40th Anniversary Retrospective

Editor's Note: To commemorate the 40th anniversary of the Society for Neuroscience, the editors of the *Journal of Neuroscience* asked several neuroscientists who have been active in the society to reflect on some of the changes they have seen in their respective fields over the last 40 years.

Neurotransmitters, Receptors, and Second Messengers Galore in 40 Years

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The past four decades have witnessed extraordinary advances in the molecular understanding of neurotransmitters, their receptors, and second messengers. This essay highlights a selected group of particular notable discoveries, emphasizing seminal findings that have transformed thinking in the field.

Introduction

To say that much about neurotransmission has changed in the past four decades is a gross understatement. In 1970 the biogenic amines were well established as neurotransmitters. Amino acids were making inroads with GABA accepted and glycine strongly suspected as inhibitory neurotransmitters. Hints abounded for glutamate, but the jury was still out. Few thought of peptides as transmitters. Substance P had been identified in the 1930s as an agent in brain extracts with smooth muscle activity, but its designation (P for powder) indicated our ignorance. In 1970 Susan Leeman isolated the substance P peptide and obtained its amino acid sequence, but there was still no evidence that it was a neurotransmitter. Of course, no one even dreamed of gases, "abnormal" isomers of amino acids, such as D-serine, or lipid-derived endocannabinoids as transmitters. Receptors were presumed to be proteins localized to synaptic membranes, but none had been biochemically identified. The only characterized second messenger was cAMP. So much has transpired in the intervening years that this brief review perforce highlights only a few themes and key investigators.

Neurotransmitter transporters

The founding of the Society for Neuroscience in 1970 coincided with an important event for neuroscience, especially for the world of neurotransmitters. The Nobel Prize in Physiology or Medicine was awarded to Julius Axelrod, Bernard Katz, and Ulf von Euler for "their discoveries concerning the humoral transmitters in the nerve terminals and the mechanisms for their storage, release and inactivation." Katz was honored for elucidating the quantal release of acetylcholine from nerve terminals at the neuromuscular junction. Von Euler was cited for establishing definitively that norepinephrine is a neurotransmitter at nerve terminals of the sympathetic nervous system. The citation for Axelrod emphasized his discovery of "the mechanisms which are involved in the inactivation of noradrenaline, partly under the influence of an enzyme discovered by himself." The Nobel Assembly did not specify Axelrod's discovery of the reuptake of norepinephrine by nerve terminals as a mode of synaptic inactivation nor did it comment on his discovery that tricyclic antidepressants act by inhibiting this reuptake process. This tells us that in 1970 these concepts, catechism today, were still controversial. In the early 1970s monitoring the uptake of radiolabeled neurotransmitters into pinched off nerve terminals, synaptosomes, of the brain led to fairly thorough characterization of the process and the ability to discriminate between transport of different biogenic amines, such as norepinephrine and serotonin (Iversen, 1999). Dogma held that nerve terminals selectively reaccumulated the transmitter molecules they had released. Thus, increasing appreciation that glia are the predominant mode of transmitter inactivation in the brain, especially for glutamate, was revolutionary.

In 1972 Lilly scientists used synaptosomal transport to identify fluoxetine (Prozac) as a selective inhibitor of serotonin uptake (Kramer, 1993; Torres and Amara, 2007). A series of serotonin-selective reuptake inhibitors were shortly followed by norepinephrine-selective antidepressants. Both classes of drugs are clinically effective, leading to resolution of the long fought battle between those favoring either serotonin or norepinephrine as critical in regulating mood. The answer—both are important.

The field of neurotransmitter uptake was somewhat dormant until 1991 when Susan Amara and coworkers cloned norepinephrine transporters, followed by cloning of transporters for all the transmitter amines, amino acids, and related neuroactive substances

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(Torres and Amara, 2007). Molecular genetic techniques identified a repeat of 20–23 bp within a polymorphic region of the serotonin transporter gene, occurring as two alleles, the "short" variant of 14 repeats and the "long" 16 repeat variant (Belmaker and Agam, 2008). The short form leads to decreased expression of the serotonin transporter and less serotonin uptake. This short allele interacts with stressful life events and correlates with the recurrence of depression. Thus, besides mediating actions of antidepressants, serotonin appears to have an etiologic role in some forms of affective illness. Buttressing this conclusion, polymorphisms in the gene for the brain-specific tryptophan hydroxylase-2, the rate-limiting enzyme in serotonin biosynthesis, are associated with depression in discrete populations.

