Vasovagal syncope in humans and protective reactions in animals

Jean-Jacques Blanc1*, Paolo Alboni2, and David G. Benditt3

1The Universite´ de Bretagne Occidentale, 2 rue de kerglas, Brest 29200, France; 2The Division of Cardiology, Ospedale Privato Quissana, Ferrara, Italy; and 3The Cardiac Arrhythmia Center, University of Minnesota Medical School, Minneapolis, MN, USA

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Vasovagal syncope (VVS) is not known to occur in animals, although other similar reflex responses are common. This review examines the possible relation of these latter presumably protective reflexes in animals to VVS in humans. The goal is to provide practitioners, and ultimately their patients, a meaningful understanding of the origins and appropriate management of this unpredictable affliction.

This report utilized review of computer databases (e.g. PubMed) addressing VVS pathophysiology and origins, spontaneous transient loss of consciousness in animals, and comparative physiology. We also examined articles cited in the publications obtained by computer search and others suggested by colleagues. Articles were chosen based on those providing original observations and/or suggestions of novel mechanisms.

In animals self-preservation is directed towards protection of the body through an escalation of behaviours depending on severity and proximity to danger. In humans self-preservation is directed not only to protection of the body, but also to protection of the brain’s functional integrity. By virtue of loss of postural tone, the faint causes the body to assume a gravitationally neutral position, thereby offering a better chance of restoring brain blood supply and preserving brain function.

Vasovagal syncope may seem to be a disadvantageous evolutionary adaptation. However, it is a reversible condition, that while exposing risk of injury and embarrassment, ultimately favours brain self-preservation in potentially threatening circumstances.

Keywords
Vasovagal syncope • Pathophysiology • Self-preservation reactions

Introduction

Vasovagal syncope (VVS) is by far the most common cause of fainting encountered in humans.1 However, although other species exhibit a variety of protective reflexes that may be similar to VVS, for unknown reasons VVS seems to be restricted to mankind. The aims of this manuscript are to examine possible origins of protective reflexes observed in animals and derive explanations for the basis of VVS as an apparently unique human behaviour. Inevitably, the arguments offered here are speculative, but nevertheless they may help physicians better understand VVS.

Possible origin of vasovagal reactions

In an idyllic world, conflicts would never occur between groups or among individuals. Unfortunately this is not the case, and as a result the everyday struggle for life has generated a self-preservation instinct. This instinct may be defined as the behaviour that endeavors to ensure the survival of the organism. In vertebrates the responses that are generated are mediated by the autonomic nervous system (ANS).

Self-preservation reactions in animals

In the setting of suspected or obvious peril, and in order to improve the chance for self-preservation, fear responses in animals escalate from ‘freeze’ to ‘fight’ as a function of the proximity of the danger; intermediate responses are termed ‘flight’ or ‘fight’. All of these reactions are mediated by the ANS, but our understanding of which action is triggered by which element of the ANS is far from complete. For example, an increase in parasympathetic nervous system (PNS) outflow may produce very much the same effect that occurs with a decrease in sympathetic nervous system (SNS) activity.

What is observed during most experimental studies of the physiologic state surrounding the ‘freeze to fright’ continuum is interpreted to be the net result of the balance between the two principal ANS branches. For example, Sheldon et al.2 reported that induction of auditory stimuli in rabbits induced bradycardia and hypotension, a consequence of transient PNS predominance. A comparable

* Corresponding author. Tel: +33 2 98 42 28 25, E-mail address: jacques@jjgblanc.fr
response known as ‘approach reflex’, in which bradycardia and hypotension is observed in various fish species when a human hand is gently passed over the aquarium.³

