Spenmann’s organizer experiment in 1924 suggested that neural tissue is induced from prospective epidermal tissue by a secreted factor. Since then, neural induction has been a focus of biological interest; however attempts to isolate a neural inducing factor1 remained unsuccessful for decades. Thus, while the amphibian early organizer is equivalent to the blastopore lip, the avian organizer is first recognizable as the nodal node located 1.8 mm away. Clearly, the experimental advantages of other animals need to be exploited.

In several recent papers, neural induction in the chick embryo has been analyzed at the molecular level3–5. Some of the striking results and interpretations challenge models derived purely from work on amphibia.

The amphibian and the avian organizer

In amphibia, the formation of the organizer, the dorsal blastopore lip, indicates the presence of a dorsal–ventral axis and the beginning of gastrulation (Fig. 1a). Cells of the blastopore lip invaginate and become dorsal midline structures, first the prechordal mesendoderm and then notochord. Before, and soon after, internalization these cells can induce neural tissue from otherwise epidermally fated cells. Clearly, the appearance of the organizer precedes the anlage of the neural plate6.

In birds, reptiles and mammals, the first recognizable embryonic axis is the primitive streak, which demarcates the later anterior–posterior axis. The fate of mesodermal cells along the streak resembles the alignment of mesodermal fates in the amphibian marginal zone. Prospective dorsal mesoderm is located in the tip, and ventral mesoderm more towards the base (reviewed in Ref. 7). The avian organizer is Hensen’s node, the tip of the posterior embryonic region from a primordium near Köller’s sickle (Fig. 1b). Cells from the posterior embryonic region can be traced into the tip of the streak by expression of the homeobox gene goosecoid8. These cells are the first indication of the organizer in the chick embryo. The fully developed avian organizer is Hensen’s node, the tip of the maximally elongated primitive streak. Cells from Hensen’s node ingress to become anterior mesendoderm, which before and after internalization are also identified by the molecular marker goosecoid and maintain some organizer functions9–10.

Thus, while the amphibian early organizer is equivalent to the blastopore lip, the avian organizer is first recognizable in the posterior embryo, and only 18 hours later it is fully established in the neural plate located 0.8 mm away. It is of note that the early avian, as well as the amphibian, organizer precedes the anlage of the neural plate, whereas the node cells are already surrounded by a neural plate.

Neural induction by BMP-antagonism in amphibia

In the amphibian Xenopus laevis, genes for the three secreted proteins, Follistatin, Noggin and Chordin are expressed in the dorsal mesoderm, that is, the organizer, the prechordal mesendoderm and the notochord11–13. It turned out that each factor alone can induce neural ectoderm from prospective surface ectoderm, thus qualifying as the long sought neural inducing factor. In addition, the factors possess a more general dorsalizing ability and inhibit epidermis formation. Ventralizing factors, which inhibit neuralization, were identified among the bone morphogenetic proteins, in particular BMP4 (Ref. 14). At the beginning of gastrulation, the BMP4 gene is active in the complete ectoderm of the animal.
prising negative results: (1) Chordin
affected cells (Fig. 1b–d). They obtained
ized ectopic expression from trans-
inductive capacities and the interplay
likely (Fig. 1c).
BMP4–Chordin protein complexes
expressing, prospective epidermal
is significantly distant from BMP4-
pare Fig. 1a with Fig. 1b). However,
the chick, as is the case near the dor-
cent to BMP4-expressing ectoderm in
the notochord. Thus, the early ex-
tive streak, the node, and later on in
embryos, then in the tip of the primi-
chick with homologous genes in the
comparative study suggests. In chick
expression data suggest. In chick
expression domain appear to induce a primitive
rather than neural ectoderm
implantation. Neural induction by FGF
either becomes fused, or remains
neural fates in the periphery of the
neural fates in the periphery of the
animal describes BMP4 and Chordin
results that transplants contain-
the early Chordin expression
domain. It seems that Chordin
induction, respectively. The outcome
ence of Chordin activity is, however, not so
dissimilar. Chordin can induce sec-
ondary embryos in chick as well as in
in frogs, even under completely dif-
ent experimental contexts, that is, the
application of factor or the injec-
tion of RNA (Refs 5, 13). Observations
from the Stern laboratory therefore
clearly recognize the conservation of
Chordin–BMP4 antagonism as a major principle in dorsal–ventral pattern-
ing of avian embryos.
What about neural induction? Why
is Chordin unable to induce neural fate in the
periphery of the chick embryo? Currently, the only
conclusion that can be made is that other factors, possibly emitted by the
node, are involved. Streit et al provide
preliminary evidence to show that such a factor could act upstream of Chordin. Neither Noggin nor Follis-
alin seems to be the putative factor, although combinatorial experiments
have been suggested. At least for the
chicken Noggin gene no appar-
ent role in neuralization can be
detected. An insight into neuraliza-
tion has been gained, however, in
amniotes because a factor capable of
inducing neural fate of the uncom-
mented ectoderm has been identified.
Neural induction by FGF in chick embryos
The laboratories of Alvarez and
Storey have demonstrated neural
induction in avian embryos by fibro-
blast growth factor (FGF), in particu-
lar FGF4 (Refs 3, 4). Storey et al describe the activation of FGR8, AXX1
and CASH4. All genes normally found
active in the primitive streak and the
posterior neural plate, which supports
the notion of direct signalling within the
prospective neural epithelium. Alternat-
ively, FGF might act indi-
rectly through induced mesoderm,
and the available experimental data
need further analysis (e.g. in order to
eliminate a direct role). Alternatively,
induced mesoderm
are signals required from the pri-
mary embryo in addition to the ectopic
FGF signal? Both laboratories demonstra-
te that FGF does not redirect cells
from the primary neural plate to the
periphery, but induces neural fate at
the node. The induced neuroepithelium
either becomes fused, or remains
independent of the primary embryo,
apparently depending on the stage
of the host and the site of FGF bead
implantation. Neural induction by FGF
is restricted to early posterior
neuroectoderm, and neither anterior nor
late neural markers are switched on. Storey et al conclude that FGF sig-
nalling only elicits the initial steps of a
neural programme, including the
maintenance of neural competence.
These observations in the avian em-
byos are reminiscent of results in
Xenopus laevis, where some evi-
dence for FGF-induced neural fate is
found, depending on experimental conditions and markers. Thus, while some details of FGF involvement

