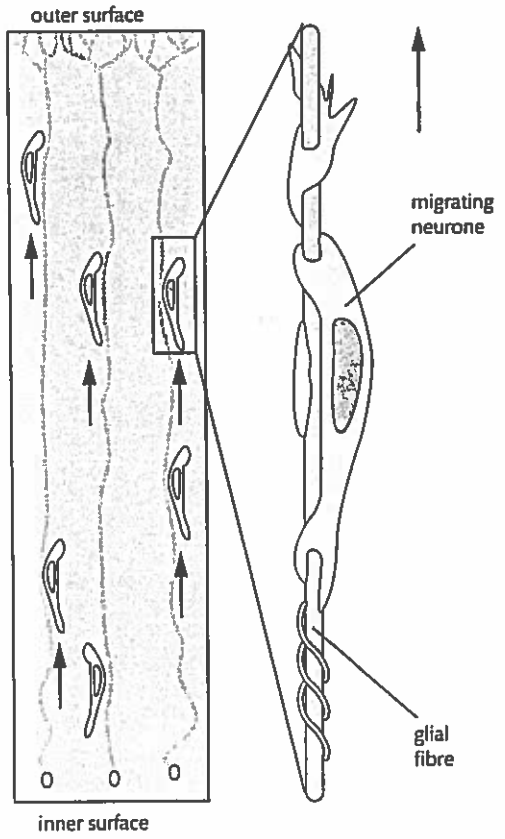
The closure of the neural tube does not take place simultaneously all along the body of the embryo. The area where the brain forms is well advanced compared with the caudal (tail) area. Closure of the neural tube in the tail area occurs more slowly and may not even completely close during embryonic development. This failure to close the human posterior (caudal) neural tube at day 27 of development results in the condition of *spina bifida*. How severe this is depends on how much of the spinal cord remains exposed.

Neurogenesis and migration of neurones

The neurones of the central nervous system (CNS) in the developing vertebrate embryo originate in the neural tube. Neuroblasts are immature neurones that are the precursor cells of neurones. The process of differentiation from neuroblast to neurone is called neurogenesis. As soon as the neural tube begins to transform into specific brain parts, two major families of cells begin to differentiate. These two types of cells are neurones and glial cells. Neurones carry messages, while glial cells do not carry messages. Ninety per cent of brain cells are glial and have many functions. One important function is physical and nutritional support of the neurone. Most of the new neurones in the human cortex are formed between the fifth week and the fifth month of development.



Glial cells provide a scaffolding network along which the immature neurones migrate. Along this scaffolding of the glial cells, immature nerve cells can migrate to their final location, mature, and send out their axons and dendrites.

Closure of the human neural tube seems to be controlled by a combination of genetic and environmental factors. Certain genes have been found to control the formation o the mammalian neural tube, but dietary factors also seem to be critical. The US health service recommends that wom take supplemental folic acid during pregnancy to prevent neural tube defects. One estimate suggests that using vitar B_{12} as a supplement car prevent 50% of neural t defects.

Helen Cooper and her team at the Queenslanc Brain Institute have identified signalling molecules that may be used to promote the birth of new neurones, which will then migrate to damaged regions of the brain. This could be a major step forward in achieving functional recovery in a damaged brain.

Figure 7.4 Scaffolding glial cells allow neurones to reac their final destination.

Neuroblasts are cells in the embryo that wi become neurones.

Two cell types formed by neurogenesis are neurones, which carr messages around the brain, and glial (glue) cells, which provide the support and the nutrition for the neurones.

'Glia' means glue in Gre The word neurogenesis comes from 'neuro' meaning nerve cell and 'genesis' meaning beginning.

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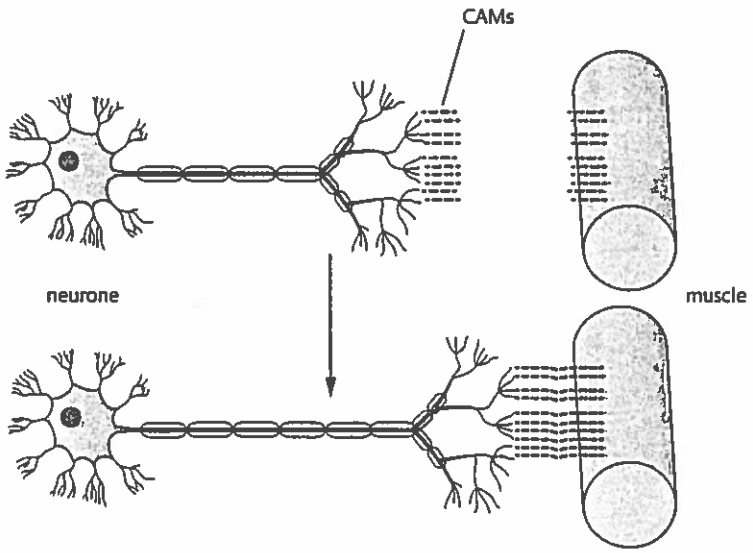
Axon growth

