

Run for it



No one likes to be called a coward. Yet admitting to fear is not necessarily a sign of weakness. It can also be a salutary warning against danger. Whether you run for your life or stand petrified in the face of a worrying situation, fright makes us react instinctively and fast. How does our organism prepare to escape danger or face up to it? Is it possible *not* to experience fear? These are far reaching questions to which certain types of molecules can provide an answer and, in particular, a number of proteins which control this deep-seated ancestral emotion.

Emotions, emotions...

Night has fallen. You are alone at home, comfortably seated in front of a fire, enjoying the warmth and reading a book. Suddenly, there is a loud noise. You sit up with a jolt, all senses alert. Your heart is thumping, your muscles tense, your hands damp and your breathing short. Within the space of seconds however, you realise that it was just the cat that had upset a lamp. Relieved, you sink back into your chair. No one had tried to break in, and yet for a brief moment your blood had turned cold as though your last moment had come.

Fear is a powerful and intense emotion. It acts as an alarm that, in the face of imminent danger, sets off behaviour that will ensure our security and physical integrity. Fear functions as a reflex that puts us on the alert. Our brain then immediately analyses the situation, at full speed. If the reality of danger is confirmed, there are a number of options: escape, hide or fight if confrontation is inevitable. Such a defence

mechanism is highly efficient because the events are memorised and, as a result, you avoid similar situations in the future. Take the example of a dog bite which leaves a deep-rooted mark in the memory of an individual and it will be a long time before he or she can approach a dog with confidence again.

Why are we afraid? It is an emotion we share with all animals, from flies to molluscs and fish to monkeys. Fear is an ancestral emotion which can be related to a reflex of flight and has been remarkably preserved throughout evolution. It provides species with a means of adapting to the environment - typically by running away from a predator - and so plays a fundamental role in their survival.

Small fright or blind panic, fear comes in all shapes and sizes in humans and not only in situations where life is endangered. Fright can also be part of our everyday life the moment our well-being is threatened. Reasons for being unnerved are numerous. Many of us fear solitude

or the unknown and the dark while others are afraid of spiders. Likewise, the prospect of a difficult interview can be daunting just like stage-fright before making a speech in public.

If there are situations we dread and fears we can overcome, do innate fears exist? The answer is yes. But it is difficult to define them because our reactions are greatly influenced by our faculty to learn. It seems however that we are all born with a dislike of heights and loud noise, which we manage to tame over the years.

The paths of fear

A muffled sound, a disturbing smell, a fleeting shadow or a sudden sting are only a few of the unexpected sensations which can raise fear in us. And, within a split second, an alarm is directed to the limbic system in the recesses of our brain, also known as the emotional brain. It is there, in a small almond-shaped structure called the amygdala, that the emotion of fear begins (Fig.1). If, by any circumstance, this region is damaged - as can be the case in patients who have suffered cerebral lesions for instance - any sensation of fear is checked, which goes to show how essential a role the amygdala plays. Indeed, two cerebral paths which signal danger converge towards it: the first is quick and short while the second is long and slow.

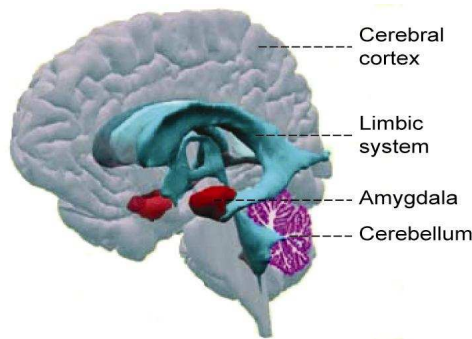


Fig.1 Fear arises in the brain at the level of the amygdala (shown in red) of which there are two: one in the right hemisphere and one in the left.

No taste for danger

Fear has no taste for danger. The first reaction doesn't give a chance to luck or bad luck. The sensory information transmitted by the brain is immediately directed towards the amygdala. With a heart already beating hard, the organism is ready to react and has a choice of two options: run away or stand and fight.

Thinking it out

What about the noise that made you jump out of your skin while you were reading quietly in front of

the fire? Should it worry you? Is it a noise that you have heard before? And if so, in what context? The slow path will give an answer to these questions. First, the sensory alert signal will be directed towards the cortex which will identify the noise - such as a slammed door or a fallen object - then on to the hippocampus which roots around in your memory to see if you haven't already encountered a similar situation. All this information then converges towards the amygdala.