Chordin and BMP4 in the avian embryo
A recent paper from C. Stern’s lab-
atory describes BMP4 and Chordin
activity in the avian embryo. A compari-
on the expression patterns in the
chick with homologous genes in the
first two primitive streaks with given the
complex developmental differences.
The chick BMP4 gene is widely ex-
pressed in the same region of pre-streak
embryos, then transcription becomes
restricted to the area opaca, before it
surrounds the neural plate forming
around the node (Fig. 1b, c). The
expression domain of Chordin is adja-
cent to BMP4-expressing ectoderm in
the chick, as is the case near the dor-
sal blastopore lip of the frog (com-
pare Fig. 1a with Fig. 1b). However,
the fully developed avian organizer is
significantly distant from BMP4-
expressing prospective epidermal
ectoderm, making the formation of
BMP4-Chordin protein complexes
unlikely (Fig. 1c).
A Streit et al have analyzed the
inductive capacities and the interplay
between BMP4 and Chordin, BMP4 and
Noggin, and Follistatin and BMP7 were
found to be inhibitory. These observa-
tions suggest that the function of a neural
inducing factor in the organizer
began clear when the protein com-
between BMP4 and Chordin, BMP4 and
Noggin, and Follistatin and BMP7 were
found to be inhibitory. These observa-
tions suggest that the function of a neural
inducing factor in the organizer

