Developmental Plasticity

Karl Kandler
Dept. Neurobiology

kkarl@pitt.edu
Outline

1. Normal circuit development requires activity (two examples: visual cortex, LGN)
   - Basic organization of visual system of mammals
   - Experimental evidence (deprivation studies)
   - Critical period

2. General rules of activity-dependent refinement
   - Hebb-like neuronal competition
   - LTP and LTD

3. Neurotrophins as “molecular currency” for activity-dependent competition
Optic nerve

Optic chiasm

Left visual field but from both eyes

Right visual field but from both eyes

Lateral geniculate nucleus (LGN)

Lateral geniculate nucleus: Eye specific layers

Striate cortex (primary visual cortex)

Right visual field but from both eyes

Left visual field but from both eyes
Eye-specific areas in the striate visual cortex

Ocular Dominance Columns

Recording electrode

Layer 4

LGN

Left eye

Right eye

Left eye

Right eye

Left eye

Right eye

1 2 3 4 5 6 7

Electrode track

David Hubel and Torsten Wiesel
Nobel prize 1981
Using transynaptic transport to label ocular dominance columns

Transynaptic transport through LGN

Radioactive proline

Labeled terminal in layer 4

Terminations visible as bright bands on autoradiogram

Visual cortex layer 4

Tangential section

H3-proline

transsynaptic terminals

Coronal section

Purves et al., 2001
Ocular dominance columns emerge gradually during development.

Gradual segregation of LGN terminals in L4.

(A from LeVay, Stryker and Shatz, 1978.)
The cortical space race

**Normal**
18 moth old monkey

**monocular deprivation**
(monkey right eye was sutured from 2 weeks of age until 18 month open eye was injected with H3-proline)

Hubel and Wiesel

From left eye right eye From open eye closed eye

LGN axon terminals (from cat)

Antonini & Stryker, Science, 1993
Normal monkey

Monocular deprived monkey

ipsi
contra

Number of cells

Ocular dominance group

Contralateral  Equal  Ipsilateral

Contralateral  Equal  Ipsilateral

Eyelid sutured closed
Ocular dominance plasticity is restricted to a **Critical Period**.
Formation of eye specific layer in LGN

In utero (pretty dark)

+ TTX (no spikes)
Before eye opening, retina is spontaneously active

Spontaneous Calcium waves

P5 ferret retina.
2 square millimeters
13 seconds of activity recorded in real time

From Shatz lab
Interim Summary

✓ Ocular dominance columns in primary visual cortex
✓ OCD emerge gradually during development
✓ Formation of ODC is activity dependent and competitive
✓ Plasticity is restricted to a Critical Period
✓ Activity can be sensory evoked (vision)
  or spontaneously generated (retina)

Next: Activity-dependent plasticity seems to follow general rules
  ➔ Hebb-like learning rules
Hebb-like learning rules, (Hebb, 1949)

**correlated activity**

- Pre-synaptic
- Post-synaptic

**uncorrelated activity**

- Post-synaptic
- Pre-synaptic

**Fire together – Wire together**

- Synapse becomes stronger

**Use it – or loose it**

- Synapse becomes weaker
Binocular driven L4 neuron

Open eye Activity ↑
Closed eye Activity ↓
Open eye Activity ↑

VisualCortex
Layer 4

Monocular driven L4 neuron

(postsynaptic response)

(black stripe)  (white stripe)
Experiment 1:
ODC in strabistic animals

Both eyes open

But eyes see different worlds

Activity from both eyes is uncorrelated to each other,

→ unlikely that both eyes connect to same neurons
Normal
Activity mostly correlated

Strabismus
Activity uncorrelated
Experiment 2: Monocular deprivation but cortex silenced
Cortex silenced with Muscimol (GABA$_A$-R agonist)

Hata and Stryker, Science, 1994

Inject
open eye

Inject
closed eye

Control cortex

Muscimol cortex
Summary
ODC plasticity seems to follow Hebb-like rules

Three examples:
1. Monocular deprivation
2. Strabismus
3. Silenced cortex

Next: Cellular basis?
A cellular substrate for Hebb-like plasticity: **LTP and LTD**

Record synaptic responses in layer 4

Brain slice

Electrical stimulation of LGN-axons in white matter

**Correlative evidence!**

Dark rearing of animals can prolong the critical period and can also prolong the period of LTP expression. Correlative evidence!
**LTP** and **LTD** depend on activation of NMDA-receptors
Block NMDA-receptors $\rightarrow$ Block Block ODC plasticity?