These two paths - the fast and the slow - take place simultaneously. And if, in the end, there turns out to be no real danger, your heart stops thumping and you can go back to your reading!

Cold sweat

How do the amygdala transfer the sensation of fear through the body? By stimulating another structure in the limbic system: the hypothalamus. The hypothalamus activates two parallel paths along which the sensory information is despatched, i.e. the nerve cells and the blood cells. Their targets are the suprarenal glands which subsequently release numerous hormones into the bloodstream (Fig.2), namely adrenalin. Adrenalin is a chemical molecule derived from an amino-acid known as tyrosine. The secretion of adrenalin has an instant effect on many organs, with the aim to prepare the organism physically in the face of imminent danger. The heart beats faster, blood pressure rises and breathing quickens. The level of sugar - glucose - in the blood rises so that the brain and muscles are provided with more energy. As a result, pupils dilate as alertness increases and muscles are tense and ready for action, whereas the digestive system - not requested in such circumstances - slows down. This sudden activity produces heat. So, in order to avoid the body overheating, perspiration increases causing shivers down your spine and dampness of your hands.

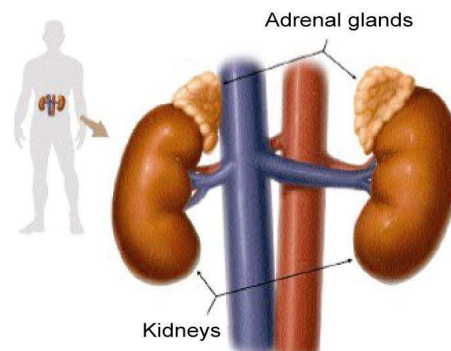


Fig.2 The suprarenal glands are located above the kidneys; these are the glands that release the hormones of fear, one of which is adrenalin.

Switch it off

Surprisingly, fear is less visceral than it is cerebral. The body is subjected to what the brain has decided. We now know that fear arises in the amygdala but do we know how it is shaped from a molecular point of view? The mechanisms of fear are still hazy in spite of numerous studies on the subject. Some proteins however seem to be determinant. Researchers have identified three proteins among others: GRP, stathmin and ASIC1a. All three are present in various regions of the brain but they are particularly plentiful in the amygdala and are gathered in great numbers in essential cellular structures of the brain - the synapses.

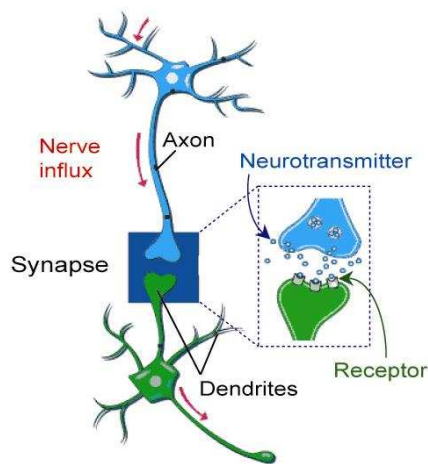


Fig.3 The structure of a synapse. The nervous influx passes from one neurone to the next by way of neurotransmitters that are released in the synaptic cleft.

A synapse is the zone in which contact and communication is made between two neurones. Nervous information is transmitted in the brain by crossing the synapses. The upstream neurone releases neurotransmitters - small chemical molecules - into the synaptic cleft, while the downstream neurone captures them with the help of proteins called receptors which are located on the cell's surface. (Fig.3). There are two large neurotransmitter families and consequently two types of neurones: the excitatory neurones and the inhibitory neurones. Excitatory neurones promote the propagation of a nervous message while the inhibitory neurones counter its transmission.

GRP is one of the first proteins to have been identified in the mechanisms of fear. Initially described as a growth factor in the gastrointestinal system and studied for its role in the development of several types of cancer, GRP is also a neurotransmitter. Mice, in which GRP activity has been silenced, become abnormally fearful. More precisely, they memorise - very rapidly - the fact that harmless stimuli precede danger when both events are systematically associated. (cf. box). How can this be explained from a molecular point of view? GRP is released by the excitatory neurones in the amygdala and acts on the inhibitory neurones which in turn slow down the excitatory neurones. As a consequence, without GRP the excitatory neurones are at 'cruising speed', which reinforces the learning process of fear thus making the mice more fearful. Researchers have finally come to the conclusion that GRP tones down the learning of fear but it doesn't seem to initiate it.

