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PROSPECTS

Bellini, Carpaccio, and Receptors in the Central Nervous System

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Abstract With the convergence of science from the fields of neurobiology and immunology, many exciting and challenging surprises have emerged regarding cytokines, neuroendocrine hormones, neuropeptides, excitatory amino acids, and their receptors. For some time neurobiologists have known that subsets of neural cells had different receptors for the same ligand. Those subsets of cells could be as different as neurons and astrocytes and as closely related as astrocytes from different lineages or anatomical areas. The neurobiological puzzle has been to determine the functional meaning of these differences. Immunologists in contrast have long understood the clear cut differences between T and B lymphocytes or T helper/inducer and T cytotoxic/suppressor cells and their response to cytokines. However, it is only very recently that they have discovered preferential use by these cells of different receptors for an identical cytokine ligand. Indeed, identical cytokines in the central nervous system and immune response may induce their pleiotropic responses by utilizing different receptors in these two systems. Immunologic paradigms may help neurobiologists predict the existence of subsets of neural cells and their function. Likewise, neurobiology may enable immunologists to predict roles for receptors in gene families as well as the existence of as yet unidentified receptors.

Key words: neurobiology, immunology, cytokines, neuroendocrine hormones, neuropeptides

If one has the chance to spend any time in the interesting city of Venice, Italy, one will encounter and be enriched by its historical and contemporary splendors. This can happen because the beauty of Venice's past, its buildings, fountains, canals, and piazzas, is kept alive by daily modern life. The ancient treasures of this rich environment are indeed used rather than enshrined as untouchable monuments. It is precisely because of this that I learned an important scientific lesson. If, for instance, you go to a popular restaurant on Giudecca called Harry's Dolce, and you order a Bellini and Carpaccio, you will be served a peach nectar-champagne cocktail and thinly sliced raw beef with a mustard sauce, both considered Venetian delicacies. If, however, you go to the Accademia on the Grand Canal and ask for a Bellini and Carpaccio, you will be shown paintings by these 15th century Venetian painters. Indeed, their names were used for the gourmet menu items in the Venetian tradition of celebrating and making practical use of history. The pleasant surprise of a fine Bellini and well-executed Carpaccio will match one's anticipation providing one knows where one is in Venice.

Just as a Bellini and Carpaccio are different in different places, IL1 and IL2 receptors in the brain differ from those on T cells. GABA and glutamate receptors on neurons and glia are different. Insulin receptors in liver and brain are different. What you get depends on where you are.

The purpose of this prospective is to promote the exploitation of parochial hypotheses and scientific findings and observations in neurobiology by immunologists as well as the use of predictions in immunology by neurobiologists. This may prove helpful for understanding how the immune system and CNS function and more interestingly how the two systems interact during development and disease.

NEUROTRANSMITTER RECEPTORS ON NEURAL CELLS

Neuropeptide Receptors

Receptors for neuropeptides and excitatory and inhibitory neurotransmitters have been

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studied for some time with information accruing about the subsets of receptor types involved in binding a given ligand and the relationship of these differences to neuroanatomical location and target neural cell. Nevertheless, the functional response after signal transduction by peptide receptors depends on the physiology and biochemistry of the receptor bearing cell. Other than emerging data on calcium fluxes and an inferred biological role in regulation of extracellular potassium concentration, neurotransmitter uptake, and glycogenolysis, there is a virtual absence of information on receptor function in astrocytes. In the field of astroglial cell research, there are relatively recent suggestions that heterogeneity of receptors, related to regional expression could imply subsets of astrocytes. Work from Wilkin and Cholewinski on vasoactive intestinal peptide (VIP) responses of astrocytes demonstrated marked differences in neonatal rat cortex compared with cerebellum [1]. Chneiweiss et al. suggested that heterogeneity in VIP responses could exist within a given area of the mesencephalon [2]. This group also measured effects of somatostain or VIP inhibition of isoproterenol stimulated adenylate cyclase in mouse brain astrocytes. Inhibition was seen in astrocytes of striatum and mesencephalon but not cerebral cortex [3]. Measurements of inositol-phospholipid turnover in cultured astrocytes also have pointed to probable regional heterogeneity [1]. Cortical and cerebellar astrocytes generally respond similarly by up regulating turnover in response to ACTH, oxytocin, and vasopressin in contrast to lack of a response by spinal cord astrocytes. Indeed spinal cord astrocytes respond to tachykinins, substance P, and neurokinin α and β, while the cortical and cerebellar cells do not. These differences are not totally explained by differences in density or affinity of receptors since, in the case of substance P, cultures of glial cells from stiatium, hypothalamus, cerebellum, mesencephalon, and spinal cord all possess a single population of high affinity binding sites ($Kd = 0.33$ nM) [1].

