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73. We thank members of our laboratories for their contributions, particularly U. Ashery and J. Sørensen for supplying parts of Fig. 1. Work in our laboratories has been funded in part by the Deutsche Forschungsgemeinschaft (SFB 523 to E.N. and SFB 530 to J.R.).

VIEWPOINT

Neural and Immunological Synaptic Relations

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A synapse is a stable adhesive junction between two cells across which information is relayed by directed secretion. The nervous system and immune system utilize these specialized cell surface contacts to directly convey and transduce highly controlled secretory signals between their constituent cell populations. Each of these synaptic types is built around a microdomain structure comprising central active zones of exocytosis and endocytosis encircled by adhesion domains. Surface molecules that may be incorporated into and around the active zones contribute to modulation of the functional state of the synapse.

Although at present there is no direct connection between immunological specificity and specificity in the nervous system, some fruitful ideas may be generated by comparing the two biological systems. For example, in both systems there is specific recognition of a wide range of structures, and also storage of information acquired.

—G. Edelman, 1968. (*1*)

There is the notion that we should be able to make meaningful comparisons between the nervous system and the immune system. Both systems utilize specific molecular recognition events between discrete cells, cell:cell adhesion, positional stability, and directed secretion for communication to fulfill their respective functions. Both systems have evolved highly sophis-

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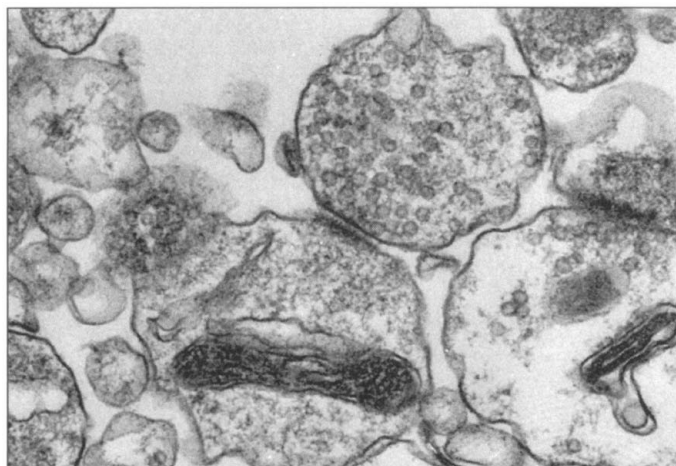
ticated forms of information storage. A focal point for this comparison has become the concept of the synapse. The high degree of functional organization of synapses makes them ideal models for general understanding of cell-cell communication.

The concept of the synapse as a nexus of communication between neurons is now well over 100 years old. It is only recently, however, that the immunological counterpart has been identified. In the immune system, the synapse functions to provide specificity to the action of otherwise nonspecific soluble agents through confinement to the synaptic cleft and to coordinate cell migration and antigen recognition during induction of the immune response. The comparison of these two synaptic junctions is useful in that they appear to share common features, but more importantly the two synapses have been approached from such different and complementary angles that some fruitful ideas should be generated by the comparison. We will argue that the immunological synapse is a valid concept by many criteria, but we must first get past some major differences.

Differences in Neural and Immune Architecture

A critical difference in the functional context of the neural and immunological synapses is in the basic "wiring" of the systems. The central nervous system (CNS) is to a great extent hard-wired and retains precise connectivity patterns throughout adult life, with neurons projecting long axonal processes that form synapses on complex dendritic trees of other neurons that may be quite distant from the cell nucleus. Whereas CNS synapses may be formed and pruned back in the adult, the long dendritic and axonal processes anchor the cell bodies and prevent cell migration. Thus, the CNS synapse is an "action at a distance" junction, in relation to the nucleus where transcription takes place. Therefore, most functions of CNS synapses may be considered "postnuclear" in that they are carried out without a requirement for immediate transcriptional regulation, although synaptic stimulation can lead to transcriptional changes in the long term. CNS synapses can alter their efficacy by processes such as receptor clustering by scaffold proteins (*2*). Synapse-forming neurons are terminally differentiated.