Acquired fear. Innate fear.

Acquired fear

The learning of fear refers to an experimental method known as conditioning where laboratory mice are trained to be afraid. As a result, this type of fear is qualified as "acquired fear". In practice, the mice are first submitted to a neutral sound which doesn't arouse any form of stress. They are then submitted to an electric shock on the underside of their paws, which is slight but disagreeable. Little by little, normal mice recognise the association of the two events and memorise the fact that a harmless sound precedes danger. Consequently, they show fear - detected by sudden immobility for instance - the moment an otherwise harmless sound is emitted, and well before feeling the electric shock.

Innate fear

One test of innate fear is based on the observation of instinctive fear in mice when they are in open spaces and there is nowhere to hide from predators. The mice are placed on a high platform without edges. Normal mice remain in the middle, afraid that they might be exposed to a predator.

Stathmin, on the other hand, is necessary for the surge of fear. Located in the synapse of the excitatory neurones, it delays the formation of microtubules. Microtubules are protein assemblies are involved in the architecture of neurones and play a role in the transfer of cellular components. Suppressing stathmin in laboratory mice makes them surprisingly less fearful. Not only do they learn not to be afraid any more, but they actually venture onto a high platform - a form of behaviour which goes against their natural instinct. (cf.box). Researchers had been inclined to believe that innate fear was independent of acquired fear but it appears that stathmin controls both, though how is still not clear.

Suppressing ASIC1a in mice has the same effect on their behaviour as suppressing stathmin, i.e. it takes the edge off their fear. Yet the molecular role of ASIC1a is very different. Lodged in the membrane of the excitatory neurons close to the synaptic cleft, ASIC1a is a pore composed of an assembly of four copies of the protein. Its function is to allow ions - sodium and calcium - to pass through the membrane, but only if the synapse's environment is sufficiently acid. This implies that the opening of the canal is determined by protons which control the acidity. The protons are probably released with the neurotransmitters in the synaptic cleft. Caught between the two neurons, they bind to the surface of the ASIC1a complex thereby causing a change in its shape, which propagates to the centre of the complex - much in the same way as a line of dominoes would do. As a result, the canal opens and ions can pass through. An influx of ions is subsequently

established, and closely linked with the synapse's activity. Hence, ASIC1a appears to promote the transmission of fear in the amygdala.

Chronic fear

Why be concerned with proteins on which we could intervene in the hope that we can moderate our behaviour in the face of fear? Therapies currently practised on patients suffering from chronic fear aim to calm an unreasonable intensity of fear. Although fear is an emotion common to all, out of control it can become a pathological state. Panic attacks or anxiety marked by intense psychic ill-ease and characterised by fits of trembling and palpitations, or even phobias such as an exaggerated and specific fear of spiders or of crowds are some examples.

The possibility of blocking the activity of ASIC1a and stathmin opens up new fields of research in the quest for novel therapies. However, one protein is rarely involved in only one function. Not only does ASIC1a play a part in the processes of fear but it also has some say in spatial memory and the perception of pain. Like so many other biological systems, cerebral systems are complex, and tinkering with them by way of surgical or medical treatment will always be hazardous. Anything to be afraid of?

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For further information

On the Internet:

- About the adrenaline: <http://en.wikipedia.org/wiki/Epinephrine>
- About the fear: <http://people.howstuffworks.com/fear.htm>

Illustrations:

- Heading illustration (The Scream by Edvard Munch), Source : http://lecerveau.mcgill.ca/flash/a/a_04/a_04_p/a_04_p_peu/a_04_p_peu.htm
- Fig.1, Source : http://lecerveau.mcgill.ca/flash/d/d_04/d_04_cr/d_04_cr_peu/d_04_cr_peu.htm
- Fig.2, Source : <http://fr.wikipedia.org/wiki/Image:Surrenale.jpg>
- Fig.3, Adaptation : <http://www.droques.gouv.fr>

At UniProtKB/Swiss-Prot:

- Gastrin-releasing peptide (GRP), Mus musculus (mouse) : Q8R1I2
- Gastrin-releasing peptide (GRP), Homo sapiens (human) : P07492
- Stathmin, Mus musculus (mouse) : P54227
- Stathmin, Homo sapiens (human) : P16949
- Acid-sensing ion channel 1 (ASIC1a), Mus musculus (mouse) : Q6NXX8
- Acid-sensing ion channel 1 (ASIC1a), Homo sapiens (human) : P78348

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