Developmental Neurobiology

Questions we are interested in:

-How are ectodermal cells induced to become neuronal cells?

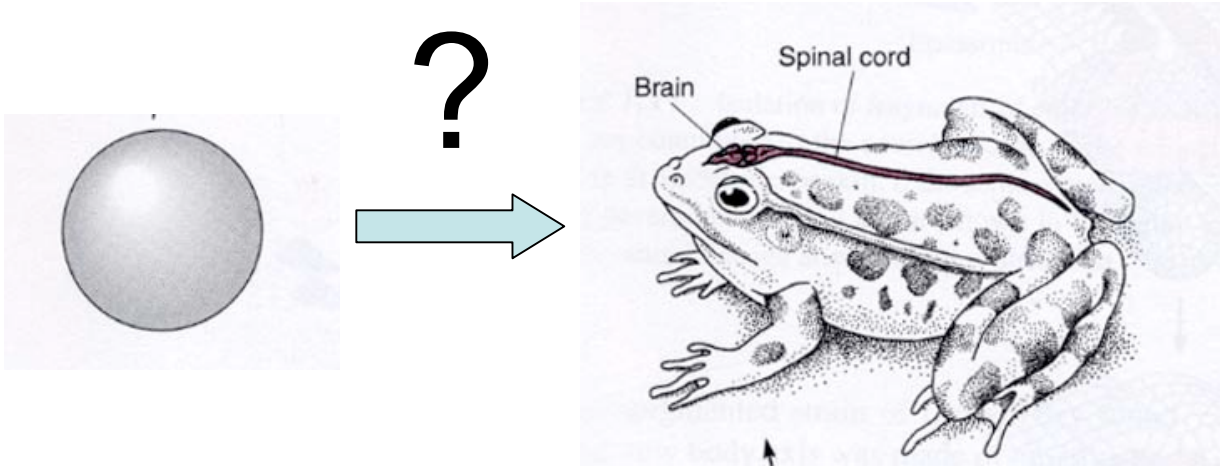
- How is Dorsal-Ventral polarity established?

-How is Anterior-Posterior polarity established?

-How are neurons born?

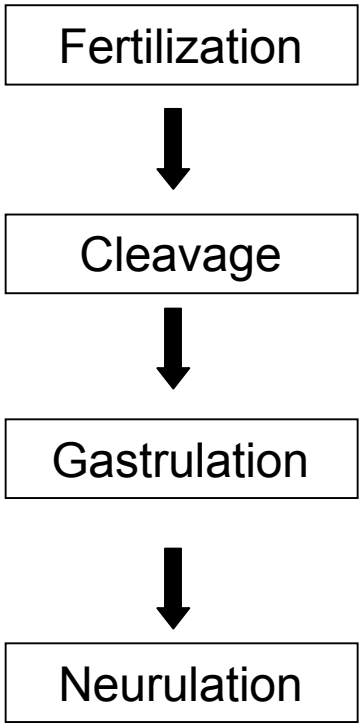
-How do neurons acquire their fates?

-How are different neuronal types established?



With thanks to Natalia Caporale, Outstanding GSI 2003
MCB 160

Initial Steps in the Development of the Nervous System:



The **determination** of different cell types (cell fates) involves progressive restrictions in their developmental potentials. When a cell “chooses” a particular fate, it is said to be determined, although it still "looks" just like its undetermined neighbors.

Differentiation follows determination, as the cell elaborates a cell-specific developmental program.

Competence is the ability of a cell to respond to a signal. It depends on the receptors, transcription factors, etc expressed by the cell

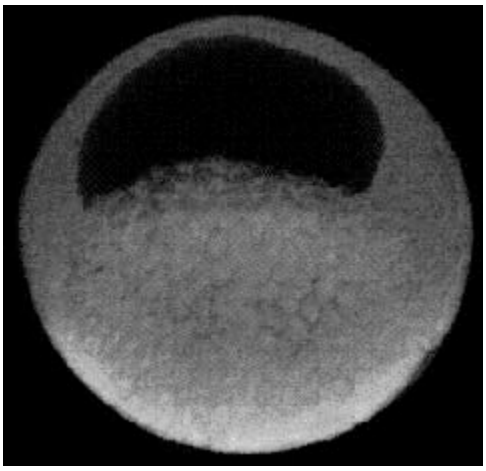
Gastrulation :

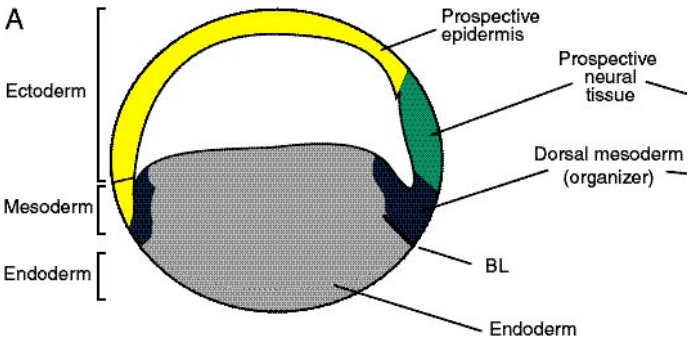
Gastrulation can be defined as the process by which the embryo acquires 2-3 germ layers. There are extensive cell movements and rearrangements.

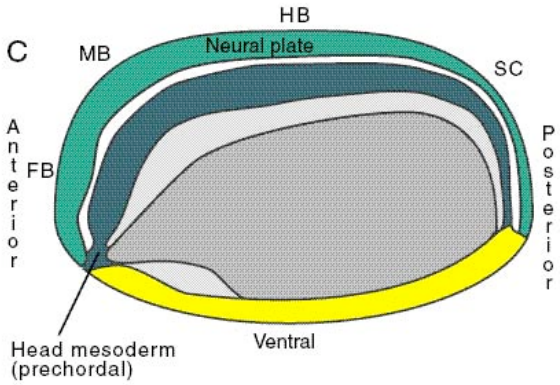
Ectoderm→ Major tissues of the Nervous System, Epidermis

Mesoderm→ Connective Tissue, Muscle, Blood, Blood Vessels

Endoderm → Gut







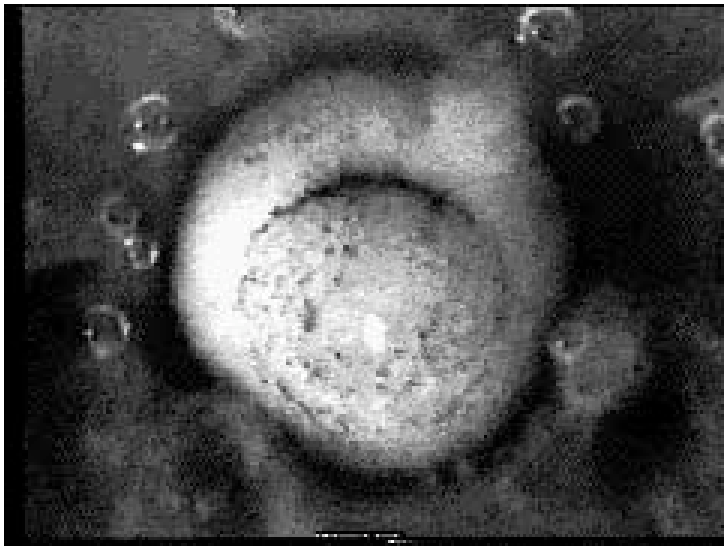
Blastula

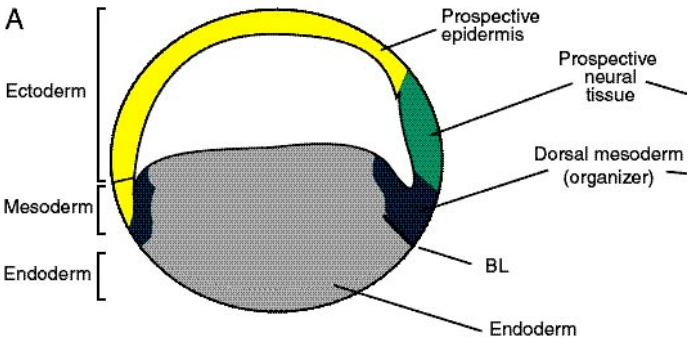
Gastrula

Neurulation: Formation of the Neural Tube

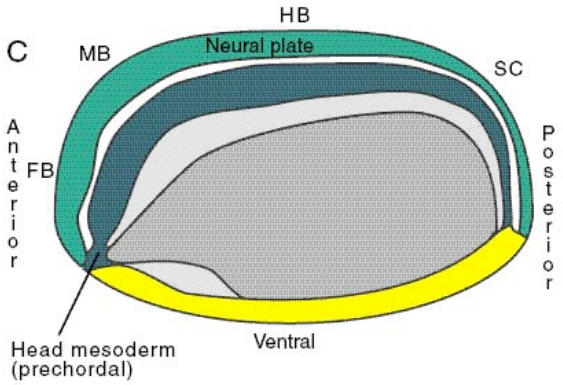
After Gastrulation comes **Neurulation.**