GABA Receptors

Because glia do not possess chemical synapses, in contrast to neurons, information passes from cell to cell through gap junctions. These gap junctions create, in effect, cytoplasmic syncitia allowing electrical and chemical responses in one cell to spread to adjacent cells. Glial cells can utilize uptake systems for a variety of neurotransmitters including aspartate, β alanine, and GABA. All these systems have been well characterized. A comparison of astrocytes and neurons reveals the possibility of higher open channel density on glia than neurons since glial cells have a higher membrane conductance than neurons. In addition, agonists and antagonists of GABA receptors on neurons have different effects on astrocytes. The $GABA_A$ receptor agonist, muscimol, is effective, but $GABA_B$ receptor agonist baclofen is ineffective at mimicking the effect of GABA on astrocytes. In addition, $GABA_A$ receptor modulators such as methyl-4-ethyl 6,7-dimethoxy-β-carboline-3-carboxylate (DMCM) behave differently on neurons and astrocytes with respect to depolarization [reviewed in 4]. These data support the idea of different $GABA_A$ receptors on neurons and glial cells. Again, the functional role of these receptors is unknown, and unlike the regional heterogeneity for neuropeptide receptors, nothing is known about in vivo GABA receptor distribution on astrocytes.

Glutamate Receptors

The most complex set of receptors for a single ligand, but the one about which we know most, is that of the glutamate receptor. The reason for this is that many glutamate receptors or their subunits have not only been purified but also molecularly cloned. In addition, we have some developmental clues about subsets of responding astrocytes, and some knowledge of functional results of glutamate exposure in vitro and in vivo.

Glutamate has been identified as playing a role in the pathogenesis of some neurodegenerative disorders [5], long-term potentiation, memory and learning [6], regulation of neurotransmitter release [7], hypoxic-ischemic damage and neuronal death [8], as well as fast excitatory synaptic transmission [9]. These pleiotrophic functional responses of diverse electrophysiology and pharmacology occur through specific signal transduction associated with one of the members of this set of receptors. The classification of glutamate receptors has delineated neural cell subsets and suggested some functions. There are ionotropic receptors gating cation-selective ion channels and a metabotropic receptor activated by 1-amino-cyclopentyl-1,3,dicarboxylic acid (ACPD). The ionotropic receptors are named for their selective agonists and include those binding N-methyl-D aspartate (NMDA), found on neurons but not astrocytes

[10]. Non-NMDA receptors seem to mediate fast glutamatergic neurotransmission, and synaptic plasticity [6,11]. These include 1) α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid (AMPA); this receptor is a subclass of the quisqualic acid receptor; 2) kainic acid (KA); and 3) 2-amino-4-phosphonobutryric (APB) [reviewed in 12]. Four genetically distinct, but molecularly related, AMPA-selective glutamate receptors have recently been cloned. These receptors preferentially bind quisqualate followed by glutamate, and then kainate. There is some agreement with high affinity ^{3}H-AMPA binding and expression of the four mRNAs by in situ hybridization in the telencephalic regions [13].

Three closely related genes encoding receptor subunits for the glutamate receptor regulated by kainate gated ion channels have also been cloned recently. There is preferential activation by the primary ligand kainate but binding sites for quisqualate may coexist on single receptor chains [14]. Indeed, these receptors exist as homomeric individual subunits or heteromeric combinations of subunits, another possible explanation for the existence of KA-AMPA receptors. Within this receptor subfamily of the glutamate receptor family, there may be further structurally distinctive subtypes. Whole cell voltage clamp recording data reveal the presence of two KA responses differing in rectification properties and permeability to Ca^{++} [15]. In contrast to AMPA receptor binding in telencephalic regions, KA sites seem to be restricted to hippocampal CA3 areas, deep cortical areas, striatum, and reticular thalamic nuclei [16–18].

A previously unrecognized role of long-distance signalling by astrocytes has been implied by studies of calcium flux and oscillations in astrocytes in response to KA and AMPA. These studies point toward some functional meaning for disparate glutamate receptors on subsets of astrocytes and in different regions of the brain. Cornell-Bell and colleagues have demonstrated in hippocampal astrocyte cultures that quisqualate-preferring glutamate receptors respond by releasing intracellular calcium which moves through the astrocyte syncitia in waves followed by oscillations. The response may be mediated by IP3 (inositol 1,4,5, trisphosphate) activation and turnover. KA, on the other hand, promotes surface membrane calcium influx without waves or oscillations, possibly through depolarization and voltage gated channels [19].