In contrast, the immune system operates through rapidly migrating T cells and their partners, the dendritic cells (DCs), that congregate in tissues like lymph nodes. This is essential to the operation of the immune system, because each T cell expresses a different antigen specificity and the point at which an antigen will enter the body to become associated with a DC is not predictable. So it is essential that T cells and DCs congregate and make many random contacts to possibly find

Fig. 1. An electron micrograph of a synaptosome prepared by shearing of brain tissue, showing pre- and postsynaptic compartments with retention of the adhesive contacts between the membranes at the synapse. Pre- and postsynaptic membranes are strongly adherent to one another and resist separation by physical methods. The neural synapse in the CNS has been proposed to be derived from the classic adherens junction of epithelia in that it uses cadherins and their binding partners to sustain adhesive struts across the cleft. Magnification, 60,000×.

a match and form a synapse. Migrating T cells assume morphologies similar to the growth cones of neurons but move at least 50 times faster. Thus, the T cell and DC cover greater distances than neurons in search of foreign antigens, but when the synapse is formed it is immediately proximal to the transcriptional machinery in the nucleus.

DCs are specialized antigen-presenting cells (APCs) that must engulf intact antigens, process antigens to ~1 kD fragments, and present these to T cells with the use of major histocompatibility gene complex molecules (MHCs) (3, 4). This MHC-peptide complex (MHCp) juxtaposes self and foreign determinants for interaction with the T cell antigen receptor (TCR). The vast majority of MHCps are self-peptides combined with self-MHCs, which are generally nonactivating. However, an agonist MHCp can induce T cell proliferation if present in sufficient numbers, and about 300 agonist MHCps on the APC can activate a naïve T cell (5). T cells have the ability to divide many times in response to agonist MHCps on APCs, and some of these daughter cells become memory cells, which can respond to 50 agonist MHCps per APC (5). The increase in the number and sensitivity of memory T cells is the basis of "immunological memory." The increased sensitivity may be accounted for in part by changes in receptor clustering on the T cells before interaction with the APC, although the specific scaffolding for this clustering is not known (6). Most daughter cells of activated naïve or memory T cells differentiate to form different types of "effector T cells" that can kill target cells if they are cytotoxic T cells (T_C cells) or regulate antibody production by B cells or pathogen destruction by macrophages if they

are helper T cells (T_H cells). T_C and T_H generally use different co-receptors that help the TCR with signaling, which are CD8 and CD4, respectively. There are many other types of functionally important immunological synapses, including those between antibody-producing B cells and APCs and natural killer cells and target cells (7, 8), but we will focus the current comparison on the T cell immunological synapses because these are perhaps the best studied.

The "Prototypic" Synapse

The term "synapse" is derived from Greek (9), meaning "connection" or "joining." Since the very first inkling in the middle of the 19th century that such a structure exists between nerve cells, the concept has been continuously refined to reflect the physiology and the ultrastructure as it applies to nerve cell interactions. Several key criteria are generally recognized as important in synaptic assembly.

Criterion 1: The neuron doctrine—cells remain individuals. As is the case for most cells, neurons are individual entities. The neuron doctrine emphasizes the individuality of neurons and adduces that there are points of *contiguity* but not *continuity* between neurons across which information is transferred. Implicit in the notion of discontinuity between neurons at points of contact is that there must be surfaces of separation (10)—in essence, membrane surfaces parallel to each other with a fluid-filled cleft in between (Fig. 1).

Criterion 2: Adhesion. In the initial stages of synapse formation there are recognition events through which one surface recognizes another (11). If the "fit" is right, the pre- and postsynaptic surfaces are locked together by putative and bona fide adhesion molecules (12); the latter set in nonsynaptic cell systems have been unequivocally shown to function in cell:cell adhesion (Fig. 2A).

Criterion 3: Stability. The adhesive clamp provides stability and aligns the "active zones" and postsynaptic elements in relation to one another. Certain adhesion molecules, such as N-cadherin, may also change conformation and, therefore, adhesivity in response to synaptic activity (13) and modulate future synaptic responses. The polarity of the cytoskeleton may also

influence stability as the organization of the cytoskeleton may change to further stabilize the synapse (14, 15).

Criterion 4: Directed secretion. On the presynaptic side, a secretory apparatus is assembled that is activated by appropriate signaling events (16, 17). On the postsynaptic side, a receptor surface is put in place containing molecular machinery that transduces secretory signals into relevant intracellular signals (18). The presynaptic and postsynaptic "surfaces of separation" partition certain functions in the lateral plane of the membranes, such that complex microdomains (19–21) are formed around a central "active zone" for secretory communication (Fig. 2A). The configuration of these microdomains may change in response to synaptic activity.