The formation of the **neural plate**, the **neural folds**, and their closure to form the **neural tube** is called **Neurulation**.



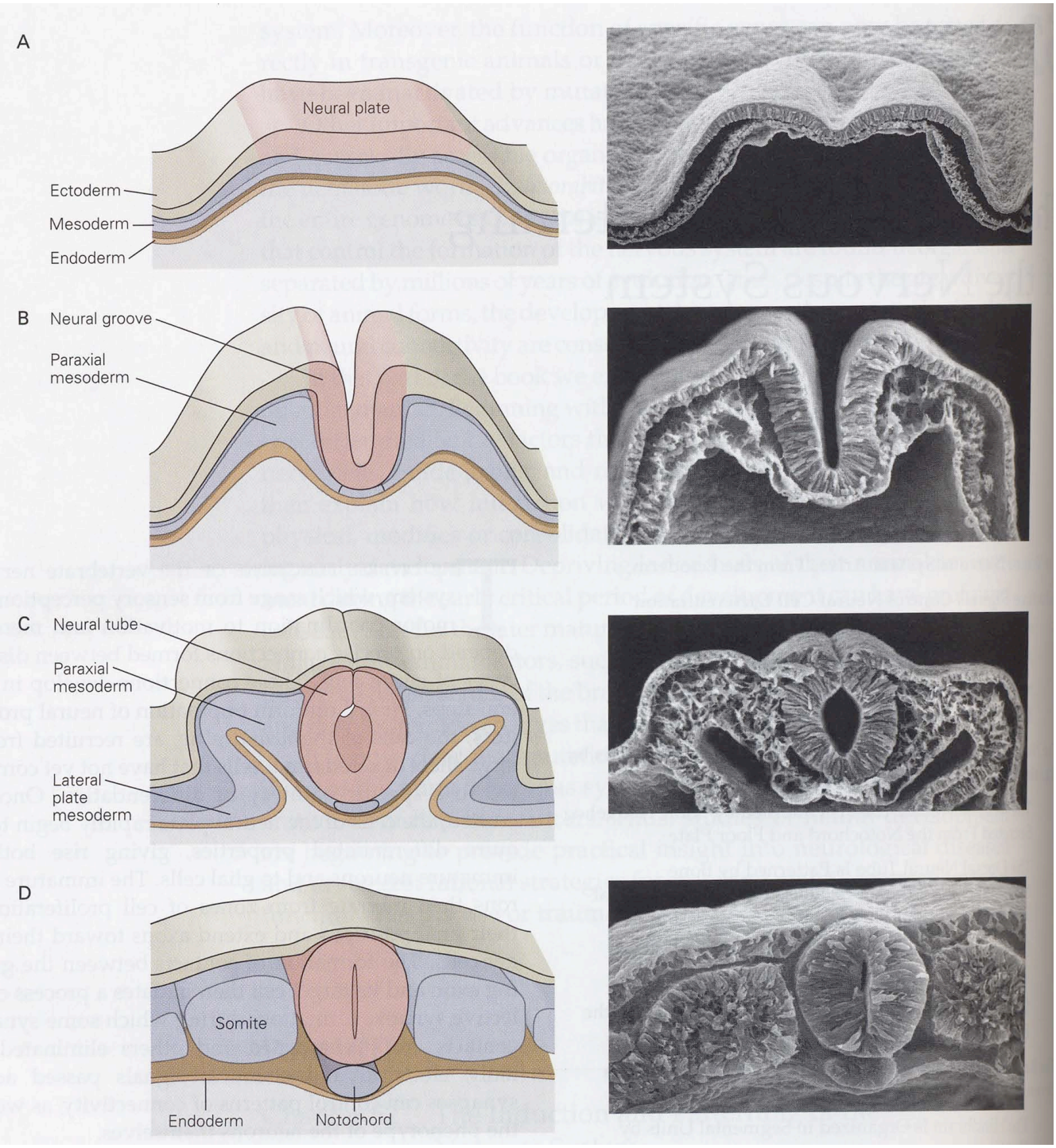


Blastula



Gastrula

Neurulation: Formation of the Neural Tube



Note: This drawing doesn't show the neural crest cells.

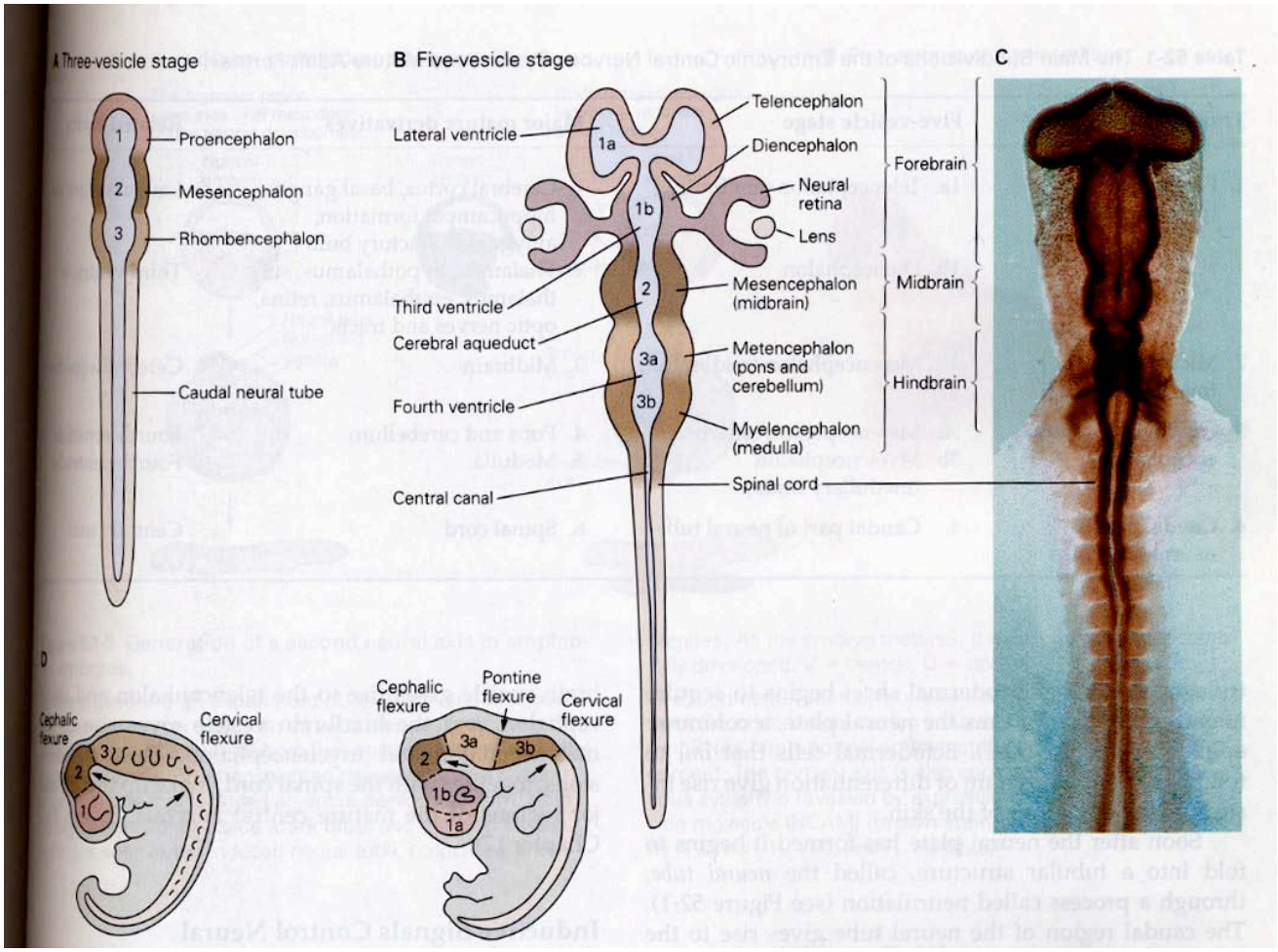
Long After Neurulation:

Neural Tube

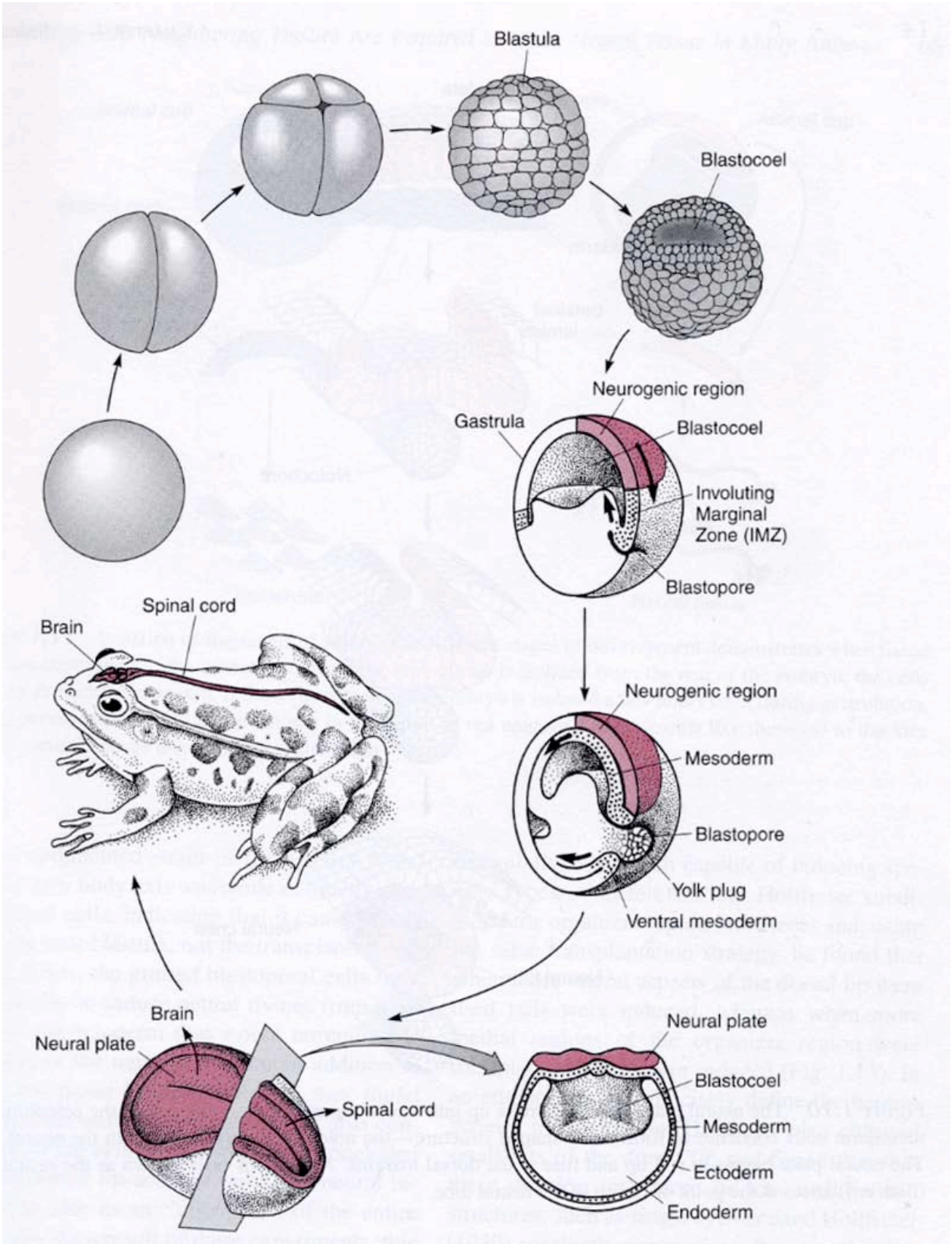
Rostral → Brain

Caudal → Spinal Cord

Neural Crest → PNS (sensoy ganglia, ANS), melanocytes, adrenal medula



Xenopus laevis (South African clawed toad)

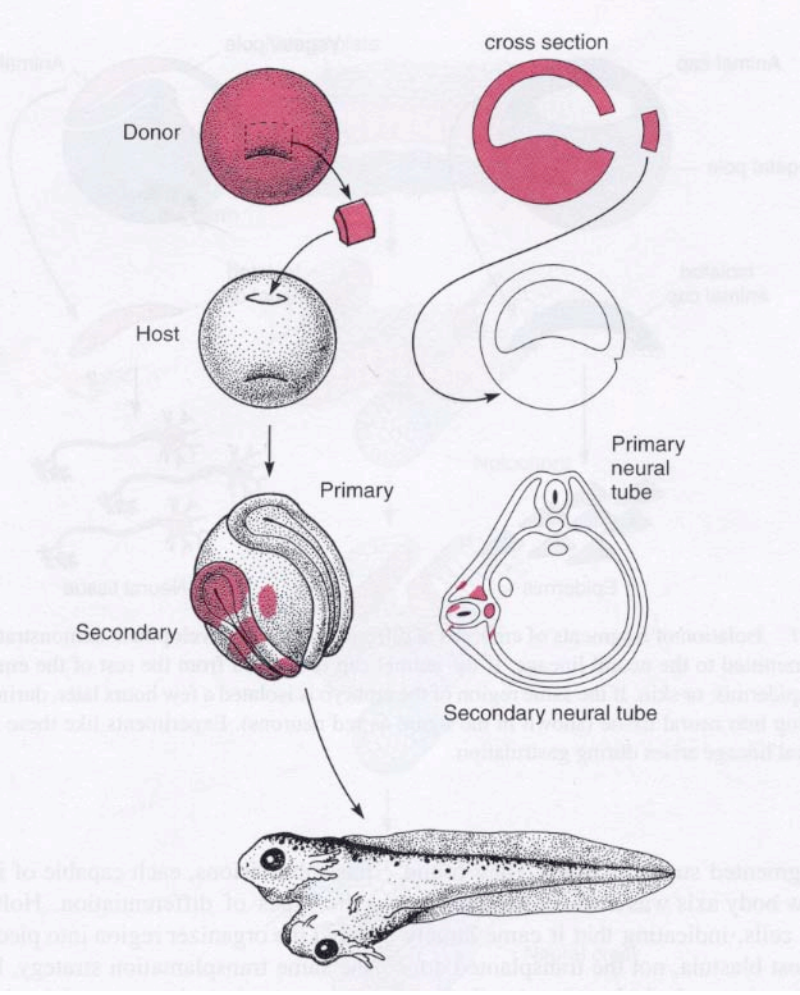


Early Induction of the Nervous System

Inductive Signals → They affect/determine which genes are expressed in a cell.