Neurotransmitter localizations and actions

The ability to visualize neurons containing individual neurotransmitters has been a profoundly important advance in neuroscience, contributing mightily to the principal mantra of the neurosciences—to link neurochemistry, neuroanatomy, and neurophysiology. This effort commenced in the mid-1960s with the development by Nils-Åke Hillarp, Bengt Falck and collaborators of procedures whereby catecholamines and serotonin fluoresce in the microscope after reaction with formaldehyde vapors. Hillarp and his students Kjell Fuxe and Annica Dahlström then mapped norepinephrine, dopamine, and serotonin containing neurons in the brain (Hillarp et al., 1966). Immunohistochemical mapping of neuropeptides, pioneered by Tomas Hökfelt, was of comparable importance (Hokfelt et al., 1984). Although carried out just before 1970, this work laid the conceptual underpinnings for the integrated molecular/cellular/neurophysiologic world of recent decades.

The 1970s were the years of neuropeptides. Identification of opiate receptors raised the question, "Why have receptors for opiates? Man was not born with morphine in him." Several groups purified peptides from the brain with selective opiate-like activity. In December 1975 John Hughes, Hans Kosterlitz, and collaborators reported the sequences of two five-amino acid containing peptides, methionine-enkephalin and leucine-enkephalin (Hughes et al., 1975). In the months leading up to this denouement, opiate researchers had conclaved to name the hypothetical morphine-like substances and selected "endorphins." Hughes and Kosterlitz preferred the designation enkephalin from the Greek "in the head." They wished to free the scientific community from prejudice that these substances would relate only to opiate-associated behavior. With the discovery of other opioid peptides incorporating the enkephalin sequence, the term endorphin came to be used generically for any peptide with opioid activity. Since "we are not addicted to ourselves," many pharmaceutical concerns attempted to develop enkephalin derivatives as less addicting analgesics—they all failed. At opiate receptor complexes, stable drug-like enkephalin derivatives are just as addicting as most opiates. The rapid degradation of synaptically released enkephalins precludes their persistent receptor occupancy, which is necessary to initiate the addictive process.

Isolation of the enkephalins sparked a massive interest in peptides as potential transmitters. Immunohistochemical mapping revealed several dozen peptides highly localized to specific neuronal populations in the central and peripheral nervous systems. The localization of substance P, calcitonin gene-related peptide, and others in thin, unmyelinated pain fibers led to efforts to develop analgesics blocking receptors for these peptides.

Edward Herbert as well as Shosaku Numa elucidated how neuropeptides are generated, introducing some startling new concepts (Douglass et al., 1984). Many years earlier Donald Steiner had shown that insulin is generated from a large protein precursor, proinsulin, in two steps. Within the precursor, insulin is surrounded by pairs of basic amino acids. First, a trypsin-like enzyme cleaves to the right of each of these basic amino acids leaving insulin with a single lysine or arginine at its C terminus. A carboxypeptidase then removes the attached basic amino acid. A similar pattern was elucidated for the enkephalins and β-endorphin. But there were surprises. The β-endorphin precursor, pro-opiomelanocortin, contains within its sequence ACTH and melanocyte-stimulating hormone along with β-endorphin. The enkephalin precursors provided other surprises. One of the precursors contains six copies of methionine enkephalin and a single copy of leucine enkephalin, while the other contains three copies of leucine enkephalin.

Among the amino acids, the past four decades have witnessed enormous interest in glutamate as the principal excitatory neurotransmitter in the brain. Differentiation of glutamate receptor subtypes was key to this effort, especially the discrimination of NMDA and AMPA receptors. It is now well accepted that most "bread and butter" excitatory transmission involves AMPA receptors. NMDA receptors are both voltage and ligand gated. Thus, depolarization by AMPA receptor activation opens NMDA receptors permitting the influx of calcium, a critical event in the synaptic plasticity underlying long-term potentiation. Work of Roger Nicoll, Robert Malenka, and others showing that many AMPA receptors are "silent" led to numerous studies showing that cycles of internalization and externalization of AMPA receptors are also critical to synaptic plasticity (Kerchner and Nicoll, 2008).

