How Neurons Communicate at Synapses

Jose Rizo-Rey
White gives check mate in two moves
So beautiful!
Neurons are the key cells that make the brain so unique

(drawings by Santiago Ramon y Cajal)
Neurons form amazing networks

(drawings by Santiago Ramon y Cajal)
The brain is an extremely complex communications network.
Interneuronal communication occurs at synapses.
There are many types of neurons. A common feature is their polarity.
The membrane potential arises from differences in the concentrations of ions inside and outside the cell.
Some ion channels can open and close depending on the membrane potential, and help to propagate electrical signals with a very fast speed.

A single ion channel opening and closing.
These electrical signals are known as actions potentials and are propagated by opening and closing of sodium and potassium channels.
Synaptic transmission occurs at synapses.
Chemical synaptic transmission

- **action potential**
- **docking**
- **priming**
- **Ca\(^{2+}\)**
- **fusion**
- **synaptic vesicles**
- **presynaptic terminal**
- **synaptic cleft**
- **postsynaptic cell**
- **neurotransmitter receptors**
- **Ca\(^{2+}\)**
- **synaptic vesicles**
- **action potential**
- **docking**
- **priming**
- **Ca\(^{2+}\)**
- **fusion**
- **postsynaptic cell**
- **neurotransmitter receptors**
Binding of neurotransmitters to postsynaptic receptors can cause excitatory or inhibitory postsynaptic potentials (EPSPs or IPSPs), depending on the type of synapse and the neurotransmitter released.
Different inputs are integrated at the cell body, leading to an action potential in the axon depending on the balance of the inputs.
• Repetitive stimulation can lead to stronger or weaker postsynaptic potentials

• This plasticity can arise from:
  presynaptic changes in the efficiency of neurotransmitter release
  and/or changes in the postsynaptic responses

• Synaptic plasticity underlies many forms of information processing in the brain
The knee-jerk reflex illustrates a behavior controlled by a system of distinct neurons.
Synaptic vesicle fusion is key for interneuronal communication
Structures and Ca$^{2+}$ binding modes of the synaptotagmin-1 C$_2$ domains

Ubach et al. EMBO J. 17, 3921 (1998)
Synaptotagmin I acts as a Ca$_{2+}$ sensor in neurotransmitter release

In vitro Ca$_{2+}$-dependent phospholipid binding

In vivo Ca$_{2+}$-dependence of neurotransmitter release

The SNARE complex

Synaptic vesicle

Plasma membrane

Fernandez et al. (1998) Cell 18, 841
Widespread, SNARE-centric model of synaptic vesicle fusion
Model for how synaptotagmin cooperates with the SNAREs to induce calcium-dependent membrane fusion
LIPID MIXING ASSAY TO STUDY MEMBRANE FUSION IN VITRO
SNAREpins: Minimal Machinery for Membrane Fusion

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Donor:
Fluorescent v-SNARE vesicles

Acceptowr:

Viral hairpins
Cellular SNAREpins

Weber et al. (1998) Cell 92, 759
Efficient membrane fusion in vitro with SNAREs and Synaptotagmin-1


But without Munc18-1 or Munc13!
Total abrogation of neurotransmitter release
In the absence of Munc18-1 or Munc13s

Model of Munc18-1 and Munc13 function

Dulubova et al. EMBO J. 21, 3620 (2002)
Dulubova et al. PNAS 104, 2697 (2007)
Xu et al., Biochemistry 49, 1568 (2010)

Dulubova et al. EMBO J. 18, 4372 (1999)
Dulubova et al. PNAS 100, 32 (2003)
Ma et al., Nat. Struct. Molec. Biol. 18, 542 (2011)
Reconstitution of membrane fusion with Syntaxin-1/Munc18-1 liposomes
+ Synaptobrevin liposomes
+ Munc13-1, SNAP-25 and Synaptotagmin-1

Ma et al. Science 339, 421 (2013)
Efficient fusion with Syntaxin-1/SNAP-25 liposomes + Synaptobrevin liposomes + Synaptotagmin-1

Ma et al. Science 339, 421 (2013)
Fusion with Syntaxin-1/SNAP-25 liposomes + Synaptobrevin liposomes + Synaptotagmin-1 is inhibited by NSF, α-SNAP

Ma et al. Science 339, 421 (2013)
Reconstitution of synaptic vesicle fusion
with Syntaxin-1/SNAP-25 liposomes + Synaptobrevin liposomes
+ Munc18-1, Munc13-1, NSF, α-SNAP and Synaptotagmin-1!!!!!!

Ma et al. Science 339, 421 (2013)

WE GOT IT!
Highly efficient calcium-dependent membrane fusion supported by the SNARES, Synaptotagmin-1, Mun18-1, Munc13-1, Synaptotagmin-1 and NSF-α-SNAP.

**Lipid mixing**  
{T+VSyt1 +NSF/αSNAP}

**Content mixing**  
{T+VSyt1 +NSF/αSNAP}

![Diagram showing SNARE proteins and their interactions](image-url)

- **Synaptobrevin**
- **Syntaxin-1**
- **SNAP-25**
- **Synaptotagmin**

**Graphs**

- **Fluorescence (% of max)**
- **Time (s)**

**Legend**

- **Ca**

**Data Points**

- +Munc13-1 +Munc18-1
- +Munc13-1
- +Munc18-1
- T+VSyt1
Model of synaptic vesicle fusion integrating the functions of SNAREs, Munc18-1, Munc13s, NSF/SNAPs and synaptotagmin-1.

Ma et al. Science 339, 421 (2013)