As the neurone grows, it will send out one long axon moving towards a distant area. At the tip of the axon is a growth cone, which directs the axon. In cell cultures it is possible to watch axons grow. When an axon contacts an unfavourable surface it contracts, but with a favourable surface it persists. An axon can move forward at about 1 mm a day.

When neurones have reached their final location, synaptic connections must be made with their target cells. These target cells produce chemical messages that the neurone responds to. The signal molecule from the target cell can be secreted into the extracellular environment or carried on the target cell's surface. The neurone responds to the chemical messages by forming synapses with the target cell.

Certain molecules from the target cell can act as signals to the growth cone. One type of signal molecule is called a cell adhesion molecule (CAM). CAMs are located on the surface of cells in the growth environment of the axon. The growth cone of the axon has a receptor called a CAM-specific receptor, so that when a CAM and its receptor recognize each other, chemical messaging takes place within the neurone. This results in the activation of enzymes within the neurone that contribute to the elongation of the axon.

Some receptors on a growth cone can also pick up the signal of molecules secreted by the target cell that diffuse into the extracellular environment. These are called chemotrophic factors. These factors can be attractive or repellent. Chemoattractive factors attract the axon to grow towards it. Chemorepellent factors repel the axon, so that the axon will elongate in a different direction. The growth cone responds to the various chemical stimuli that show it what path to follow and what connections to make.



igure 7.5 Signal molecules lled CAMs attract the axons to their target muscle cells.

iroblasts differentiate neurones. Neurones w towards their target s. The target cells give mical signals, e.g. M, to the neurone.

Some axons extend beyond the neural tube

Some neurones, for example mammalian motor neurones, have to send their axons out of the area of the neural tube and travel much further in their journey towards other target cells. This gives the mammal the ability to control voluntary muscular movement. The motor neurones must extend their axons out of the CNS (the brain and

spinal cord) in order to form these circuits. Newly developed motor neurones, which extend axons from the spinal cord, are some of the longest neurones in the body. During embryogenesis, these cells follow the same pathways to synapse with muscle targets as other neurones located within the CNS. The muscles that need to attract the axons will produce CAMs. The CAM receptor in the axon will activate enzymes to cause the growth cone of the axon to grow towards the muscle.

Even new muscle cells in the embryo are producing CAM, attempting to attract a growing neurone from the spinal cord.

The growth cone in th axon will respond by growing towards the muscle cell.

Multiple synapses

A huge number of synapses are formed during early brain development. Imagine if you could not remember your password and were desperate to download a movie. You would try all of the passwords you have ever used until one of them worked perfectly. A developing neurone does the same sort of thing, trying out all the possible connections to see which is the best fit. A single nerve cell can make a myriad of connections with its neighbouring nerve cells at the many points of branching that radiate from the main cell body. Not every cell will be the best partner. The job of the neurone is to find the best fit. In other words, only those synapses that have a function will survive, and the rest will gradually weaken until they disappear. Just think how easy it is to forget a password that you never use.

An axon that begins in t spinal cord and innervat a muscle in the foot car be as long as 1 m (3 fee

The neurones of the brain try to form a synapse with any nearby target cell, and then attempt to test out the connection. Will the connection work? Many do not, and those connections are eliminated. When the connections are between functionally compatible neurones, the result is a strengthening of communication.

Neuroscientist Z. Josh Huang, at Cold Springs Harbor Laboratory, in an article published in the *Journal of Neuroscience*, described the behaviour of neurones making tentative connections with almost every available partner. Lots of partners are tried, and eventually one is found that is compatible. Huang goes on to state that one mechanism at work during these rapid connections is controlled by a type of neural adhesion molecule that is recruited to the site of the connection. This adhesion molecule is also a type of CAM, called immunoglobulin CAM (IgCAM), and it acts like a lock and key. CAMs form a physical but reversible glue-like bond between the tentative projection of one cell's axon and the receiving structure on a neighbouring cell. Eventually, many of these connections are lost because it turns out they are not with the right partner cell.