Observations in the late 1980s that nitric oxide mediates endothelial dependent relaxation of blood vessels piqued the interest of ourselves and others in the possibility that NO might be a neurotransmitter in the brain (Bredt and Snyder, 1994). Stimulation of cyclic GMP by glutamate receptors was shown to be mediated by NO. Purification and cloning of the neuronal NO synthase (nNOS) permitted its characterization in depth and the identification of inducible NOS and endothelial NOS. Although nNOS occurs in only 1% of neurons, their processes ramify so extensively that every cell in the brain is probably exposed to NO. When released in excess following hyperstimulation of NMDA receptors, NO is neurotoxic and may mediate brain damage from vascular stroke. In the peripheral nervous system, NO is also an important neurotransmitter, well established as the transmitter that mediates penile erection. The alleviation of erectile dysfunction by inhibitors of phosphodiesterase-5 such as sildenafil (Viagra) reflects augmented levels of cyclic GMP, the second messenger for NO. Although the vascular actions of NO stem from activation of guanylyl cyclase, it is increasingly appreciated that most signaling by NO involves nitrosylation of numerous prominent cellular proteins such as the sodium pump, actin, and tubulin (Jaffrey et al., 2001; Hess et al., 2005).

NO is not the only gaseous neurotransmitter. Carbon monoxide is formed by cleavage of the heme ring by heme oxygenase (HO) (Mustafa et al., 2009). The neuronal form of the enzyme, HO2, occurs in discrete neuronal populations in the brain and periphery. In the myenteric plexus of the intestines, nNOS and HO2 are colocalized. Mice with deletion of nNOS and HO2, respectively, display 40–50% decreases in non-adrenergic non-

cholinergic (NANC) transmission with NANC transmission virtually abolished in the double knock-outs.

Recently hydrogen sulfide (H2S) has been established as a major endothelial-derived relaxing factor (EDRF) (Yang et al., 2008). EDRF activity declines profoundly in arteries of mice with deletion of cystathionine-γ-lyase, the principal H2S forming enzyme in the periphery. In the brain, cystathionine-β-synthase generates H2S, also from cysteine. H2S appears to signal by forming a persulfide linkage to cysteines in target proteins, a process referred to as sulfhydration, analogous to NO nitrosylating proteins (Mustafa et al., 2009). Whether H2S is a bonafide neurotransmitter remains to be determined.

Receptors

Most of us in the receptor field would regard 1970 as a banner year. I recall vividly the excitement attendant upon the identification of the nicotinic acetylcholine receptor in the electric organ of Torpedo, an electric eel, monitored by the binding of the pseudo-irreversible snake toxin α-bungarotoxin labeled with iodine-125 (Changeux and Taly, 2008). Jean Pierre-Changeux was a key figure in these events, while the laboratories of Ricardo Miledi and Michael Raftery were important contributors. This breakthrough was made possible by several important factors. The electric shock delivered by eels is mediated by massive numbers of the receptor, comprising up to 20% of the total protein of the electric organ. Nature evolved α-bungarotoxin to interact with extraordinarily high affinity and virtual irreversibility in order for snakes to attack their prey. Binding studies were facilitated by the ability to label the toxin with iodine-125 to extremely high specific radioactivity. Several neuropharmacologists noted that the very success of this effort portended the impossibility, for the foreseeable future, of biochemically labeling neurotransmitter/drug receptors in the brain, which were correctly estimated to represent no more than one millionth by weight of brain tissue.

In 1973 binding studies using [^{3}H]opiates enabled identification of opiate receptors in crude brain homogenates using reversibly binding ligands (Snyder and Pasternak, 2003). What contributed to the success of this unanticipated advance? Opiates labeled with tritium to high specific radioactivity permitted the use of very low radioligand concentrations, which would selectively interact with pharmacologically relevant receptors. Vigorous but extremely rapid washing permitted dissociation of nonspecifically bound radioligand while preserving interactions with the pharmacologically relevant receptor, which should have much higher affinity for the ligand than nonspecific binding sites. Within 3 years, appropriate radioligands, generally with low nanomolar dissociation constants for receptors, labeled receptors for the principal biogenic amine and amino acid neurotransmitters. This work permitted elucidation of the actions of many drugs. For the opiate receptor, heroin and codeine had negligible receptor affinity, indicating that they are only prodrugs, respectively, deacetylated and demethylated to form monacetylmorphine and morphine.