Summary

Significance of receptor usage will require the linking of electrophysiology, anatomical locale, as well as phenotypic differences of target cells to the cloned receptor subunits in these neurotransmitter families. Some differences in receptor usage and response have already been established with respect to type 1 and type 2 astrocytes. These cells derive from different glial lineages [20,21] and may have region specific functional roles. Type 1 astrocytes may possibly regulate activity at the blood brain barrier where astrocytic end feet abut endothelial cells. Type 2 astrocytes may regulate electrical conduction at the Nodes of Ranvier [22]. These same sorts of anatomically specific differences are also seen in lymphoid cells where liver macrophages (Kupffer cells) or skin macrophages (Langerhans cells) perform tissue specific functions. In other words, immunology poses some useful precedents for experimental modeling by neurobiologists. Aware of distinct anatomical localization and some developmental differences of target cells, neurobiology is thus gradually expanding its ability to conceive of specialized subsets of neural cells, a paradigm long established in immunology. The search for these subtypes of neurons and astrocytes will be facilitated by molecular analysis of subset specific genes. The actual function of these receptors, currently being inferred by the repertoire of gene products coding for related receptor proteins, receptor subunit composition, and ligand generated effects such as calcium changes, can then be confirmed.

HORMONE, VIRUS, NEUROTRANSMITTER, AND CYTOKINE RECEPTORS IN THE NERVOUS AND IMMUNE SYSTEMS

Hormone, Virus, and Neurotransmitter Receptors

Similarities between the insulin and insulin-like growth factor (IGF) II receptor exist although these receptors differ in ligand binding properties, alpha and beta subunit size, and immunodominant epitopes. IGF I and IGF II receptors are less similar in that type II receptors do not exhibit tyrosine kinase activity and that ligand dependent phosphorylation is different on the two receptors [reviewed in 23]. Tissue specific [24–26], neuronal cell subtype specific [27,28], and development specific [29] alterations in alpha subunit size of all three types of receptors as the result of differences in N-linked glycosylation suggest a functional relationship. Neurons utilize IGF-I R to a greater extent than IGF-II R compared to glia. They respond to the ligand by growth and differentiation, not by alteration of their glucose metabolism [27]. Neuronal IGF-I receptors are 115 Kda or 20,000 daltons smaller than receptors on astrocytes [28]. Typically, brain IGF-I and II and insulin receptors are smaller in size than those in liver (140 Kda); adult brain receptors are smaller than fetal brain receptors of the same ligands [29]. The functional significance of these differences is unknown just as in the case of brain receptors for the neurotransmitters discussed in this review.

The possibility of receptor heterogeneity for a given ligand in the brain and immune system indeed within subpopulations of lymphoid cells themselves is still somewhat a speculative and even novel idea. However, biological and molecular data are emerging to demonstrate that this motif is not unique to cells of the central nervous system. T lymphocytes respond by proliferation to IGF-II but not insulin [30], suggesting differences between the brain and immune system in receptor usage.

CD4 is the protein on T cells and macrophages that acts as the receptor for the HIV-1 virus. This virus has neurotropic properties. Indeed, AIDS is frequently accompanied by CNS disorders. Madden et al. performed Northern blot analysis of RNA prepared from human and mouse brains to determine whether CD4 mRNA sequences existed in the CNS. In contrast to the single 3 kb CD4 mRNA in T cell lines, human cerebral cortex contained some 3 kb and a smaller more abundant 1.8 kb mRNA which was absent from T cells [31]. They suggest the possibility that this resulted from either alternative splicing or alternative 5′ or 3′ termini. In addition, though unpublished, this group also found differences in L3T4 mRNA in mouse forebrain (2.2 kb messenger RNA in cortex and striatum) compared to hindbrain samples (absent in cerebellum, brain stem, and spinal cord) suggesting localization of CD4 within the CNS.

Neuropeptides may also use different receptors in the CNS compared to the immune system. Dam et al. [32] demonstrated 46 Kda substance P (SP) receptors on rat brain by photoaffinity labeling; this is in comparison to a series of molecular weight entities (33, 58, 78, and 116 Kda) revealed by covalent affinity cross-linking of radiolabeled SP to a B cell lymhoblastoid cell. Goetzl and colleagues have suggested heterogeneity of VIP receptors within human leukocyte subsets [33]. In addition, lymphocytes and mast cells bind VIP peptide ligands which are cleavage products of their bona fide neuropeptide analogues, suggesting a difference in VIP R in the nervous system compared to the brain [34].