In contemporary view, therefore, a neurochemical synapse comprises two lipid barriers with a gap or cleft in between. It should be emphasized that this is a functional gap, not a structural one; the gap is not empty, as has been frequently diagrammed, but is filled with electron-dense material (22) (Fig. 1), some of which consists of interlocking adhesion molecules that adhere pre- and postsynaptic membranes together. Other components include the extracellularly disposed domains of receptor molecules (20, 23).

How Does the Prototypic Synapse Function in the CNS?

The CNS synapse comprises two related but distinct subdomains that overlap structurally and functionally as well. First, there is the synaptic scaffold that is observed by electron microscopy. This is the apposed parallel plates of pre- and postsynaptic plasma membrane thickened at their points of apposition and seemingly attached by filamentous material that spans the synaptic cleft. In the pre- and postsynaptic compartments, a cytomatrix is observed, which is somehow attached to the pre- and postsynaptic thickenings (Fig. 1). This scaffold is recovered even after high shear force cell fractionation followed by detergent extraction, and there is compelling evidence that the synaptic junctional complex in the CNS is maintained by strong adhesive interactions.

A second subdomain is the neurotransmissional machinery with which the synapse fulfills one of its major physiological functions, and this machinery is integrated within the scaffold, interacting with it via molecular linkages we do not understand at this time. Of great interest is the notion that each individual synapse has a microdomain organization in the plane of the plasma membrane, and intracellular molecules on both sides of the membrane may be restricted to "molecular laminae," which may be

recognized in high-resolution immunoelectron microscopy studies (*24*).

There are several groups of cell recognition and cell adhesion proteins that have been characterized and implicated in synaptic organization in the CNS (*25–30*). Whereas adhesion in the immune synapse is integrin mediated, cadherins are believed to function in an analogous capacity at the CNS synapse, in concert with molecules from other families. Cadherins function generally in epithelial adhesion and can be expressed in mutually exclusive distributions in CNS synapses (*31*). One model for synaptic junction formation postulates that once correct axonal targeting has been achieved, it is the differential distribution of cadherins at incipient synaptic surfaces that locks in nascent synaptic connections (*32*). There is evidence that cadherins function at least in part as synaptic specifiers in the molecular recognition phase of synaptogenesis, as well as participating as adhesive struts in gluing together pre- and postsynaptic membranes across the synaptic gap (*29, 33–35*).

The recent wide adoption of the term "immunological synapse" to describe the T cell–APC interface recognizes the important contributions of prior studies on the neural synapse to the general understanding of cell-cell communication. Concepts such as quantal release of neurotransmitters and the molecular mechanisms of receptor clustering have provided important guidance for immunologists. However, there are open questions about CNS synaptogenesis that could be tackled by using paradigms developed for the immunological synapse.

Formation of the Immunological Synapse

A synaptic basis for immune cell communication was suggested in the early 1980s after the identification of T cells, APCs, lymphocyte·cell adhesion molecules, and the TCR (*36*). Although this proposal was untested in 1984, many T cell–APC interactions now pass all four criteria we defined above for a synapse. The T cell and APCs remain as discrete cells during their interaction (*3*). Bona fide adhesion molecules link the T cell and APCs (*37*). The TCR:MHCp interaction delivers a stop signal to ensure positional stability (*38*). Vectorial secretion is a property of immune cell interactions (*39–41*). Thus, we feel that it is interesting to consider how the immunological synapse forms and works in relation to the CNS synapse.

The immunological synapse is composed of micron-scale supramolecular activation clusters (SMAC) (*42–45*) (Fig. 2, B and C). The dominant stable synaptic pattern is a mature immunological synapse with a central cluster of TCR:MHCp interactions (central or cSMAC) surrounded by a ring of LFA-1:

ICAM-1 (integrin mediated) interactions (peripheral or pSMAC) (*42, 44*). At this point, the microtubule organizing center and Golgi apparatus are positioned within a micrometer of the cSMAC, and radiating microtubules appear to contact the pSMAC (*40, 46*). This pattern forms through a distinct early intermediate in which the LFA-1:ICAM interactions are dominant in the center and the TCR:MHCp interaction is peripheral, referred to as an immature immunological synapse (*44, 47*) (Fig. 2D). Mature synapse formation takes minutes but can be stable for hours (*44, 48, 49*). Evidence of molecular rearrangements associated with synapse formation has been demonstrated in vivo and in ex vivo intact lymph node organ cultures (*49, 50*).

