subsets of neurons, or they may have more of a scaffolding function.

A scenario of multiple transsynaptic signaling proteins for different subsets of glutamate synapses is a rather daunting possibility that must now be considered. Such a possibility would allow for the extensive heterogeneity found in molecular composition of individual glutamatergic postsynaptic specializations, depending on pre- and postsynaptic cell type, stage of development, and activity (Rao et al., 1998). Interestingly, there are two proteins closely related to Narp, neuronal pentraxin 1 and neuronal pentraxin receptor (Dodds et al., 1997). The latter has a putative transmembrane domain, and all three can bind to each other in a calcium-regulated manner. These proteins may function in overlapping sets of neurons to regulate glutamatergic synaptogenesis. Considering the complexity and diversity of central synapses, and the specific role of Narp in AMPA receptor clustering, O'Brien et al. (1999) may have opened the first chapter in the "Narp hypothesis" for CNS synaptogenesis.

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Leaky Synapses

The concept that neurotransmitters can act diffusely and at some distance from their release site has long been associated with monoamine- and peptide-mediated synaptic transmission, in which communication is dictated more by the location of the receptors than by the specific site of transmitter release. On the other hand, based on the structure and a number of the physiological properties of fast synapses, it has long been assumed that transmission at these synapses is point to point. Yet, during the past few years, evidence has accumulated suggesting that for excitatory synapses glutamate may, under some conditions, be able to spread out of the synapse and activate both pre- and postsynaptic receptors at adjacent synapses. For instance, it has been shown at hippocampal mossy fiber synapses that during repetitive stimulation, glutamate can leave the synaptic cleft and act on presynaptic mGluRs at neighboring synapses (Min et al., 1998; Vogt and Nicoll, 1999). It has also been found that synaptically released glutamate can rapidly activate glutamate transporters on surrounding glial cells (Bergles and Jahr, 1997), indicating that glutamate is capable of spilling out of the synaptic cleft even during low-frequency synaptic activity. Finally, it has been suggested that glutamate spillover may selectively activate postsynaptic NMDA receptors (NMDARs), which are of much higher affinity for glutamate than AMPA receptors; this might explain the occurrence of so−called silent synapses, which exhibit synaptic responses mediated solely by NMDARs (Kullmann and Asztely, 1998). However, the evidence for activation of NMDARs by glutamate spillover has, for the most part, been circumstantial.

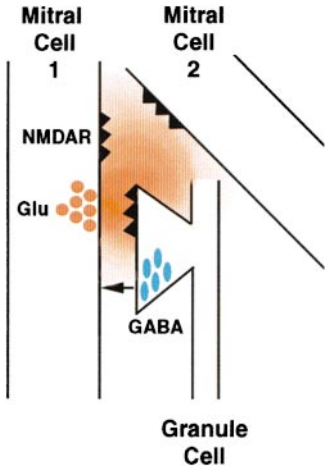

Diagram of Dendrodendritic Inhibition in the Olfactory Bulb and of Glutamate Spillover from One Mitral Cell Dendrite onto a Neighboring Mitral Cell Dendrite

In an elegant series of experiments reported in this issue of *Neuron*, Isaccson (1999) has unequivocally shown in the olfactory bulb that the synaptic release of glutamate can spread from one cell and activate NMDARs on a neighboring cell. Mitral cells, the primary relay neurons of the olfactory bulb, release glutamate from their dendrites onto the processes of inhibitory granule cells, which in turn release GABA directly back onto the mitral cell dendrite (see figure) (Jahr and Nicoll, 1982; Isaacson and Strowbridge, 1998; Schoppa et al., 1998). When this inhibitory feedback is removed pharmacologically by a GABA antagonist, a direct self-excitation of mitral cells by glutamate is revealed (Nicoll and Jahr, 1982). Isaccson now shows that this action is entirely due to the direct activation of NMDARs. This synaptic response appears to be very efficient. The release of glutamate

occurs with a probability close to 1, and the open probability of NMDARs when bound by glutamate is high. Finally, the lack of effect of glutamate uptake blockers on the response suggests that glutamate is near saturation.

The ultimate experiment demonstrating the spread of glutamate involves recording from two mitral cells and showing that release of glutamate from one mitral cell can activate NMDARs on the neighboring cell (see figure). Since these responses were recorded after blockade of action potentials with tetrodotoxin and there is no anatomical evidence for direct synaptic interactions between mitral cell dendrites, glutamate must be capable of spreading from one dendrite to another. This response has two features that would be predicted for glutamate acting at a distance. First, the rise time is slow, as expected for a low concentration of glutamate. Second, blockade of glutamate uptake markedly enhances the response, and was often able to bring out a spillover response when one did not exist in control conditions. Finally, evidence is presented suggesting that this spread of glutamate can serve to synchronize the activity of a population of mitral cells and thus contribute to the oscillatory network activity that is presumed to be of importance to the processing of olfactory information. One limitation to this study is that all of the experiments were done in the absence of extracellular Mg^{2+}. This would both enhance glutamate release and allow NMDARs to pass current at hyperpolarized potentials at which, under normal concentrations of extracellular Mg^{2+}, considerably less current would be generated by NMDARs. Thus, in future experiments, it will be important to determine the degree to which spillover of glutamate onto NMDARs plays a functionally important role in synaptic communication within the olfactory bulb.

Recently, the issue of glutamate spillover has received attention because it has been advanced as an alternative explanation for "silent synapses." It is now well established that when one activates only a few excitatory synapses it is possible to record synaptic responses that are mediated entirely by NMDARs with no detectable AMPAR component. Based on this observation, it was postulated that such synapses lacked functional AMPARs (Malenka and Nicoll, 1997). However, if glutamate were able to spill over onto adjacent synapses, the lower concentration might activate the high-affinity NMDARs but fail to activate the lower-affinity AMPARs (Kullmann and Asztely, 1998).

Do the present results have an impact on the silent synapse hypothesis? Probably not. First, the present results were obtained in the olfactory bulb, where glutamate is released from dendrites and acts on extrasynaptic NMDARs. Thus, it is unclear whether one can extrapolate results from this unique synaptic arrangement to other "classical" excitatory synapses. Second, even if spillover of glutamate does occur at other excitatory synapses, this certainly does not exclude the possibility of silent synapses that lack functional AMPARs. Indeed, there is now strong anatomical support for the existence of a population of excitatory synapses which contain NMDARs but not AMPARs (Nusser et al., 1998). In addition, it is possible to record NMDAR-only synaptic responses in autapses, a preparation in which glutamate spillover cannot explain synaptic events mediated only by NMDARs (Gomperts et al., 1998). Finally, a study of the rise time of the NMDAR response at silent synapses failed to find a slowing as would be expected and, in fact, was found in the present study for the synaptic response generated by glutamate spillover (Haas et al., 1998).

Thus, the present convincing demonstration of spillover of glutamate in the olfactory bulb can live in peaceful coexistence with the silent synapse hypothesis. It is not necessarily an either/or situation. The important question now is whether there is a functional role for spillover of glutamate onto NMDARs at conventional synapses.

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Thalamocortical Synapses: Sparse but Stentorian

Nearly all of the sensory information that enters the cortex passes through the thalamus, and the most important thalamocortical (TC) projection is onto spiny neurons in layer 4. These TC synapses thus represent the main conduit through which information from the periphery flows into the cortex for further processing. One might imagine that this conduit would be correspondingly wide, but in fact it is remarkably narrow, comprising only about a tenth of all synapses onto a typical neuron in layer 4. The vigorous and rapid responses of