Important therapeutic effects of drugs were elucidated by receptor binding studies. Work of Arvid Carlsson on dopamine turnover had suggested that the antipsychotic effects of neuroleptic drugs might involve receptor blockade followed by feedback systems accelerating dopamine turnover (Carlsson and Lindqvist, 1963). The antipsychotic clinical potencies of a large series of neuroleptic drugs correlated closely with their affinities for dopamine receptors labeled by [^{3}H]haloperidol but not with receptors labeled by [^{3}H]dopamine (Creese et al., 1976; Seeman et al., 1976). We now know that the haloperidol and dopamine labeled binding sites, respectively, reflect D2 and D1 subtypes of dopamine receptors with blockade of D2 receptors being most therapeutically relevant. Muscarinic anticholinergic atropine-like side effects of first generation antipsychotic and antidepressant drugs hinder their use. Ligand binding to muscarinic cholinergic receptors afforded the drug industry a simple means for screening out such adverse actions leading to a new generation of safer and much more extensively used antidepressants.

Discrimination of binding sites by various ligands elucidated receptor subtypes. In the case of opiate receptors, Hans Kosterlitz differentiated binding sites for receptors designated μ, δ, and κ, which corresponded elegantly with evidence from pharmacologic studies in intact animals and various organ systems (Paterson et al., 1983). This advance led to efforts by the pharmaceutical industry to develop subtype-selective opiates that might be analgesics with less addictive potential, a goal that remains unfulfilled. Differentiation of serotonin receptor subtypes has facilitated the development of diverse agents, including 5-HT3 antagonists, in relieving the nausea of cancer chemotherapy and the triptan class of antimigraine agents.

A giant step forward in appreciation of receptors came from their molecular cloning, an effort in which the laboratory of Numa pioneered, with the cloning of the nicotinic acetylcholine receptor of the neuromuscular junction in 1982, an area in which Jean-Pierre Changeux also made major contributions (Numa, 1987). Cloning the receptor protein revealed that it harbors both the recognition site for the neurotransitter and the associated ion channel. This observation was presaged by work of Richard Huganir and Ephraim Racker who reconstituted the acetylcholine receptor protein, purified by conventional biochemistry, into vesicles loaded with radiolabeled sodium and demonstrated that the pure receptor protein contains the relevant sodium ion channel (Huganir and Racker, 1982). Today we take this concept for granted, but many investigators felt that ligand-binding proteins and ion channel proteins were separate entities that migrated through the membrane by lateral diffusion with binding of the neurotransmitter triggering their linkage. Robert Lefkowitz cloned the first biogenic amine receptor, the β-adrenoceptor (Dixon et al., 1986). Like Numa and others, Lefkowitz laboriously purified the receptor protein to homogeneity, obtaining partial amino acid sequence, then screened a cDNA library with a nucleotide probe. The β-adrenoceptor turned out to be a homolog of rhodopsin, cloned by Jeremy Nathans (Nathans and Hogness, 1984), who then cloned genes for the three visual pigments that mediate color vision (Nathans et al., 1986).

Intracellular messengers

In 1970, cAMP and cyclic GMP were the only established second messenger molecules. It was assumed that hormone/transmitter mediated deformation of receptors somehow impacts adenylyl cyclase. In 1969–1970 Martin Rodbell and Lutz Birnbaumer discovered that hormonal stimulation of receptor-coupled adenylyl cyclase required the addition of GTP leading to Rodbell's proposal of a "G protein," which binds GTP and interfaces with the receptor (Rodbell, 1992). Alfred Gilman sought and isolated such proteins using the S49 leukemia cell line variant, which contains receptor and adenylyl cyclase but still does not respond to hormone treatment (Gilman, 1995). In 1994 Rodbell and Gilman shared the Nobel Prize in Physiology or Medicine for this

effort. Today's scientists are often obsessed with publishing only in journals with high "impact factors." Virtually all the key Rodbell and Gilman publications appeared in the *Journal of Biological Chemistry*.