The earliest step in synapse formation can be directly correlated with topologically driven receptor segregation based on the size of the different receptor-ligand pairs (*37, 51, 52*). For example, the 15-nm CD2:CD58 pair segregates from the ~40-nm LFA-1:ICAM-1 pair (*43*). Receptor topology appears to be very important, because the similarity in size between the CD2:CD48 pair and the TCR:MHCp pair at around 15 nm is critical for sensitive T cell activation on the basis of experiments where CD48 with additional domains added to lengthen it inhibited T cell activation by APC (*53*). The driving force for this segregation might be the thermodynamic advantage of aligning the membrane surfaces with nm precision, which serves to enhance interactions (*54*). An energetic penalty associated with membrane bending may define the minimum size of the segregated domains.

The mechanism of SMAC organization is less clear. One leading hypothesis is that the process of cSMAC formation is very similar
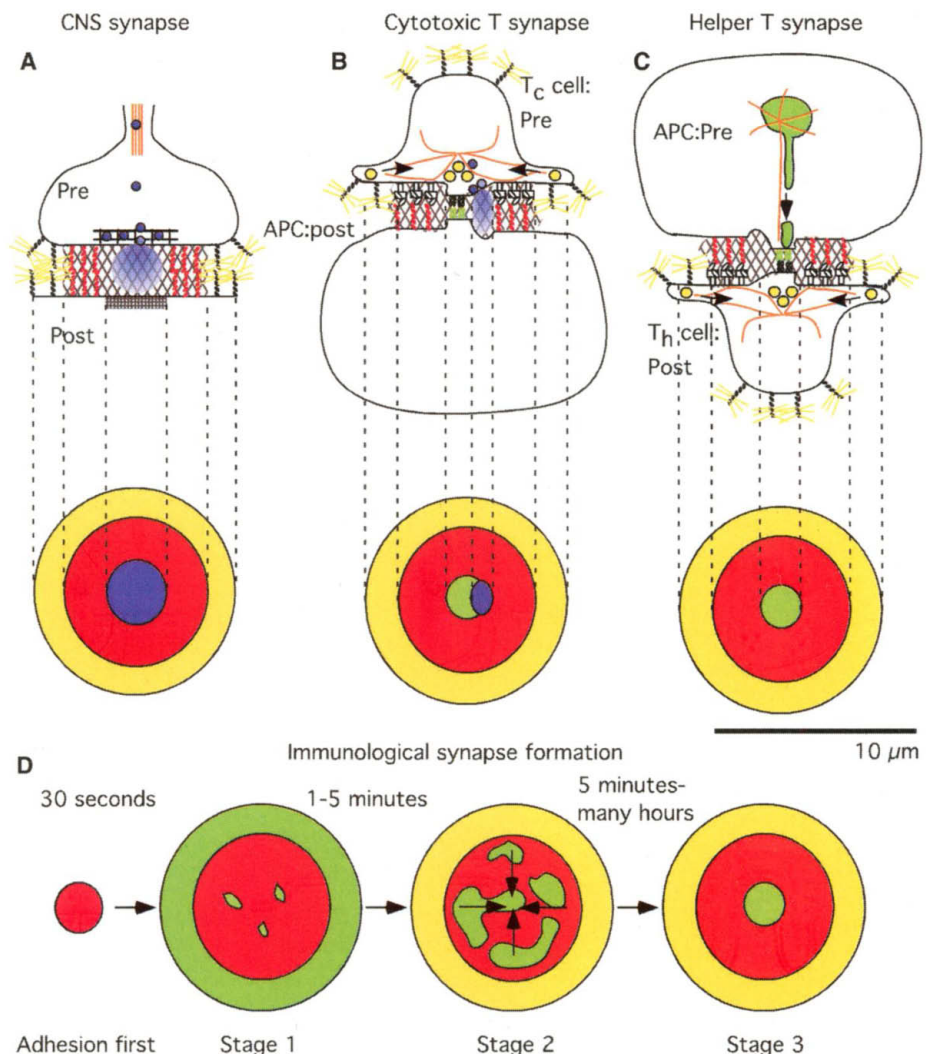

Fig. 2. Schematics of immunological and neural synapses. (**A**) Effector immunological synapse with T_C as presynaptic and target cell as postsynaptic. (**B**) Inductive immunological synapse with DC as presynaptic and T_H as postsynaptic. (**C**) CNS synapse. (**D**) Diagram of immunological synapse formation. Green, TCR-MHCp interactions and MHCp in exocytic vesicles; red, LFA-1:ICAM-1 interaction; blue, soluble contents of exocytic vesicles and diffusing contents after release; yellow, CD43 at boundaries; orange, microtubules; cross-hatch, material in synaptic cleft.