1920s-Spemann & Mangold

Before Gastrulation, they transplant the DLB from a pigmented animal to a non pigmented one and they place it in the ventral ectoderm.

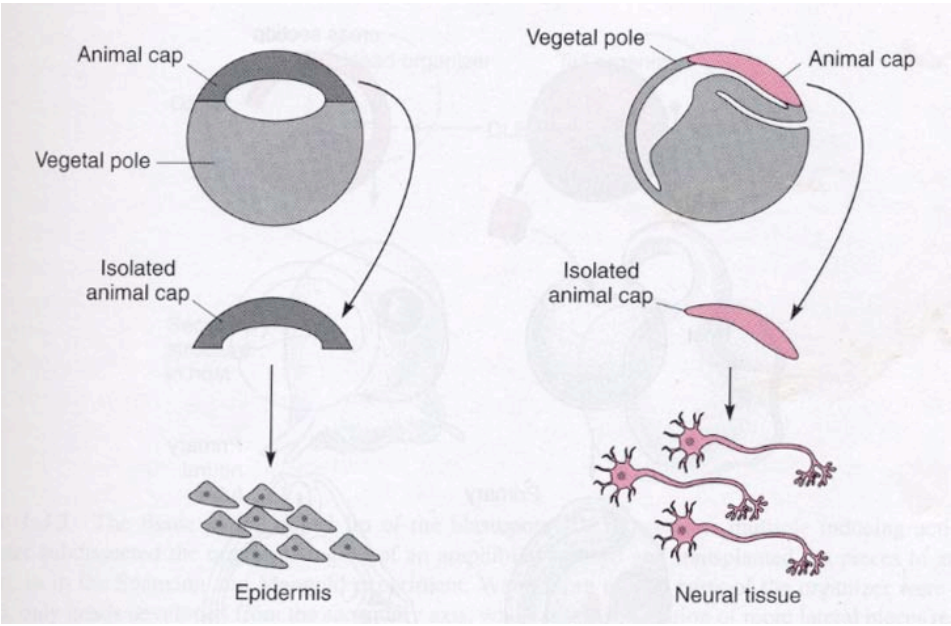


There is a 2nd neuraxis, that contains cells form the host and the donor embryo. ➔Cells in the **Dorsal Lip of the Blastopore (DLB)** or **Organizer** induce ectoderm of the host embryo to become neural tissue. This is an INDUCTIVE EVENT.

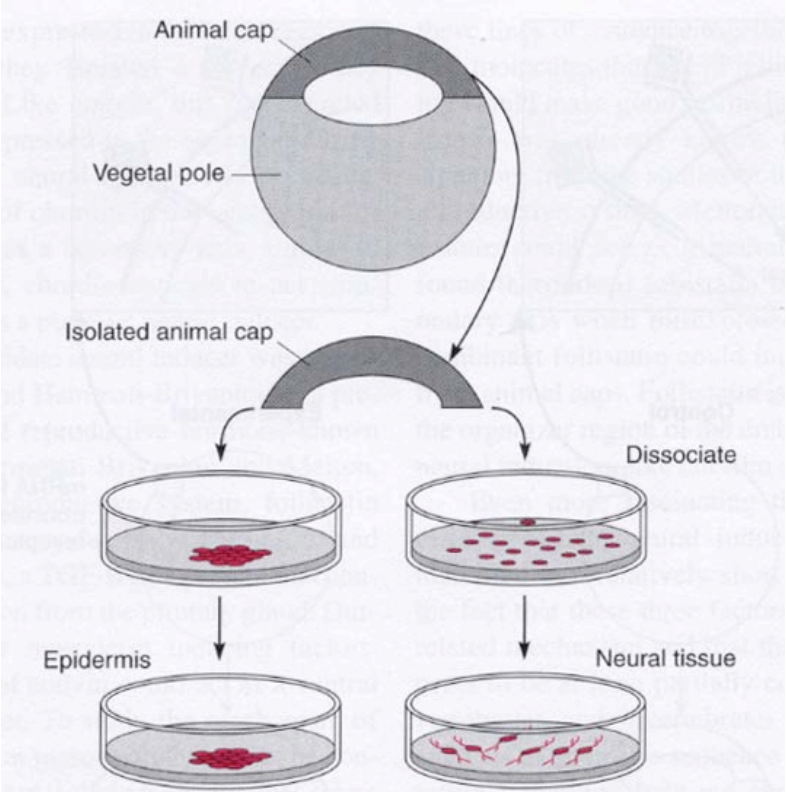
What makes cells become neural?

A cell's fate will depend on the signals to which it is exposed as well as the developmental history of the cell.

Background: early late



Experiment 1:

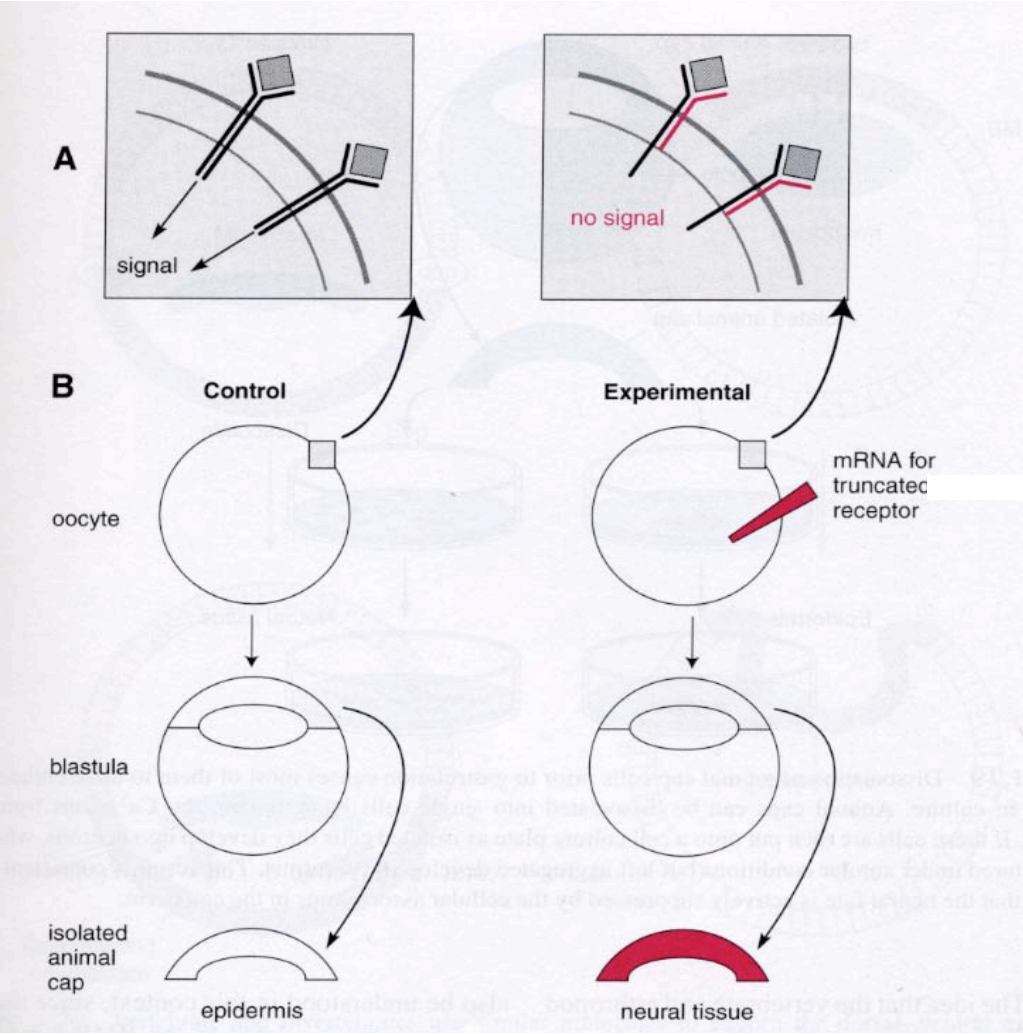


➔The default is to become neural

What makes cells become neural?