Freeze

The freeze reaction may be regarded as the initial step of self-preservation behaviour in anticipation of possible danger. This phase can be considered as ‘stop, look and listen’;⁴ at this moment life is not considered to be immediately menaced but some sensation alerts the animal that danger may be imminent, and all senses are set in alert ‘mode’ to assess an impending risk. The utility of the freeze attitude is quite evident since, if the danger is confirmed, it provides more time to escape before the attack. Furthermore, it has been shown that during threat, a ‘frozen’ potential prey is more likely to avoid capture, because the visual cortex and retina of mammalian carnivores evolved primarily for detecting moving objects.⁵

The bradycardic reactions of rabbits and fishes during auditory or visual stimuli noted earlier are examples of ‘frozen’ attitudes, and reflect transient predominance of PNS activity. However, the two principal ANS branches can be successively activated; Lang et al.¹ presented examples in which heart rate first decreases and then accelerates as a function of the distance of the threat. An analogous biphasic response also appears in human VVS to be discussed later.

With a further increment in threat, the heart rate response also reverses direction; changing from a vigilance-related fear bradycardia to mobilization and cardiac acceleration.⁵

Flight or fight

‘Flight or fight’ is the most common response of animals faced with immediate danger. These two strategies are characterized by an intense increase in physical activity with an obvious enhancement of SNS outflow resulting in tachycardia, hypertension, and dilatation of skeletal muscle vessels. However, it is difficult to investigate the instantaneous ‘choice’ that has to be made between escape and struggle. Not surprisingly, the choice varies from one animal to another and from one moment to another, which strategy is selected is most likely determined by multiple factors including experience, physical circumstances, as well as the type and size of the opponent.

Fright

The ‘fright’ reaction is essentially the opposite of the ‘flight-or–fight’ strategies. However, ‘fright’ in this context must be interpreted broadly, and as such has given rise to numerous descriptors of its consequences, including death-feint, fright paralysis, tonic immobility, and ‘playing dead’; the last two of these are the most commonly adopted.⁶,⁷

The ‘playing dead’ phenomenon has been analysed in detail by Alboni et al.⁶ As assumed by the name, the ‘fright’ animal looks ‘dead’; it is lying, breathing is markedly decreased in rate and amplitude, bradycardia with sinus pauses > 3 s are common. The ‘playing dead’ attitude has been reported in a wide variety of vertebrates including sheep, sharks, chickens, and piglets.⁷ Interestingly, this reaction is frequent in young white-tailed deer fawns but rare in older deer.⁸⁹

The most complete expression of the ‘playing dead’ attitude is observed in the opossum.¹⁰ When confronted with a pressing risk, this animal reacts as described by Alboni et al.⁶ with apparent paralysis, prone position, and marked stiffness of the body; in addition, respiratory rate is reduced by about 30%. In some individuals “playing dead” is accompanied by a decrease in heart rate (about 50%) as well as with enhanced salivation, urination, defecation’. Bracha et al.¹¹ added further details to this description ‘the opossum’s Oscar-worthy acts completed by the peri-anal glands secreting a greenish liquid with a rotting-flesh smell, and nasal and oral frothy secretions resembling rables. The fear response of the opossum is a decomposing carcass act, off-putting to even the hungriest of predator’.

Tonic immobility occurs in animals when death appears imminent. The presumed rationale for mimicking ‘tonic immobility’ is that by pretending to be dead, the prey will avoid being killed, either because immobility prevents the predator seeing the potential kill or, because the prey, when considered to be already dead, is no longer desirable. In any case, crucial to this playing dead approach is that the immobile animals are conscious, at least to the extent that can be assessed by electroencephalographic recordings.¹²

Self-preservation reactions in humans

Homo sapiens is subjected to the same or similar protective reactions as other vertebrates when facing imminent danger. The ‘freeze’ reaction is expressed in humans as being on guard or watchful. The flight-or-fight reaction, often portrayed in cinema, is common in everyday life when individuals are faced with potential catastrophes. As is the case in animals, the SNS is the predominant driver of the flight-and-fight reaction.¹³