to antibody-mediated capping, involving an actin-myosin transport process (55–57). This transport process may be activated by early signaling that peaks during the time when the synapse is in the process of being formed (48). There is direct evidence that actin-myosin transport toward the synapse is active during synapse formation (58). However, the definitive evidence that cSMAC formation takes place through directed transport is lacking. Chakraborty and colleagues have proposed a provocative alternative hypothesis based on the coupling between thermally driven membrane fluctuations and the kinetics and mechanics of the different types of receptor-ligand interactions (59). When the membrane oscillations harmonize with the kinetics of the receptor-ligand interactions, patterns like the mature immunological synapse can be generated in a computer simulation. This "synapse assembly model" can also reproduce the correlation between the kinetics of TCR:MHCp interaction and mature synapse formation for T_H cells (60). Another interesting prediction of the synapse assembly model is that some self-MHCps may synergize with agonist MHCp to lower the threshold for mature synapse formation (60). Recent experiments demonstrate that model self-MHCps do in fact amplify TCR responses to low levels of agonist MHCp and promote mature synapse formation (61). The major difference between the "actin-myosin transport" and "synapse assembly" models is that single TCRs are expected to follow straight trajectories to the cSMAC in the former and a "jagged" path to the cSMAC in the latter. Therefore, the two models can be distinguished with fluorescence single molecule tracking (62).

Functions of the Immunological Synapse

The function of the immunological synapse can be divided into two branches based on induction and action phases of the immune response. It has been proposed that the immunological synapse has a role in signal integration in the induction of T_H cell proliferation (44, 63). Here the synapse pattern may be a stable product of early signaling that allows sustained integration of information from the APC (64). In the action mode, the pSMAC acts as a gasket to contain secretion of soluble agents (cytokines and cytotoxic agents) that are released near the cSMAC and held in the synaptic cleft (40, 65). In this way, the only cell that is acted upon is the cell with which the T cell forms the synapse, and this function is clearly analogous to that of the neural synapse. In the immunological synapse, the gasket is integrin dependent, whereas at the neural synapse cadherins and other molecules form the gasket.

In the induction phase of the response, the

roles of the T cell and DC in synapse formation are reversed (Fig. 2, B and C). It is important to consider membrane-anchored as well as soluble signals that are exocytosed into the synapse and are then precisely positioned for interactions with receptors on the apposing cell. The DC is then the presynaptic cell directing the exocytosis of MHCp into the nascent synapse (66, 67). The newly secreted MHCp can then be bound by the TCR on the postsynaptic side (63) (Fig. 2C). Cosecreted with the MHC are accessory molecules like CD86, which promote T cell activation and differentiation (68). Costimulatory molecules like CD80 and CD86 contribute to early T cell activation, and CD80 has been demonstrated to interact with one of its receptors, CD28, in the cSMAC (69). In this model, it is implied that there are a small number of agonist MHCps on the surface of the DC when the T cell first makes contact to initiate the signaling interaction; but once a low level of antigen-dependent activation is achieved, a positive feedback mechanism delivers more MHCps to the synaptic site, which supports sustained signaling.

So, what is the function of the immunological synapse pattern for a naïve T cell in the induction phase of an immune response? In order to proliferate, a naïve T cell must initiate and sustain activation of transcription factors (70). As the nascent immunological synapse is formed, the lck and ZAP-70 tyrosine kinases are rapidly activated within 2 min, which initiates processes leading to transcriptional activation (48) and is also likely to be essential for mature synapse formation (48, 64). Secondary signals required for commitment of T cells to proliferate may be sustained for hours and may involve low levels of tyrosine kinase activation (42). Activation is correlated with immunological synapse formation when MHCp dose and quality are varied, such that synapse formation appears to be determinative under these conditions. The immunological synapse may be terminated by negative signaling receptors like CTLA-4 interacting with CD80 and CD86 (also ligands for CD28) (71) and by changes in cellular interactions during mitosis (49). Both CTLA-4 induction and the first mitosis occur around 36 hours after first contact for a naïve T_H cell.

Experimental Models for Synaptogenesis

There are two major technologies that have allowed real-time evaluation of events in the immunological synapse in recent years. One is live-cell fluorescent imaging of T cells in contact with supported planar bilayers. The other is the use of real-time confocal imaging in the T cell–APC interface.