In the mid-1980s Michael Berridge and colleagues identified inositol 1,4,5 trisphosphate (IP3) as a second messenger mediating the ability of hormones to release intracellular calcium (Berridge, 2009). It soon became evident that as many or more neurotransmitters and hormones act via IP3 as through cAMP. Since intracellular calcium is released in discrete quanta, it was assumed that intracellular calcium is stored in small vesicles whose surfaces must contain receptors for IP3. The "grind and bind" techniques that permitted identification of neurotransmitter receptors in the brain also facilitated labeling of IP3 receptors and their purification (Ferris and Snyder, 1992). Reconstitution of the purified IP3 receptor protein into lipid vesicles loaded with radioactive calcium revealed that the receptor contains both an IP3 recognition site and its associated calcium channel and permitted demonstration that the pure receptor protein contains the machinery to mediate quantal release of calcium. Receptor cloning by Katsuhiko Mikoshiba revealed one of the most exquisitely regulated proteins in biology (Mikoshiba, 2007). The IP3 receptor is a very large protein, >2700 aa, with the IP3 recognition site occupying only 200 aa at the N terminus and the calcium channel comprising a similar number of amino acids at the C terminus. The large intermediate area has binding sites whereby calcium release is modulated by factors such as NADH, ATP, the immunophilin FKBP12, ankyrin, Homer, Protein 4.1, myosin, calmodulin, caldendrin, chromogranins, cytochrome *c*, TRPC C calcium channels, heterotrimeric G proteins, and Irbit.

Phosphorylation is likely the most important posttranslational modification of proteins. The pioneering work of Paul Greengard in this arena commenced in 1969–1970 (Greengard, 2001). Up to that time phosphorylation was an arcane process uniquely associated with glycogen metabolism. Greengard demonstrated that large numbers of proteins are physiologically phosphorylated, especially in the brain. He characterized a number of these in depth, such as the synapsins that regulate synaptic vesicle disposition, and DARPP32, which is highly concentrated in dopamine enriched areas of the brain and is a principal target of cAMP-dependent kinase phosphorylation. Greengard identified a series of phosphatases and phosphatase inhibitors that regulate the various phosphorylation cascades.

Summing up

Where have we been and where are we going? The molecular characterization of synaptic transmission in terms of neurotransmitters, their receptors and intracellular messenger molecules advanced enormously in the past 40 years. The goal of all biomedical research is to understand human biology and thereby find causes and cures for disease. How do we fare when judged by these criteria? The principal drugs used in psychiatry—the antipsychotics, antidepressants and antianxiety agents—were all identified in the 1950s and the early 1960s. There have since been incremental advances but no major breakthroughs. Monitoring transmitter uptake in synaptosomes permitted the development of norepinephrine- and serotonin-selective antidepressants, which are substantive advances, but not transformational. The high-throughput monitoring of drug candidates at neurotransmitter receptors has greatly facilitated the drug development process. Systematic structure–activity analysis has permitted the design of drugs with extremely high affinity for receptors and with selectivity. For instance, the first-generation tricyclic antidepressants displayed troublesome muscarinic anticholinergic side effects. Screening chemicals at muscarinic receptors led to new generations of antidepressants devoid of these adverse actions.

What about insights into causation? Polymorphisms in enzymes of serotonin synthesis and serotonin transporters do predict susceptibility to depression indicating that serotonin is more than just a mediator of antidepressant drug effects. The explosion in technology permitting gene monitoring in humans will likely lead to further insights into the underpinnings of the major mental illnesses. Whether these genetic aberrations will involve neurotransmitters, receptors, and intracellular messengers is unknown. Thus far extensive genetic analysis of patients with schizophrenia and affective disorder has identified large numbers of rare sequence alterations that each contribute in a small way to the disease phenotype. Conceivably these illnesses will turn out to be extremely heterogeneous with multiple causal gene defects. If so, our hopes of finding "causes and cures" will be disappointed. But I am an optimist. I am confident that our molecular insights into synaptic communication will escalate in coming decades and that, 40 years from today, we will both have vastly greater insights into normal function as well as profound new understanding of disease etiology and associated therapies.

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