cell can function fully for such an extended period in our organism. Therefore, such a mechanism of permanent, repeated self-renewal of the receptor apparatus within a single cell must be considered uncertain.

Unfortunately, many hormone-mediated processes, which continuously occur in the body over many years, have often been considered the result of the functional activity of the receptor apparatus of target cells. However, in certain, even routine situations, it is not always possible to explain these mechanisms exclusively through receptor activation [*Gao T, McPhaul M, 1998; Olah M, Stiles G, 2000; Schneider M et al., 2015*].

First, the lifespan of cells themselves is relatively limited in our body, even in the absence of receptor-mediated signaling. Under normal physiological conditions, all cells eventually undergo apoptosis, accompanied by a programmed restoration of the population's overall cell number.

Consequently, at a certain stage of their activity in the normal body, a pool of target cells may begin to lose their potential to synthesize the receptor apparatus.

Secondly, many secretory target cells are pluripotent. They possess the capacity to simultaneously produce multiple endogenously active substances: hormones, cytokines, and mediators, which provide the integrative functions of tissues, organs, and systems in the human body. Consequently, from the nucleolus to the membrane, such a target cell must simultaneously or shortly thereafter synthesize a broad spectrum of receptors corresponding to each individual ligand. It is unlikely that our cells can function at such an extreme rate without overloading all the functional capabilities of target cells.

Third, there are situations when the body encounters previously unknown exogenous ligands, including those of synthetic origin, as well as a broad spectrum of exogenous pathogenic and opportunistic microorganisms. It turns out that in addition to their secretory and mediator functions, the same target cells can take on an additional heavy "burden" themselves. However, in this case, we are referring to specific populations of target cells, such as monocyte–macrophage cells, which exhibit both phagocytic and secretory-mediatory functions, and immunocompetent T- and B-cell populations and subpopulations, which are responsible for forming cellular and humoral immune responses and producing biologically active factors.

Conclusion

It has long been established that the actions of various endogenous biologically active substances – hormonal, mediator and immune in nature, are carried out exclusively via receptor-mediated mechanisms, transmitting signals to target cells. This mechanism underlies their primary function, i.e. direct involvement in the activity of specific intracorporeal systems of the organism.

However, in our opinion, such a "specific function" is highly debatable, since many endogenous biologically active substances, and primarily hormones, are also endowed with other indirect auxiliary functions that go far beyond their activity within particular systems.

It should be noted that these "non-primary" functions are also mediated exclusively via receptor mechanisms.

On the other hand, the receptor-mediated action of certain hormones and mediators on a specific secretory target cell may also involve the immunoreactive fragment present in the structure of these biologically active substances.

Hormones producing different biological effects on the same target cell may possess immunoreactive components that are structurally very similar. Thus, the same receptor on the surface of a target cell appears capable of interacting with at least two hormones, since their antigenic determinants (fragments) are nearly identical. However, the biological effects of these two hormones on the same target cell often differ, depending on the structural organization of the biologically active, rather than the immunoreactive, fragment.

The evolution of receptor mechanisms has been thoroughly studied.

In this context, it is appropriate to note the influential statement of our compatriot, the Armenian physiologist and academician **Levon Abgar Orbeli**: "We cannot properly understand a function without going deeper into the history of its origin". Orbeli noted the importance of studying the mechanisms underlying biological activity from the perspective of ontogenesis. According to him, "it is precisely this evolutionary approach that allows us to elucidate those hidden, previously unknown mechanisms of biological systems' activity, especially at stages of evolutionary development when the mechanisms of integrative function are "not yet unified into a common system and are therefore easier to study" [*Orbeli L, 1961*].

This scientific and methodological approach became the basis for extensive fundamental research. A significant contribution to understanding receptor mechanisms and the pathways mediating the hormonal response in target cells was made by the well-known specialist in molecular endocrinology and evolutionary biochemistry, M. N. Pertseva (1989).

We have found answers to several key questions addressed by researchers in Pertseva's monograph (1989):

- At what stage of onto- and phylogenesis do cells acquire hormonal competence for hormonal signals, that is, the ability to function adequately and effectively within, at least, the hormonal system?
- What appears first in the process of ontogenesis of living beings — a hormone, or a receptor molecule capable of recognizing and binding it?