Experiment 2:

Expression of a dominant negative mutant of one of the receptors for one type of BMP in xenopus oocytes results in neural fate.



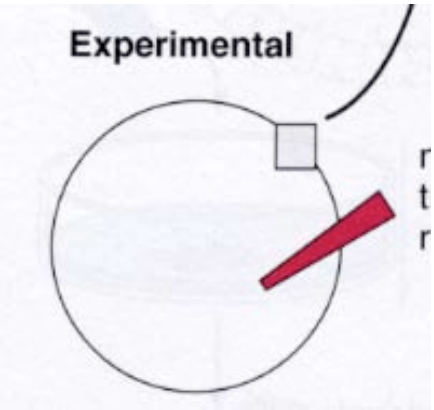
➔ The interpretation is that the BMP signal instructs the cells not to become neural

Note: Adding extra BMP to the animal cap cells results in a lager number of cells going to epidermal fate. This suggests that BMP promotes epidermal fate.

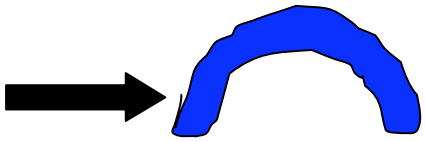
What makes cells become neural?

Experiment 3:

Richard Harland was looking for genes that would induce neural fate.



Inject “Random” mRNAs (first pools till you isolate the mRNA you are interested in)



Take the animal cap

Neural fate (?)

(looking at neuronal markers)

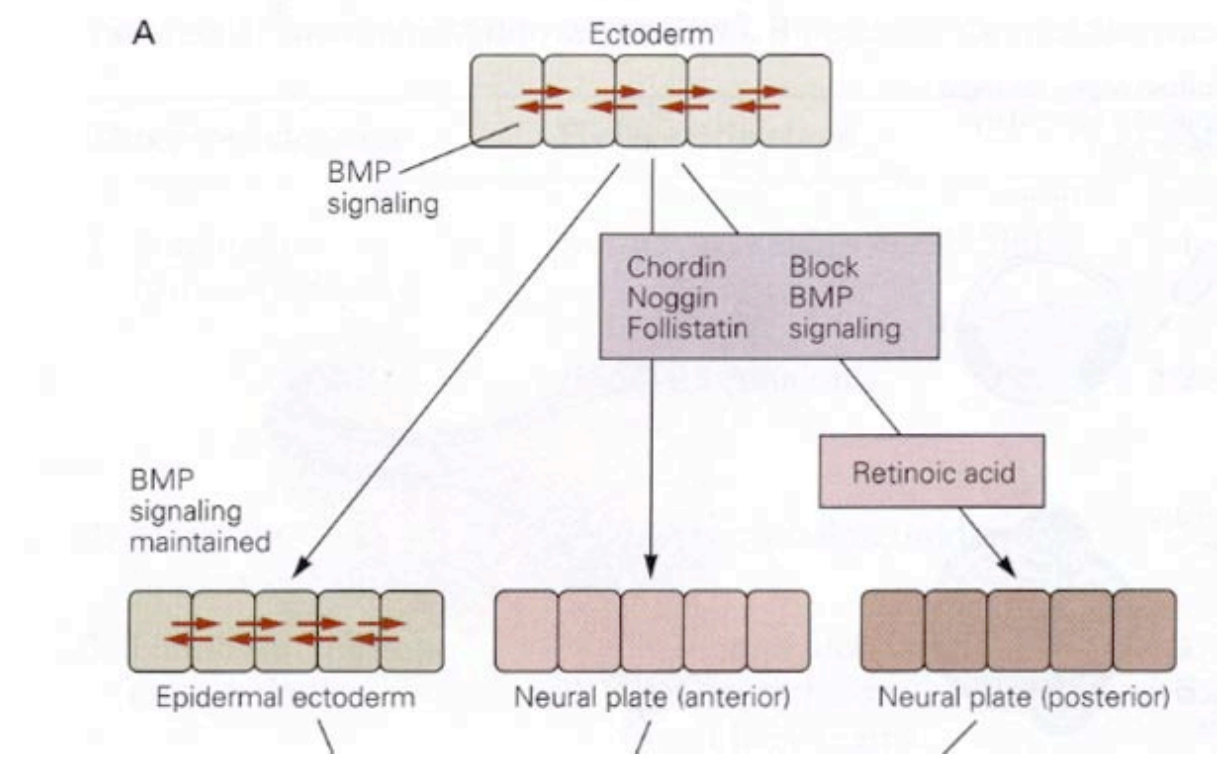
In this way he identified **noggin**. Which is a secreted protein, expressed in the organizer and later in the notocord.

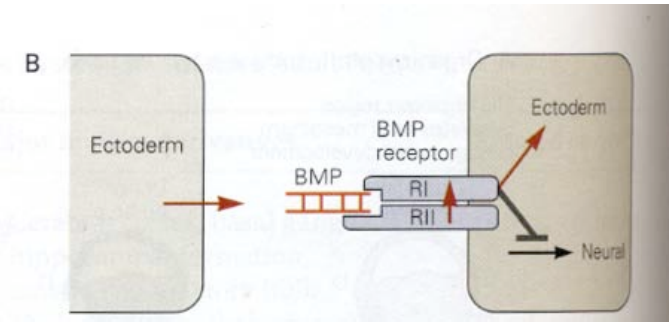
Other people identified **follistatin** and **chordin** as having similar functions.

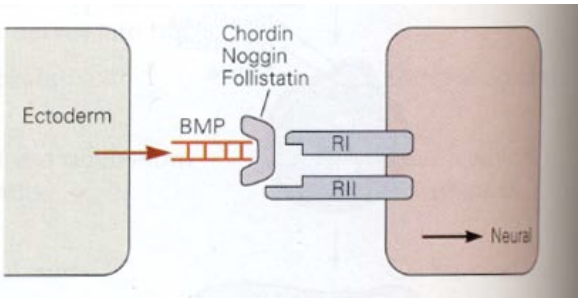
What makes cells become neural?

Model: The ‘double inhibition model’ for neural fate

Members of the BMP family of proteins inhibit the neural fate by binding heterodimeric receptors in the ectodermic cells and initiating a cascade of events. These BMP proteins are secreted by the ectodermal cells. Inhibition of this binding by molecules such as **chordin**, **noggin** and **follistatin**, allows the cells to adopt the neural fate. These molecules are all expressed by cells in the organizer region. The fate (neural vs epidermal) depends on a **threshold.**