Cytokine Receptors

While there is much evidence for glial cell (microglia, astrocyte, oligodendrocyte) response to immune-derived cytokines and growing evidence that astrocytes, at least, produce some of these cytokines such as IL6, TNF, IL1, and colony stimulating factors [35–37], practically nothing is known regarding the cytokine receptors utilized by glial cells.

There is recent evidence that IL1 receptors on immune cells exist in two distinct forms. These two forms are coded for by separate genes; there is apparent preferential use of one or the other of these receptors by different lymphocyte subsets. This emerging story begins to thus resemble the leitmotif of neurotransmitter receptor heterogeneity within the central nervous system.

Initial data from two different research teams has demonstrated the presence of IL1βR (87 Kda, type 1) on resting T cells, keratinocytes, fibroblasts, and T cell lines. A second IL1βR (66 Kda, type 2) is seen on preB and macrophage lines and bone marrow cells [38,39]. These receptors are the product of two different genes [38–40]. These two receptors may also be discriminated on the basis of affinity and preferential binding of IL1α and IL1β [41,42]. Dower has examined IL1 receptors in brain tissue and is unable to block IL1 binding by monoclonal antibodies to IL1βR_1; radiolabeled ligand binding cross-linking studies suggest that the brain utilizes the IL1βR_2 (S. Dower, personal communication). Furthermore, Kd values for IL1 receptors in brain tissue differ from those in lymphocytes and fibroblasts (Kd = 1 nM in hypothalamus vs. Kd = 8–200 pM in lymphocytes or fibroblast). CNS regional heterogeneity also may exist for IL1βR with hypothalamus maximal binding capacity being four times that of cerebral cortex for IL1β [reviewed in 43].

Two chains of the human IL2R chain complex have been cloned: the IL2Rα chain (TAC antigen, p55) coding for a low affinity (10^{-8} M Kd), non-signal-transducing IL2 binding moiety and the IL2Rβ chain (p70–75) binding with intermediate affinity (10^{-9} M Kd). Together these chains bind IL2 with high affinity (10^{-11} M Kd) [44]. The intermediate affinity receptor may actually consist of two distinct polypeptides (β and α or H1 and H2) [45,46].

IL2 and IL2 receptors in the CNS, until recently, were only clearly identified in inflammatory lesions such as those in multiple sclerosis [47]. However, IL2R have been detected by immunohistochemical techniques in white and gray matter cells with microglial and astroglial morphology in normal and Alzheimer disease patients. Nieto-Sampedro and Chandy demonstrated that IL2 activity in injured rat brain had ion exchange properties similar to splenocyte IL2 but an apparently higher molecular weight [49]. These findings argue for endogenous brain sources of both ligands and their receptors [48].

In vivo injections of IL2 into rat brain cause histopathological and blood-brain barrier changes as well as significant decrease in neuronal discharge frequency in the ventromedial nucleus of the hypothalamus and increase in the supraoptic and paraventricular nuclei [50,51]. Ishida and co-workers created human IL2/IL2R (TAC) transgenic mice hoping for mice with leukemia or autoimmune diseases. They produced animals which died of interstitial pneumonia. These animals developed ataxia at 2 weeks after birth and had 40–70% loss of purkinje cells at 3 weeks [52]. These studies suggest that IL2 receptors exist on neurons. In vitro IL2 induces propiomelanocortin mRNA transcription and ACTH production [53,54]. Interestingly, affinity purification of IL2R from murine pituitary cells produced an α-like chain of 58 Kda and a 36 Kda species [54]. The authors conclude this represents an immature IL2Rα undergoing glycosylation.

Work from our laboratory has demonstrated that IL2 induces proliferation and differentiation of primary rat oligodendrocytes and proliferation of oligodendrocyte-like glioma subclones [55,56]. The IL2 binding proteins on these cells share epitopes with those on the p50 chain of the T cell IL2R complex [56,57]. On rat oligodendrocytes the shared amino acid sequence lies outside the IL2 binding site of the rat T cell receptor [58]. On the human brain cells, epitopes within (H31, TAC) and outside the IL2 binding site (H47, H48) are seen on the surface of these cells [56,57,59]. The dose response range and receptor affinity on the human cells both suggest low affinity binding sites (Kd = 4 nM). Radiolabeled ligand binding studies detect a series of ligand receptor complexes, some of which are smaller in size than those on T cells [57]. Reducing the stringency for the hybridization with the pcTAC probe allows us to detect novel-sized mRNAs (2.8 and 2.2 kb) in these brain cells [58]. All of these data suggest a p50-like protein on IL2 responsive glioma clones which is similar but not identical to that on T cells.