The word synapse is 113 years old. It was firs coined in a textbook of physiology written in 1897. The author, Mich Foster, derived the wor from the Greek words 'syn' and 'haptein', whic mean together and clas respectively.

Some synapses do not persist

Just as you would not use any passwords that do not work, the neurone will not keep any synapses that do not work. Most of our information about how the growth cones of an axon find their way to the target cell comes from the study of neurones that have travelled to a muscle from the spinal cord. Where they connect is called the neuromuscular junction. The axons form synapses that compete for the ability to innervate a muscle fibre. Specific molecules from the neurones and muscles facilitate these connections. The strongest connection will survive, and the rest are eliminated.

A muscle fibre is the site of a heated competition, with multiple synapses trying to win. Eventually, the connection made will be the best one between one motor neurone and the muscle fibre. As development proceeds, the other synapses are eliminated. Finally, the strength of the remaining synapse is increased. This is how the circuitry of the nervous system is formed.

Neural pruning

Pruning results in the overall number of neurones being reduced. When an infant is 2 or 3 years old, he or she has 15 000 synapses per neurone. This is twice as many as in an adult brain. Neural pruning eliminates axons that are not being used. The purpose of neural pruning seems to be to remove the simpler connections made in childhood and replace them with the more complex wiring made in adulthood. As we have seen with other descriptions of neurone activity, pruning seems to follow the 'use it or lose it' principle. Synapses that are rarely used are eliminated, and those with strong connections are maintained. The removal of unneeded connections leads to improvement in brain efficiency.

Scientists supported by the National Institutes of Health in the USA have been studying pruning using the mouse as a model organism. They have discovered that cells called microglia, a type of glial cell, can prune unused synapses. This precise elimination of synapses that are unused and the strengthening of the more active synapses is a key part of normal brain development. Researchers hypothesize that microglia select a synapse for removal based on the inactivity of the synapse.

young child is deprived timulation, certain rone pathways synapses may be arded. This is neural ning. Synapses that highly active will be served, while those are underactive will pruned. As we have ı, a 2–3-year-old child the most synapses. y childhood is the best e to learn language s, when the excess apses provide the raw erial for the language erience to act on. earch into bilingualism gests that exposure to e than one language ı excellent means of nitive strengthening n young.

earn more about n plasticity, go to the inks site, search for the or ISBN, and click on pter 7: Section A.1.

Worked example

What is neural pruning and why is it important?

Solution

The neurones of the brain try to form a synapse with any nearby target cell and then attempt to test out the connection. Will the connection work? Many do not and the connection is eliminated. This is neural pruning. When the connections are between functionally compatible neurones, the result is a strengthening of communication.

The purpose seems to be removal of the simpler connections of childhood and replacement by more complex wiring present in adulthood.

The plasticity of the nervous system

Brain plasticity is the concept, now widely accepted, that the brain has the ability to change and adapt as a result of experience. Until 1960, researchers believed that only the brain of an infant or child could change, and that by adulthood the brain was unchangeable. Modern research has demonstrated that the adult brain does have plasticity. It can rewire itself after suffering massive strokes. Today we understand that the brain can create new neurones and new pathways. Scientists have shown that plasticity can vary with age, and that it is influenced by both environment and heredity. Thus we now know that the brain and nervous system are not static as previously thought.

The brain exhibits two types of plasticity: functional and structural. Functional plasticity is the ability of the brain to move functions from a damaged area to an undamaged area. Structural plasticity refers to the fact that the brain can actually change its physical structure as a result of learning.

An example of a functional shift can be illustrated by studying a tennis player who has suffered a stroke and has a paralysed left arm. During his rehabilitation, his good arm and hand are immobilized by the physical therapist, so that he can't use them.

The tennis player is then given the task of cleaning tables. At first the task is impossible for him, but slowly his bad arm begins to remember how to move, and eventually he is back playing tennis. The functions in the brain areas that were killed by the stroke are transferred to healthy regions. New connections are formed between the intact neurones; these neurones are stimulated by activity.

An example of a structural shift in the brain is has been shown in a study of London taxi drivers by McGill University scientists. By observing London taxi drivers using magnetic resonance imaging (MRI) techniques to obtain images of their brains, the scientists discovered that experienced drivers have a larger hippocampus area in their brain than other drivers. This seems to be because their job needs their brain to store large amounts of information and to have good spatial understanding. London taxi drivers have to pass an extensive test on 320 standard routes throughout the city before they can start working. Most drivers prepare for the test over 34 months by practising the routes on a moped. MRIs have shown a structural change in the hippocampus of these taxi drivers, which increases with the length of time a driver has been doing the routes.