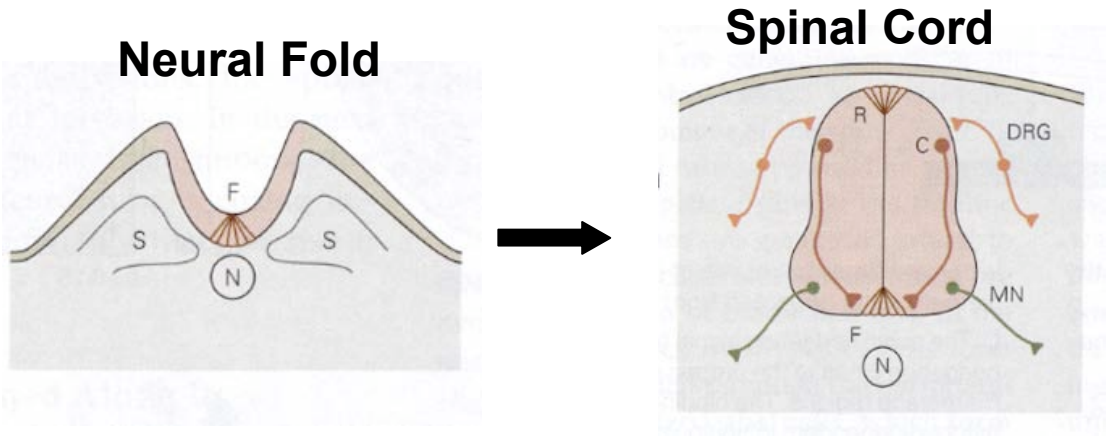


Dorsal-Ventral Patterning

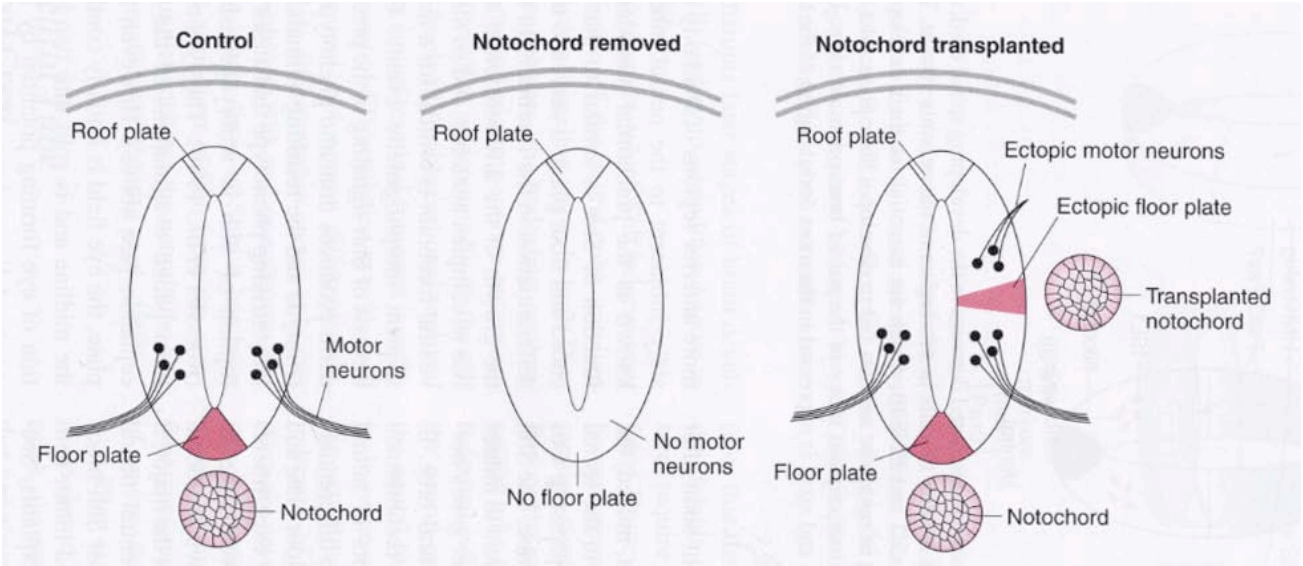
Let's consider the chick spinal cord as our model system.

During development, various structures are formed as the posterior part of the neural tube becomes the spinal cord:

Dorsal	Ventral
•Roof Plate	•Floor Plate
•Sensory Interneurons	•Motor Neurons



Experiment 1: Ventral Induction

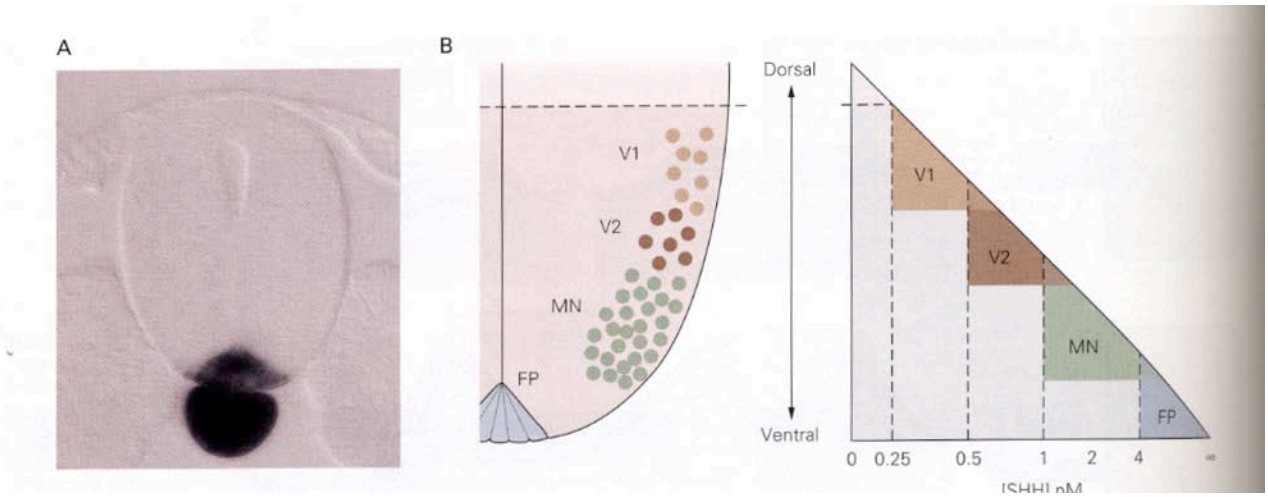


➔ The Notochord induces ventral fate in the spinal cord.

Dorsal-Ventral Patterning

What is the signal released by the notochord?

Sonic Hedgehog (**Shh**) is a secreted protein expressed in the floor plate and notochord and it is the signal that induces the ventral fate.



The particular fate of the different cells depends on the amount of Shh that they are exposed to.

Low Concentration → Ventral Interneurons

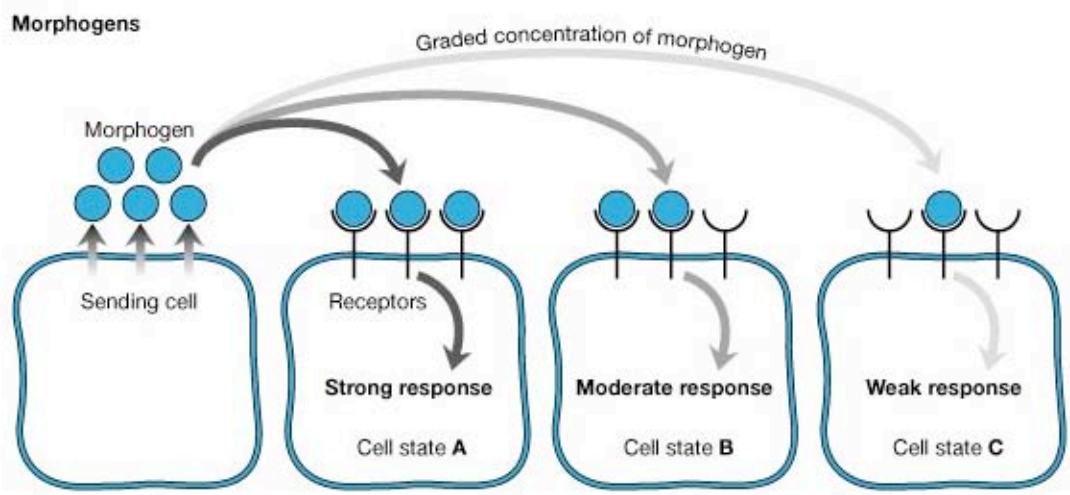
Medium Concentration → Motor Neurons

High Concentration → Floor Plate Cells

} **Threshold effect**

Experiments by Tom Jessell and colleagues…

Thresholds, in general terms:



The Coiled Spring: How Life Begins, © 2000 by Cold Spring Harbor Laboratory Press

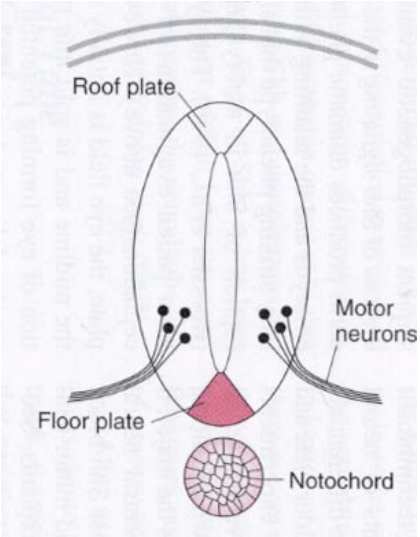
FIGURE 1.9. Graded concentrations of morphogens.