Okamoto and colleagues have also examined the ability of an oligodendroglioma cell line to proliferate in response to IL2 and have demonstrated a p70, IL2Rβ chain on this line by monoclonal antibody staining and detection of low levels of IL2Rβ mRNA by S1 nuclease mapping. The receptor appears to be similar or identical to the IL2Rβ on lymphoid cells [60]. When transfected with the cDNA for the p70 chain, these cells are capable of binding and internalizing IL2 and undergoing modest proliferation. A similar transfection of fibroblasts did not result in a functional response to ligand. Thus, oligodendrocytes may have the receptors and internal machinery for response to this cytokine. Whether the endogenous ligand is IL2 or an analogue remains to be determined.

Cytokine Receptor Families

As with IL1, TNF receptors have now been shown to come in two types, the protein products of two genes [61,62]. Eventually the functional relevance of this finding will emerge as preferential expression on cells of one or the other TNF receptor is observed. The immunoglobulin supergene family contains receptors for the immunomodulators granulocyte colony stimulating factor (GCSF), colony stimulating factor (CSF-1), IL1, and IL6. Nervous system specific cell surface molecules like myelin-associated glycoprotein (MAG), neural cell adhesion molecule (N-CAM), and Po appear also in this family. Two other families of receptors are 1) the haemopoietic receptor family where G-CSF and IL6 receptors may also be considered in addition to receptors for erythropoietin (EPO), IL3, IL4, IL7, IL2Rβ (p70–75), GMCSF, as well as growth hormone and prolactin [63] and 2) a small family including TNF_1, TNF_2, and nerve growth factor (NGF) receptors [64]. In other words, family members of these three receptor groups may in some cases be preferentially used by either nervous (NGF) or immune system (EPO-R). In addition, as what seems to be more the rule than exception, they may function in both systems. Cells may also have natural feedback mechanisms for negative autoregulation of the biologically functional response of ligand-receptor interaction. It is becoming evident that by a variety of mechanisms cells may produce natural, soluble isoforms of membrane bound receptors [65,66] or nonfunctional protein analogues of ligands [67] which inactivate cytokine responses at the ligand or receptor level respectively.

Observation and Predictions

Cells are sometimes required to integrate information from a single ligand and translate it into different outcomes. One prediction for the understanding in neurobiology and immunology of how a given ligand-receptor interaction can lead to either cell survival (neurons), proliferation (glia, lymphocytes), or differentiation (myelin production, neuronal sprouting, mature lymphocyte function) is based on an immunological precedent. That precedent is the dual effect of IL2 on B cells and oligodendrocytes; IL2 induces both proliferation and differentiation of these two cell types [55,68,69]. As Tigges et al. have suggested, alternative transduction pathways, up- and down-regulation of a single transduction pathway by a second ligand, and different translation of the signal in the nucleus are all possibilities [69]. Examination of the preferential usage of one of a variety of G binding proteins associating with the same receptor under different conditions in the same cell will complement examination of conventional second messenger systems of Ca^{++} flux, IP3 and diacylglycerol (DAG) production, and cAMP and cGMP dependent kinases.

Based on observations from findings in immunology, neurobiologists might explore the following predictions:

1. Existence of functional subsets of astrocytes and oligodendrocytes. These would be specialized to perform specific duties in a given region of the brain or given time of development as has been demonstrated by T cell subset specialization.
2. Existence of soluble neurotransmitter receptor isoforms capable of regulating cell survival, growth, migration, and differentiation (neuronal sprouting, myelination). These would prevent events from occurring prematurely or stop them at appropriate times. Again, a precedent exists in immunology.
3. Endogenously produced natural receptor antagonists. These could be either novel proteins/chemicals or modified ligands (nonfunctional peptides or agonists) that bind the receptor and block the functional ligand.

Likewise, neurobiology provides a basis for predictions that may be useful to immunologists in experimental hypothesis testing:

4. Developmentally and anatomically/regionally-associated preferential use of receptors binding a single ligand. This might distinguish immune responses in gut, skin, brain, etc.
5. Receptor complexes composed of multiple gene products coding for subunits which can be combined in different permutations, all of which bind a single ligand. Subunit composition might distinguish subsets, states of activation, or location of lymphoid cells.
6. Receptor diversity being created by post-translational modifications such as glycosylation as in the case of the insulin receptor. Tissue and developmental variations would be predicted.
7. Brain-specific members of receptor families. These receptors might bind the same ligand as that used in the immune system (IL2, IL1) or novel brain-specific cytokine analogues (IL2).

As tourists in a new and interesting city, scientists exploring the monuments of another scientific discipline must rely on both anticipation of finding something recognizable as well as the expectation of some pleasant surprises. Nevertheless, having some sense of where one is may help in finding one's way to the object of interest.

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