COMMENT

half and the prospective mesoderm
in the equatorial marginal zone, but
not in the organizer region (Fig. 1a).
The molecular mechanism underly-
ing neural induction became clear
when FGF protein was applied near
the blastopore lip of the frog (com-
pare Fig. 1a with Fig. 1b). It seems that Chordin
and BMP4 affect gastrulation rather
than neural induction after ectopic
application. Streit et al demonstrate
that Chordin can induce ectopic
primitive streaks in the anterior epi-
blast of pre- and mid-streak embryos.
The induced streaks are complete
and go on to generate their own neural
plate. It is of note that transplants con-
taining the early Chordin expression
domain anlage. It seems that Chordin
interfere with neural development,
formation; and (2) BMP4 does not
inhibit the formation of a primitive
streak, rather than neural ectoderm.6,7
When BMP4 protein is applied near
Köller's sickle or near the node, it
inhibits the formation of a primitive
streak and consequently any further
development. Thus, BMP4 indeed
antagonizes Chordin in the chick
embryo. Under natural conditions the
only time and place for a physical
interaction between Chordin and
BMP4 is before streak formation near
Köller's sickle; at least this is what the
RNA expression data suggest. In chick
expression becomes restricted to the area opaca, before it
surrounds the neural plate forming
around the node (Fig. 1b, c). The
chick Chordin gene is first expressed
in a relatively strong domain just
anterior to Köller’s sickle of pre-streak
embryos, then in the tip of the primi-
tive streak, the node, and later on in
the notochord. Thus, the early ex-
pression domain of Chordin is adja-
cent to BMP4-expressing ectoderm in
the chick, as is the case near the dor-
sal blastopore lip of the frog (com-
pare Fig. 1a with Fig. 1b). However,
the fully developed avian organizer is
significantly distant from BMP4-
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ectoderm, making the formation of
BMP4-Chordin protein complexes
unlikely (Fig. 1c).
A Streit et al have analyzed the
inductive capacities and the interplay
between BMP4 and Chordin, BMP4 and
Noggin, and Follistatin and BMP7 were
found to be inhibitory. These observa-
tions suggest that the function of a neural
inducing factor in the organizer
began clear when the protein com-

in neural competence, induction and patterning are still unclear, there remains the major finding that PGF signalling is sufficient for the initiation events underlying the formation of the posterior neural plate.

**Conclusion**

The analysis of Chordin and BMP4 in the chick embryo shows that the basic mechanism for dorsal-ventral patterning is conserved from the fruit fly to the frog, and also to the chick. However, it discourages the idea derived from analysis of amphibia, that dorsalization of ectoderm is equivalent to neuralization. 

Up to now it has only been possible to describe a role for Chordin in the early phase of organizer formation, but not for its later function in the node. We now understand more about the first definition of 'dorsal' in humans present as sporadic, dominantly inherited, or transmissible. Prion diseases in the chick do not yet have a factor that is sufficient for determining the posterior region, but we still do not understand the onset of neuralization. This is a very complex issue, but with two new factors having been identified we are a few steps nearer to understanding the great secret of neural induction in amniotes.

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**References**


A new mechanism broadening the role of prion proteins in neurodegeneration

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Over the past 15 years our understanding of the underlying mechanisms in the transmission and pathogenesis of the neurodegenerative diseases has fundamentally changed our concept of an infectious agent.

Research from many disciplines indicates that the infectious agent causing prion diseases is, at least in part, an abnormally folded isoform of a normal cellular protein called PrP<sup>Sc</sup> (Ref. 1). The protein isoforms are known collectively as PiP. Prion diseases in humans present as sporadic, dominantly inherited, or transmissible neurological disorders, while the known animal prion diseases are all transmissible (Table 1).

**Prion proteins and disease transmission**

The PrP-encoding gene (<i>PRNP</i>) plays a key role in the development and transmission of prion diseases in both humans and animals<sup>1</sup>. The transmissible and most of the inherited forms of these diseases are characterized by the accumulation and deposition of an altered conformational form of the prion protein designated PiP<sup>Sc</sup> (Ref. 2). Inherited forms of the disease are characterized by mutations in the PrP-encoding gene leading to amino acid substitutions and insertions in the prion protein (Fig. 1 and Table 1). The ability to transmit human prion diseases to experimental animals has been, until recently, a prerequisite for diagnosis. However, rates of transmission of prion disease have been variable (Table 1), ranging from almost 100% transmission for iatrogenic* Creutzfeldt–Jakob disease (CJD) cases, to 38% for Gerstmann–Sträussler–Scheinker syndrome GSS(P102L)<sup>‡</sup> and to non-transmissibility for GSS(A117V)<sup>‡</sup>. The role of PiP<sup>Sc</sup> in the transmission of the disease is well established but its role in neurodegeneration is less well defined. The use of transgenic mice expressing chimeric and mutant PiP-encoding genes and the development of transgenic PiP<sup>Sc</sup>-knockout mice have convincingly shown the importance of the prion protein in these diseases. The expression of the normal form of the prion protein PiP is required for the replication of the infectious prion<sup>‡</sup>, modulates the incubation time of the disease<sup>‡</sup>, and controls the development

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* Exposure to infectious agent through an accident.
‡ GSS(P102L) refers to a mutation in the human PRNP coding sequence resulting in a proline to leucine substitution at position 102 that is associated with Gerstmann–Sträussler–Scheinker syndrome. A similar nomenclature is used for other mutations in the prion protein gene.