The analysis of interactions in the cell-cell interface is the more physiological of

the two, but interpretation is difficult because the lateral and cytoplasmic interactions of each surface receptor cannot easily be controlled.

The supported planar bilayer system is a reconstitution method (72) that gets around this problem. We can, for example, present purified MHCps and accessory molecules to induce T cell proliferation (44, 69, 73). The molecules in the bilayer can be made laterally mobile (74) and fluorescently labeled, which allows direct observation of interactions of cell surface receptors with molecules in the bilayer. This is the only system where accumulation of fluorescence is sure to have a 1:1 relationship with receptor-ligand interaction. The caveat is that cytoskeletal mechanisms and membrane organization in a live APC are lost (75, 76). The rigid nature of the planar bilayer is probably not a major drawback because T cell–APC interfaces are generally flat (73) and the change in degrees of freedom before and after synapse formation is the same in the cell-planar bilayer and cell-cell situation (59). Reconstitution of neural synapses with this or similar technology would be informative (77, 78).

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79. M.L.D. is supported by NIH and the Irene Diamond Fund. D.R.C. is supported by NIH, the New York State Spinal Cord Injury Trust, the Canada Institutes of Health Research, the Canada Foundation for Innovative Programs, and a Canada Research Chair.

VIEWPOINT

Alzheimer's Disease Is a Synaptic Failure

Dennis J. Selkoe

In its earliest clinical phase, Alzheimer's disease characteristically produces a remarkably pure impairment of memory. Mounting evidence suggests that this syndrome begins with subtle alterations of hippocampal synaptic efficacy prior to frank neuronal degeneration, and that the synaptic dysfunction is caused by diffusible oligomeric assemblies of the amyloid β protein.

Among the remarkable opportunities emerging from recent progress in molecular neuroscience, the prospect of understanding and preventing neurodegenerative diseases looms large. Disorders like Alzheimer's, Huntington's, and Parkinson's diseases once epitomized the mechanistic ignorance and therapeutic nihilism surrounding human neurodegeneration. But in the past decade, genes causing familial forms of such disorders have been identified, protein pathways involving the gene products have been delineated, and specific treatments directed at these pathways have begun to enter human trials.

The example of Alzheimer's disease (AD) is of special interest to neuroscientists, not only because it is the most common of the brain degenerations, but also because it usually begins with a remarkably pure impairment of cognitive function. Patients with this devastating disorder of the limbic and association cortices lose their ability to encode new memories, first of trivial and then of important details of life. The insidious dissolution of the ability to learn new information evolves in an individual whose motor and sensory functions are very well preserved and who is otherwise neurologically intact. Over time, both declarative and nondeclarative memory become profoundly impaired, and the capacities for reasoning, abstraction, and language slip away. But the subtlety and variability of the earliest amnestic symptoms, occurring in the absence of any other clinical signs of brain injury, suggest that something is discretely, perhaps intermittently, interrupting the function of synapses that help encode new declarative memories. A wealth of evidence now suggests that this "something" is the amyloid β protein (Aβ), a 42-residue hydrophobic peptide with an ominous tendency to assemble into long-lived oligomers and polymers.

New Ways to Approach the Problem

As scientists proceed to decipher ever more precisely the basis of memory and cognitive impairments in AD, new rules for how this should be accomplished are emerging. First, it has become clear that we must focus our clinicopathological analyses on the earliest stages in the disorder. Studying the brains of individuals dying (for other reasons) with minimal cognitive impairment (MCI) (1, 2), a very subtle memory syndrome that is often the harbinger of AD, is far more likely to yield compelling mechanistic and therapeutic insights than are further studies of late-stage AD brains. The enormous number of structural and biochemical changes already documented in the latter precludes their utility in identifying events that initiate AD-type neuronal dysfunction. The same is true for rodent models in which the process can be examined dynamically: The earlier one looks, the better. Synapse loss matters; loss of whole neurons comes later and matters less. Second, we must use methods that can reveal functional rather than just structural changes in the brain. The latest mouse models that coexpress transgenes encoding mutant human tau and amyloid β protein precursor (APP) (3) are particularly compelling and can be used to perform in vivo electrophysiological analyses and correlate the results with both behavioral and biochemical measures. Third, we must emphasize studies of natural assemblies of human Aβ arising under physiological conditions. Synthetic Aβ peptides have generally been applied at micromolar concentrations (in contrast to the low nanomolar levels of natural Aβ found in the brain and cerebrospinal fluid), and they can aggregate

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