THE TRANSMISSION OF FEAR

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Definition and background

Fear is the most extensively studied emotion and is a model for all the others. There is consensus in the scientific community that animals experience fear but not so-called secondary emotions such as shame and guilt.
Fear induces the same physiological mechanisms in humans as it does in animals which are often used as model systems to investigate the activity of potential anxiolytic psychotropic drugs.
In ethology, fear is defined as a response to danger (be it real or imagined) which gives rise to defensive behaviour or flight.

Manifestations of fear

Some manifestations of fear are the same in mammals, birds, reptiles and even invertebrates. The focus here will be on those in mammals which are marked by enhanced attention and certain autonomic reactions, notably increases in heart rate and breathing frequency, sweating, piloerection, involuntary urination or defecation and secretion by the anal glands.
The classic behaviour patterns associated with intense fear are described by the three F's, namely Freeze, Flight and Fight. Milder fear is associated with behaviours aimed at communication such as low-slung or twisted posture, certain movements or positions of the tail and ears, and grimaces.

Pathology of fear and cerebral mechanisms underlying the transmission of fear

The high and low pathways

A glimpse of a snake-like twig or hearing a threatening sound results in the transmission of a message in the thalamus (the structure where messages from the sensory organs are received), and then from there to the amygdala. This non-specific message is transmitted rapidly allowing the animal to react to danger very quickly in a subconscious fashion. This is referred to as the *low pathway* which is twice as fast as the *high pathway* which goes from the thalamus to the visual cortex. The latter creates an accurate representation of the stimulus. Once the cortex has differentiated between the twig and a snake, the amygdala has already launched "snake defences" (the three F's). When the response arrives from the cortex, adaptation occurs: since it is only a twig, responses are inhibited (e.g. flight). The cortex is therefore involved in risk assessment. It is the frontal cortex and the basal ganglia which guarantee this cognitive stratification of "voluntary actions" after the amygdala response.
In most instances, traumatic events are remembered for life, even after behaviour therapy. These events can be reactivated by new stress, e.g. bereavement.

Conditioning and fear: the role of the hippocampus

One day, you are walking in the street and you see someone running towards you. He reaches you, hits you on the head and steals your bag.
The next time you see someone running in your direction, wherever you might be, the mechanisms of fear will be induced—as they will be if you witness violence in the street. These mechanisms are important from an evolutionary point of view in that certain contexts lead to heightened vigilance.
The hippocampus is not involved in the processing of stimuli but it creates a representation of the context containing the relationships which unite them. If a mouse with hippocampal damage is put into a box and given an electric shock associated with a certain sound, the animal will still react to the sound but will not show any sign of fear if it is put back in the box.
It is the hippocampus which is involved in acquired distress.

The feeling after the emotion

The feeling of being frightened arises when we become aware that our emotional defence system is active: the amygdala sends projections to many areas of the sensory cortex and interacts with the brain's alarm systems: activation of the basal nucleus which releases acetylcholine around the cortex. Activation of the alarm system by the amygdala is far longer-lasting than its activation by the senses. The feeling of fear is useful for remaining "on alert" as long as the danger threatens and makes it possible to take over from the reaction of the amygdala.

Corporeal retroaction

The involvement of the autonomic nervous system and the release of stress hormones leads to visceral and somatic responses which are themselves transmitted to the cortex.
It seems that the various "biochemical profiles" secreted by the emotions differentiate between the latter and make it possible to pass from one to another.

The purpose of fear

With the amygdala and its inputs and outputs, the brain is pre-programmed to detect danger (both the types experienced by our ancestors and those that we have learned).
Pre-conditioned responses, modelled by evolution, occur involuntarily. They are very rapid, do not require "know-how", and are extremely effective. Always identical, they are present from birth. This survival instinct is observed in the defence reactions against predators and it is also activated in natural conditions where meeting a predator is more likely (at night, in an enclosed place, etc.). Similarly, dangerous natural conditions such as a storm or being near a cliff can activate these innate fears. As for social fears, they are learnt by conditioning in the course of socialisation and help with the avoidance of conflict.