*Roberts, Meredith, Ramoa J. Neurophys., 1998*

However....

NMDA-R also participate in normal synaptic transmission
In visual cortex of mice, LTD depends on mGluR2

Renger et al., PNAS, 2002

If LTD is involved in losing input from closed eye → ODC plasticity should be blocked if mGluR2 is blocked
A long sought-after question: Does LTP induce new synapses?

The problem:
- a) What presynaptic fibers are stimulated
- b) What synapses undergo LTP

The solution:
- a) Record from 1 neuron
- b) Block synaptic transmission with 0 Ca$^{2+}$
- c) Add calcium locally → site known

Where to look?

Watch real-time!
(2-photon microscopy)

Engert & Bonhoeffer, Nature, 1999

Movie?
**Interim summary**

Hebb-like rules as mechanism for developmental plasticity:

**Pro**
- LTP during Critical period
- no LTP by blocking NMDARs → no MD plasticity
- LTP makes spines grow and LTD makes spines shrink

**Contra**
- Block of mGluR (KO mice and pharmacologically)
  prevents LTD *in vitro* but but not ODC plasticity *in vivo*

Next: What is the stuff?
- Neurotrophins
Neurotrophin: Miracle Growth for Neurons

Nerve Growth Factor: NGF
(Levi Montalcini)

Brain Derived Neurotrophic Factor: BDNF
Neurotrophin 3: NT3
Neurotrophin 4/5: NT4/5

McAllister and Katz, Neuron, 1996
Correlated pre- and postsynaptic activity increases NT secretion from active postsynaptic sites.

Axon 1 and 2 become stronger and sprout new connections.
Axon 3 becomes weaker and eventually is retracted.

Synapses are maintained by low levels of spontaneously released NT.
Support for Neurotrophin hypothesis:

1. BDNF-induced growth requires activity

McAllister et al, Neuron, 1996
Support for Neurotrophin hypothesis:

2. BDFN signaling is involved in ODC plasticity

Excess BDNF $\rightarrow$ no ODC

*Cabelli, Horn, and Shatz, Science, 1995*

Remove endogenous BDNF $\rightarrow$ no ODC

*Cabelli, Shelton, Segal, and Shatz, Science, 1997*
Support for Neurotrophin hypothesis:

3. BDNF acts locally

Recipient Neuron: green
BDNF Donor Neuron: red

Magical distance < 5 µm

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General rules of activity-dependent refinement

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Neurotrophins as “molecular currency” for activity-dependent competition
**MHCI: a new candidate in activity-dependent circuit refinement**

Discovered in the brain with unbiased differential screen (Corriveau, Hu, Shatz, Neuron, 1998)

[Diagram of antigen-presenting cell with beta 2-microglobulin (β2m) and transporter associated with antigen processing (TAP)]
Many MHC class I are highly expressed in the brain

mRNA expression for three MHC class I in adult mouse brain

Boulanger and Shatz, Nature Neuroscience Review, 2004
Expression of MHCI and CD3ζ is regulated by activity

control

Activity blocked with TTX

In situ of MHCI on cat LGN at E52 (formation of eye-specific layers)

Corriveau et al., Neuron, 1998
Does disturbance of MHC class I disturb developmental refinement?

Mouse LGN refinement

Ipsilateral arbors retract
Formation of eye specific layer in LGN

Retraction of ipsilateral projection

Stabilization of contralateral projection
Block of MHCI signaling in mutant mice – ipsilateral projection is larger

Retina projection to ipsilateral LGN in P13 mice

Hippocampal LTP is increased in CD3ζ -/-

Hu et al., Science 2000
**Interim summary**

MHCI and activity-dependent refinement

1. MHCI and CD3ζ are expressed during critical periods

2. Expression of MHCI and CD3ζ is regulated by activity

3. Genetic blockade of MHCI signaling
   - interferes with activity-dependent synapse elimination
   - increases LTP
Complete Summary

1. Developmental plasticity often follows by Hebb-like rules

2. LTP and LTD seem to be involved in developmental plasticity
   a) LTP and LTD amplitude correlate with critical period
   b) During critical period, silent synapse can be waken up
   c) LTP induces new synapses
   d) CaMKII is necessary for developmental plasticity

3. Neurotrophins transform activity into structural changes

4. MHCI et al. as new players of activity

Open question....