Based on many years of scientific work devoted to the functioning of molecular and supramolecular systems, the author hypothesized that the "hormone system – mechanism of action" emerged earlier in evolution, already in invertebrate animals, and possibly, - in some of its individual elements, - even in their unicellular representatives, including lower eukaryotes and perhaps even prokaryotes. The same opinion was expressed by D. Bückmann (1983; 1984). Moreover, the author suggests that "the mechanism of hormone–receptor interaction did not undergo significant changes over time".

In this case, it is difficult to speak of the "strict" specificity of each receptor. Apparently, in mammals, a biologically justified mechanism operates whereby the same receptors (or structurally homologous receptor groups) participate in the selective regulation of different functions, both under normal conditions and during the development of adaptive responses **to** various extreme conditions.

This view is supported by numerous findings, demonstrating that structurally and functionally diverse endogenous biologically active substances may compete for binding to the same receptors on target cells.

The findings of the past half-century, indicating the synthesis of numerous biologically active substances with widely diverse functions in tissue basophils and lymphocytes, suggest **a** reconsideration of the hypothesis proposed by J. Kimoto (1998), according to which human cells – both somatic and embryonic, synthesize mRNAs for many biologically active compounds. This may raise questions regarding the specific structural and functional characteristics of such cells. For example, can tissue basophils be considered solely as components of the APUD system, or lymphocytes only as part of the immune system? This may require the reclassification of many cells whose functions were mistakenly attributed to only a single integrative system of the organism.

Using the detection of ACTH in leukocytes as an example, based on the highly informative studies cited, J. E. Blalock suggested that the target cell (leukocyte) functions exclusively through post-translational or post-transcriptional mechanisms [*Blalock J, Smith E, 1980; 1985*].

First, what intracellular post-translational or post-transcriptional mechanisms are we talking about? It is possible that there is a subtle reorganization of subcellular structures within leukocytes that enables endocytosis and/or phagocytosis of ACTH-containing structures.

Second, to what extent does a similar situation occur in other target cells with high multipotent secretory activity, such as tissue basophils and lymphocytes?

Finally, how accurately, i.e. with a high degree of reliability, does the receptor mechanism reflect the multipotent hormone- and mediator-related functions of secretory cells in vertebrate mammals?

Our analysis of the available literature suggests that many receptor mechanisms remain unexplored. Moreover, in our opinion, aspects related to the pluripotent capabilities of specific secretory cells that produce a wide range of endogenously active substances, as well as the presence of hybrid receptors in our body, are of particular importance. This situation creates many unresolved questions and raises doubts about whether the same mechanisms function in all secretory cells.

Based on the dogmatic principles currently dominant in molecular biology, particularly those concerning the interpretation of cellular receptor mechanisms, chronomedicine continues to develop, especially in situations where ultradian, circadian, daily and seasonal fluctuations of hormones and mediators are insufficiently considered in adjusting the administration of pharmacological agents with hormonal or mediator activity.

It is important to emphasize that the "membrane theory of the cell" has been revised many times over the years as new hypotheses and concepts emerged. Some of them were accepted, while others were disproved.

Accordingly, the receptor concept of the living cell has never been "rigid", leading researchers to identify new criteria underlying the structural organization, functional activity**,** and inhibition of the receptor apparatus. However, despite the considerable number of studies in this field, many of them, even those published in prestigious scientific journals, have not been subjected to critical analysis and are limited to merely stating facts.

It is therefore necessary to reconsider the functioning of the receptor apparatus in secretory cells. Paradoxically, much of the informative data remains largely overlooked by specialists, including those actively engaged in research and in training the next generation of scientists. In both cases, the issue is not adequately addressed and continues, largely by inertia, to be based on dogmatic principles.

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THE NEW ARMENIAN MEDICAL JOURNAL

Volume20 (2026). Issue 1

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OFFICIAL PUBLICATION OF THE YEREVAN STATE MEDICAL UNIVERSITY

THE NEW ARMENIAN MEDICAL JOURNAL

Volume 20 (2026) Issue 1

The Journal is founded by
Yerevan State Medical
University after M. Heratsi.

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Our journal is registered in the databases of Scopus, EBSCO and Thomson Reuters (in the registration process)

Scopus EBSCO The GUFO

Print in "Monoprint" LLC
Director: Armen Armenakyan
Andraniks St., 96/8 Bulding
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