Transmission of fear between individuals

When an individual animal belonging to a social group notices a predator, it can communicate this vital information to the other members of the group. It does this—voluntarily or not—by whimpering, by fear postures or by releasing alarm pheromones. This communication between individuals within a social group is advantageous when it comes to survival of the species.

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Some pathological entities

Phobias

Current ideas on phobia focus on the idea of preparation. the amygdala responds to a greater extent to stimuli used as emotional signals for the species, e.g. when rats are put together with a cat, they produce sounds that warn the other rats to avoid the spot where they are. Certain neurones in the amygdala are activated by ultrasound waves similar to warning signals.
The amygdala in each species might be predisposed to respond to specific indices.
Moreover, the amygdala in certain individuals might—as a result of genetic sensitivity or following a sensitising experience—be particularly reactive, predisposing certain individuals to phobia.

Anxiety

In animal experiments, stimulation of the locus ceruleus raises its activity and generates a state analogous to anxiety. It is believed that states of anxiety result in part from excessive noradrenergic activity (which is why beta-blockers and alpha-agonists have anxiolytic activity). Another pathway involves GABA-ergic compounds which could inhibit the areas of the brain involved in anxiety, notably the amygdala.
This is how the benzodiazepines work, and also a new nutraceutical called theanine.

Investigation of a new anxiolytic

Green tea is a natural beverage known throughout the world for its pleasant taste and its relaxing effects. Both these characteristics are due to the presence of a special free amino acid called theanine which is preserved because the virgin leaf is not fermented. Today, it is possible to synthesise the laevorotatory isomer (L-theanine) which is the neurologically active species. This has led to the development of "anti-stress" dietary supplements containing this compound. These are especially popular in Japan where traditions associated with green tea endow this substance with a special place.
L-theanine or γ-ethylamino-L-glutamic acid is a structural analogue of glutamate which is absorbed in the gut and which can cross the blood-brain barrier. In rodent models, it induces subtle biochemical changes in the brain which account for its calming effect. It binds to glutamate receptors, thereby countering the stimulatory activity of this neurotransmitter. In addition, there is a rise in the intracerebral concentration of GABA, a inhibitory neurotransmitter. In humans, L-theanine promotes mental and physical relaxation, and reduces stress and anxiety without causing drowsiness. Forty minutes after the absorption of 50-200 mg of L-theanine by human volunteers, alpha waves (wakefulness, a relaxed and calm state) begin to appear on the electroencephalogram around the occipital regions extending as far as the parietal brain. In another study, the amplitude of these alpha-waves was shown to be dose-dependent. Subjects reported a relaxed feeling within thirty to forty minutes of ingestion. The compound is naturally metabolised by enzyme-mediated hydrolysis in the kidney. Acute and chronic toxicity studies show no adverse effects, even at very high doses (2,000 mg/kg). It is estimated that a heavy tea-drinker (6 to 8 cups a day) takes in between 200 and 400 mg of L-theanine a day.

Preliminary tests (described in a patent submitted by Japanese scientists) carried out on small numbers of dogs suggested that this compound may be able to attenuate certain symptoms of anxiety in this species. We recently participated in a field clinical evaluation in France in collaboration with the Medical Department of the Virbac pharmaceutical company, with a view to

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investigate the efficacy of a "nutraceutical" based on L-theanine in the management of anxious and phobic emotional states in dogs.

Thirty-two dogs of different breeds and of between 7 and 13 months of age were studied without gender, origin or living conditions being taken into account. The inclusion criterion was the occurrence for at least one month of one or more of the following manifestations of phobia: fear in the street (sensory deprivation syndrome), fear of humans, fear of dogs (social phobia), or signs of intermittent anxiety (hypervigilance, tenseness, jumping at the slightest sound), digestive problems (e.g. hypersalivation) and finally, sustained displacement activities such as licking of the body or bulimia. Exclusion criteria were chronic incapacitating disease, infectious disease, and the use of psychotropic drugs, hormones, pheromones or anti-inflammatory drugs in the preceding month.