Different cellular responses according to position of cell in concentration gradient of morphogen
=> results in discrete differences in cell fate along the gradient.

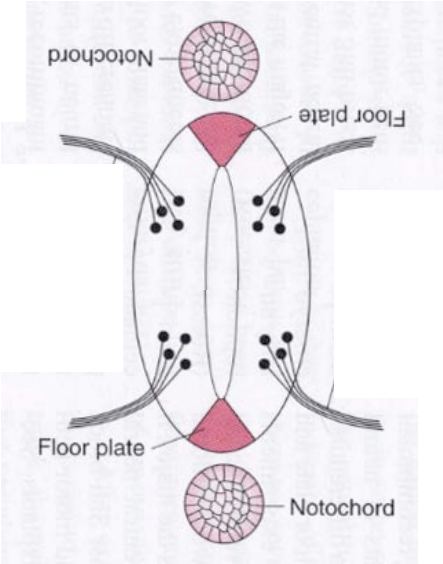
Dorsal-Ventral Patterning

Experiment 2: Dorsal Induction

Control



Additional notochord



The control presented:

- Normal dorsal and ventral development of the spinal cord
- BMP expression in the roof plate

What was observed:

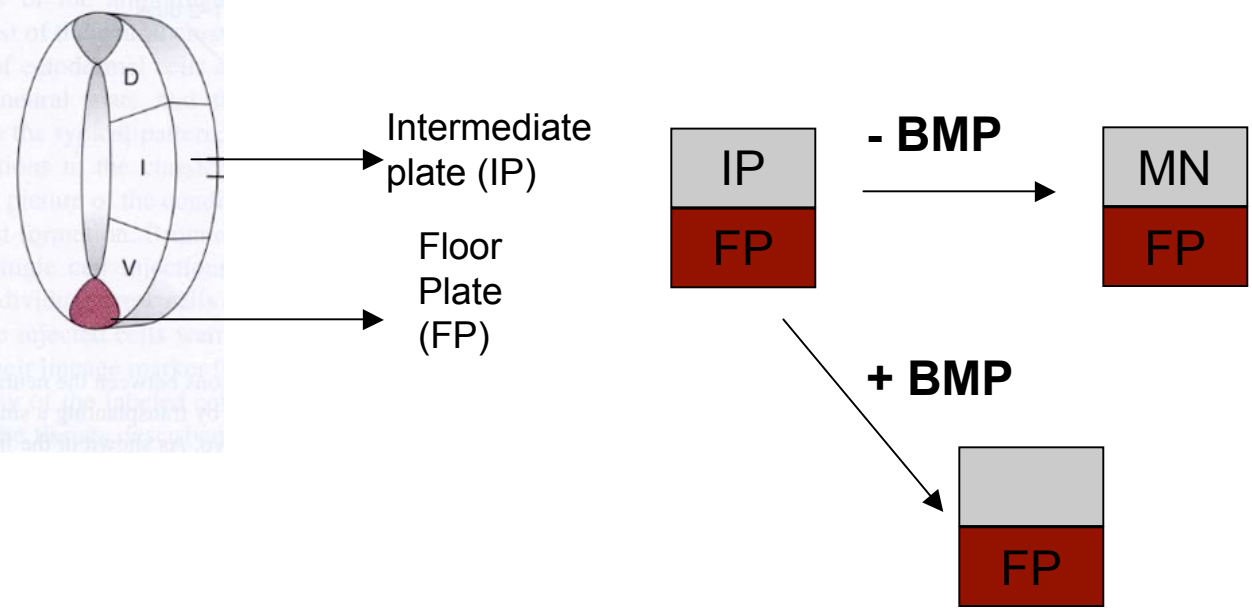
- Ventralization of the spinal cord
- Extinguished BMP expression

⬇

This suggests that BMP is needed for dorsalization but doesn't prove it

Dorsal-Ventral Patterning

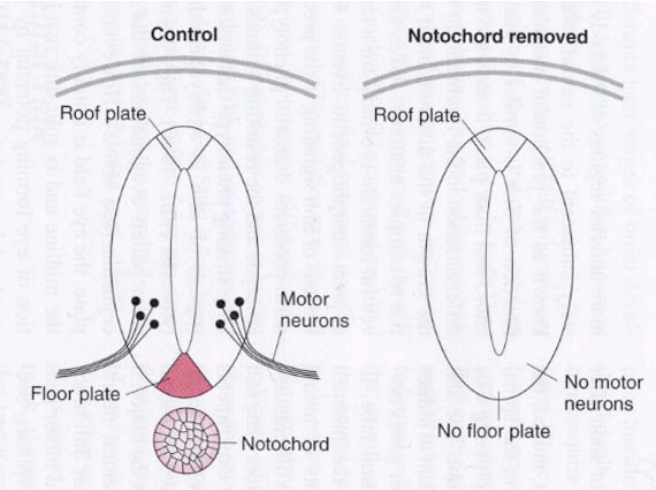
Experiment 3: Dorsal Induction



When culturing intermediate plate explants on floor plate explants, the cells adopt ventral fates (MN). However, if there is BMP in the medium, then this is inhibited.

➔ BMP inhibits ventralization (as shown by the lack of differentiation into motor neurons)

Experiment 4:

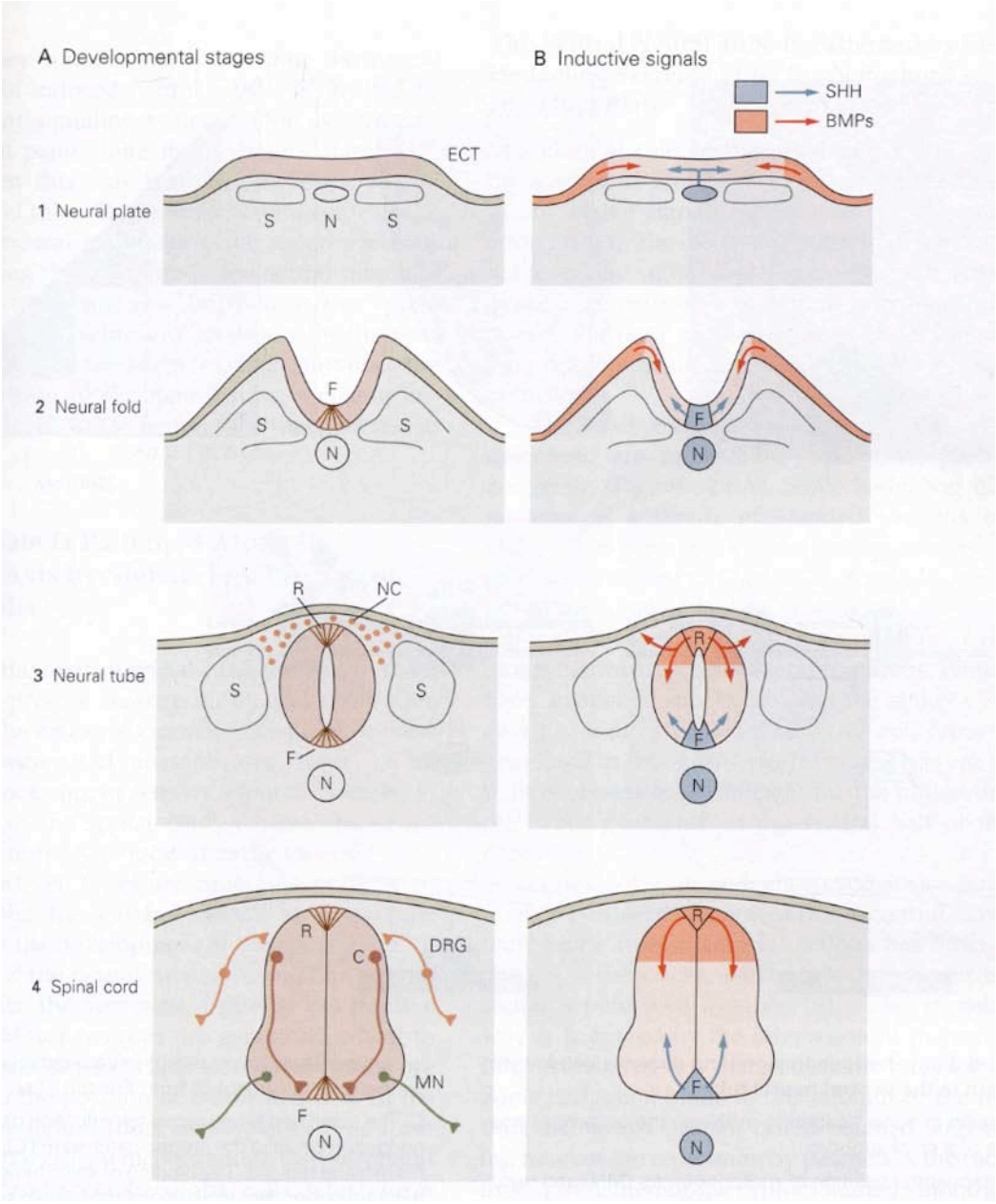


Removal of the notochord results in

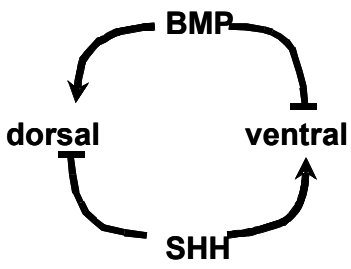
- the lack of ventral phenotype
- BMP expressed everywhere

Dorsal-Ventral Patterning

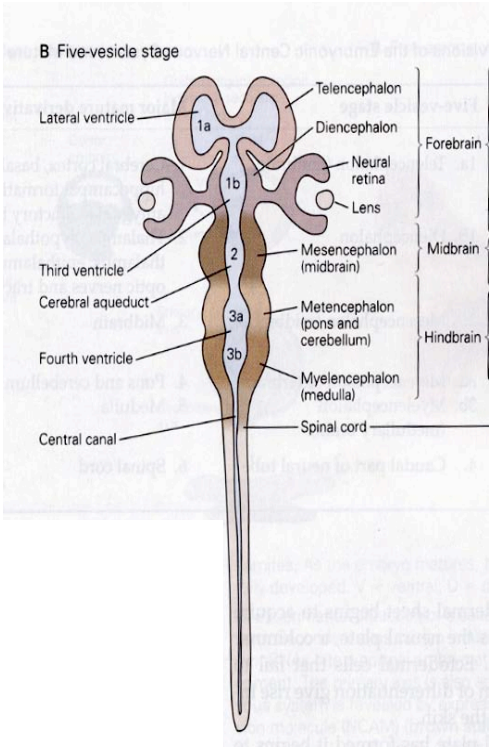
Model:



- Shh signaling: induction of ventral cell fates.
- BMP signaling: induction for dorsal cell fates.
- BMP inhibits ventral fate.
- Shh inhibits dorsal fate.

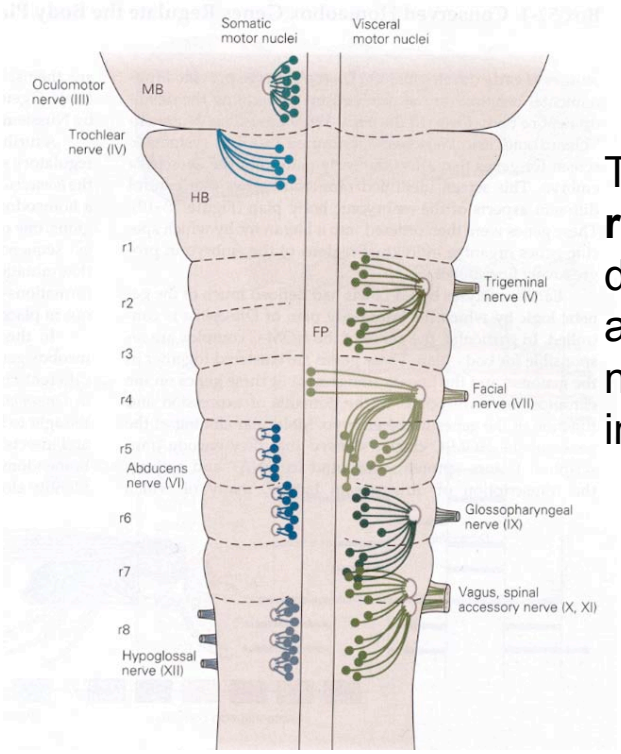


Anterior-Posterior Patterning



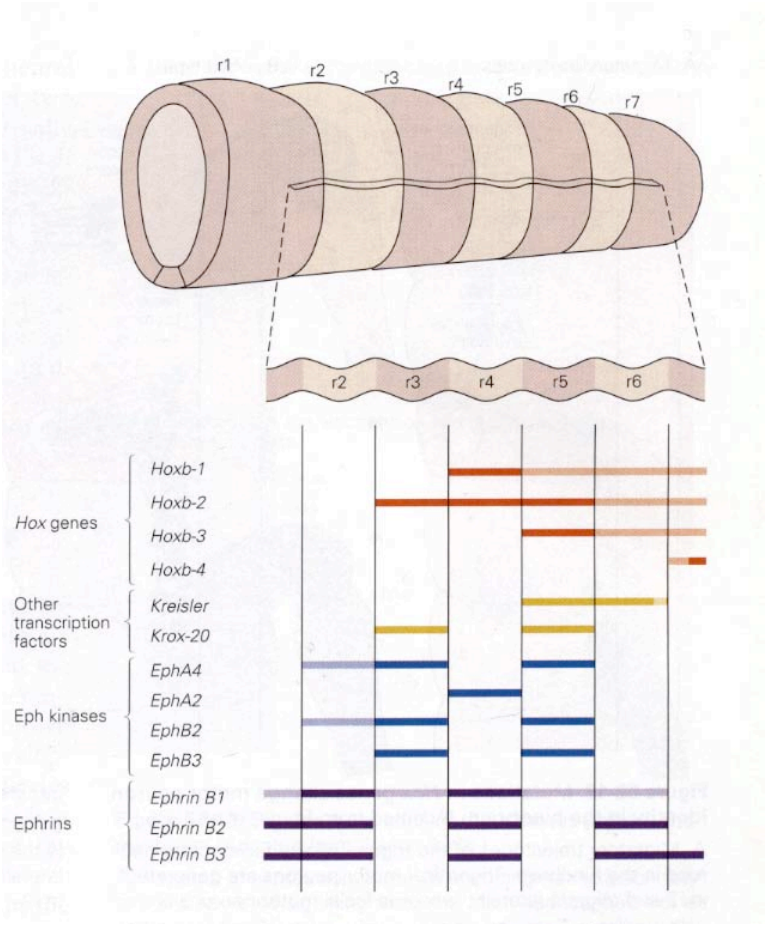
The A/P patterning begins at the stage of the neural plate. The neural tissues induced by follistatin, noggin and chordin appear to express the genes that are characteristic of the forebrain. Additional signaling is required for the induction of tissue that will give rise to the midbrain, hindbrain and spinal chord.

Focus on the Hindbrain:



The hindbrain is ‘segmented’ into **rhombomeres.** These express different genes during development and present the soma of the motor neurons of different cranial nerves in the adult.

Anterior-Posterior Patterning



Hox Genes

- Homologous to Drosophila's homeobox genes
- Implicated in determining rhombomere identinty
- Transcription factors
- Located in clusters in chromosomes.
- They are expressed in overlapping domains along the anterior-posterior axis of the developing brain and spinal chord.

Experiment: Mutate Hoxb-1