Worked example

What is adult brain plasticity? What is the difference between structural and functional plasticity?

Solution

- The adult brain can change and adapt as a result of experience.
- The adult brain can rewire after a massive stroke.
- Functional plasticity is the ability to move functions from a damaged area to an undamaged area.
- Structural plasticity means that the brain can actually change its physical structure as a result of learning.

Stroke may promote reorganization of brain function

Neuroimaging studies on stroke patients suggest that functional and structural reorganization of the brain takes place during recovery. This includes axon sprouting (new connections between axons), post-stroke neurogenesis (migration of new neurones to the site of the injury), differentiation of immature glial cells, and new associations with neurones and blood vessels.

Does the brain do this all by itself, or do we have some input into how this reorganization takes place? We know that after a stroke there are both chemical and physical changes in the pathways. What can be done to promote recovery?

In animal models with primates, it has been shown that improvement can be made with intervention. After a stroke resulting in weak hand movement in monkeys, the monkeys that did exercises with food rewards improved more rapidly than those that did not exercise. The part of the brain that improved shoulder movement took over the movement of the hand. The brain had reorganized itself in those monkeys that had received therapy.

In addition to animal models, new technologies have increased our knowledge of how the brain recovers from a stroke. Functional magnetic resonance imaging (fMRI),

positron emission tomography (PET), brain mapping (magnetoencephalography, MEG) and other technologies have unravelled the many brain changes that take place in response to rehabilitation strategies and drugs. A common condition that results from a stroke is partial or complete loss of language function, called post-stroke aphasia (PSA). It had been estimated previously that the window for improvement of PSA was the first year following the stroke. Results of modern brain imaging studies have demonstrated that the recovery of language function can occur well beyond this period. These brain imaging and mapping techniques help clinicians and researchers design better strategies to enhance recovery.

Worked example

Can you remember? Write the correct term to describe each of the following statements.

1 An animal model used in the study of neurulation.
2 Can result in both structural and functional reorganization of the brain.
3 The ability of the brain to move from a damaged to an undamaged area.
4 The ability of the brain to change its physical structure.
5 Elimination of axons not being used.
6 The brain can rewire after a stroke.
7 Incomplete closure of the neural tube.

Solutions

1 *Xenopus.*
2 Stroke.
3 Functional shift.
4 Structural shift.
5 Neural pruning.
6 Plasticity.
7 *Spina bifida.*

TOK

goire Courtine, who rks at the Brain Mind itute in Switzerland, decided to switch paradigm for those o have spinal cord nage and paraplegia. : switch is to change view of the patient n a 'non-functioning son' to a 'person who ı a dormant state'. describes his idea imagining an injured ient as a car with he parts (muscle, ne, etc.) present but engine turned off. goal is to produce a armaceutical cocktail prepare the nerves stimulation. Next he surgically implant a chanical object that will mmunicate between the in and the spinal cord. ntually the person will able to move and walk in. He has called his earch programme the valk' programme. How his a new paradigm now paraplegics are wed?

Two Mayo Clinic scientists have worked as a team to address the problem of regeneration of nerve tissue in spinal cord injury patients. Anthony J. Windebank, a neurologist, has implanted stem cells into damaged nerve tissue. He manipulated the stem cells so that they would promote nerve regeneration. The stem cells delivered the neural growth factors needed for nerve regeneration, but something else was needed for the spinal cord injury to be repaired. In order for the axons to find and connect with an appropriate target cell, a scaffold was needed. Michael J. Yaszemski, a biomedical engineer, was able to create such scaffolding. He designed tubing that acts as a synthetic, biodegradable scaffold. This scaffold can connect severed axons. Working together, these two scientists have pioneered a technique to insert stem cells into scaffold implants in injured spinal cords in animals. Eventually, this work will proceed to human trials.

learn more about work h spinal cord injuries d see the work of ofessor Courtine, go to hotlinks site, search for title or ISBN, and click Chapter 7: Section A.1.

Section summary

- Neurogenesis is the development of the brain and spinal cord from the ectoderm of an embryo. The ectoderm folds into the neural tube. Nerve cells (neurones) are formed by differentiation from the neural tube.
- Neurones grow towards target cells. Neurones respond to chemical messages produced by the target cells. The chemical messages are called CAM.