The origins and socio-familial environments of the dogs in the study were comparable with those of the general population in France. Mostly acquired by relations (37.5%), from breeders (25%) or a shelter (22%), the dogs had been adopted at an average age of 7 months, often into a home with two or three people. Intermittent signs of nervousness, tenseness or fear were recorded in 78.1% of the subjects. Manifestations of fear in the street or at people or peers were also reported in many cases (59.4%). Only one dog had digestive problems, namely bulimia and licking. The average age at which the problems had appeared was eighteen months (from adoption to 10 years), less than or equal to 1 year for 70% of the dogs. In most cases, the first signs were noticed by the owners at the time of adoption. The circumstances which were associated with problems that appeared later were a change in location (moving house) or the animal's immediate environment (owner's parental leave, death of another pet, etc.) and traumatic events (e.g. an accident). In some cases, there were other, intercurrent behavioural problems: related to separation (37.5%), hyperactivity (9.3%), a tendency to run away (9.3%) and inappropriate barking (6.3%). Most commonly, little change in the emotional picture was observed. Basal T4 levels were measured in 29 dogs, 23 of which had normal levels and six had readings slightly below normal.

The dogs were followed for two months during which the owners gave them oral L-theanine tablets twice a day at a dosage of 5 mg/kg (doses of 50-200 mg depending on the dog's weight). Any other modality to address behavioural problems, be it pharmacological, dietary or pheromonal was forbidden. The owners were not given any instructions on behavioural therapy.
Clinical and behavioural examinations were performed on D0, D15, D30 and D60. A codified grid with 18 items was filled in by the veterinarians on the basis of the dog's behaviour during the consultation and information given by the owners. The evaluation addressed autonomic manifestations (panting, shivering, mydriasis, yawning, vomiting, hypersalivation, fear-induced urination or defecation), behavioural manifestations (whining, whimpering, excessive demands for attention, seeking of the owner, threats/growling or even aggressive behaviour because of irritation or fear, aggression redirected against people, objects, furniture, avoidance behaviour) as well as the animal's emotional state and associated postures (inhibition with flattened ears/tail between the legs/tendency to cringe, agitation, hypervigilance and hyperaesthesia, tendency to panic/run away or hide, inhibition with licking/stereotypical behaviour). Each symptom was scored on a scale of 0 to 3 according to its intensity and all the scores were added together to give a global clinical score reflecting the severity of the problems observed. The investigators were also asked to make a subjective estimate of the degree of improvement at each visit.

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A significant reduction in the global clinical score was observed over the course of the study.

Global clinical score: median (95% confidence interval)					
D0	D15	D30	D60	P*	% reduction D60
16.5 (14-19)	13 (10-16)	9.5 (7-13)	7 (3-9)	<0.0001	59.2 (30-66.7)

* Friedman ANOVA

A substantial objective response was observed to L-theanine supplementation (over 50% reduction in the global clinical score) in 64% of the dogs within two months. The veterinarians' subjective estimates also clearly showed an impression of improvement vis-à-vis problems of fear in the street, fear of people and peers and in general signs of tenseness and nervousness in respectively 50%, 60.8% and 42.2% of cases. A total of 54.8% of the owners thought that the treatment had been effective. The attractiveness of the tablets was judged very good in 93.8% of cases with spontaneous ingestion or the animal asking for the tablet. Tolerance of the supplement was recorded as good or very good in all cases with no side effects reported.

This clinical trial points up the value of L-theanine supplementation to mitigate symptoms of anxiety in dogs. Despite the absence of an untreated control group, the magnitude of the effects as measured by the scores (reduction of the severity of symptoms by more than 50% in the majority of cases) together with the investigators' general impressions place the efficacy of the supplement beyond the type of effects typically seen with placebo. L-theanine would seem to be particularly effective in fearful or tense dogs or dogs that have been perturbed by a one-off or permanent change in their environment. In contrast, little improvement was seen in other types of behavioural problem presented concomitantly by certain of the dogs in this study (problems due to separation, hyperactivity).

Key words: anxiety, anxiolytic drugs, GABA, nutraceutical, fear, phobia.

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