Fright

At first sight the ‘playing dead’ reaction of animals seems to be unknown in humans; however, some authors think that it exists. For example, Bracha⁸ reports that ‘the tonic immobility survival response may be the best explanation for the behavior of some rape victims during the assault’. Others⁷ proposed that cataplexy with intact consciousness evoked by emotion could be an atavistic expression of tonic immobility. Furthermore, psychogenic pseudosyncope, a finding that is commonly associated with a prior history of physical abuse, could also be considered as a manifestation of the ‘playing dead’ attitude.¹⁴

Vasovagal syncope in humans

Vasovagal syncope is used here to encompass those occurrences of syncope that occur in an ‘emotional context’, and are often referred to as the ‘common faint’. As stated by Van Dijk⁷ there are no convincing reports on the occurrence of emotion-induced VVS in animals. However, syncope during venipuncture, a situation that commonly leads to VVS in humans, has also been observed but very infrequently in captive chimpanzees.⁷

It could be attractive to consider that the playing dead strategy in animals is a surrogate of VVS in humans. However, if immobility is observed in the two situations it is the only major similarity. Indeed if the predominance of PNS activity is consistent with marked bradycardia and/or drop in blood pressure during VVS in humans, these reactions are inconstantly observed during tonic immobility in animals. Furthermore, during VVS there is a complete loss of consciousness; conversely during ‘playing dead attitude’ consciousness is well preserved as suggested by electroencephalographic recordings.¹² Consequently, ‘playing dead’ in animals and VVS in humans
appear to be two distinct entities and should not be considered equivalent.

In humans it is well known that VVS represents more than 60% of the causes of all syncope, a common symptom that affects at least one-half of the general population during their lifetime. Thus, VVS is very common in humans, particularly in younger individuals, but non-existent or extremely rare in non-human vertebrates. One may then conclude that VVS is a reaction that Homo sapiens has acquired in addition to the other self-preservation responses observed in non-human vertebrates.

Why is vasovagal syncope frequent in humans but not in animals?

A precise explanation for why VVS appears to be restricted to humans is not readily at hand. However, a number of possible explanations have been proposed and are summarized here.

Bipedalism and upright position

One of the major consequences of human’s bipedalism with erect posture is to place the brain 30–50 cm vertically above the heart. The consequence is that systolic pressure at the level of the heart needs to be high enough to overcome a hydrostatic burden of around 30 mmHg. Another disadvantage for brain blood flow is that humans have a huge capacitance vascular bed located in the lower part of the body. As a result, in the upright position a large portion of the potentially available circulating blood volume is confined to the abdomen and legs; if the amount confined below the diaphragm is excessive, brain blood flow may be compromised. In this regard, it should be stressed that VVS occurs almost exclusively when the thorax is vertical (upright or sitting position).

In many animal species, the heart and brain are at the same horizontal level; however, in some vertebrates, such as the giraffe, the brain is several meters above the heart. Despite this situation VVS has never been observed in these animals. A possible answer is that the giraffe is a quadruped, but the ostrich, kangaroo, and apes, when they stand up and walk, are not. In all of these animals, muscle pumps in the legs are very active and the capacitance vascular bed limited. However, a more convincing explanation for the absence of fainting in these animals is that the volume of blood needed by the brain is substantially less than is the case for humans. In humans, brain blood flow requirements represent about 20% of cardiac output; conversely, brain blood flow needs are only 5% in apes and <1% in the giraffe and ostrich. Therefore, in order to decrease blood supply to the brain and disturb cerebral function significantly during a vasovagal reaction would require a much more substantial reduction of cardiac output in animals than is the case in humans.

In essence, in the evolution of humans, and despite the many possible advantages of operating in the erect position, a unique predisposition to fainting remains an important limitation. This predisposition to fainting is exacerbated by the limited metabolic reserve of cerebral tissues. Cerebral functional failure begins within 5–6 s after reduction of blood supply below the lower limit of cerebrovascular autoregulation.

Role of emotions

Although structures of the brain are fundamentally similar in vertebrates, Homo sapiens has a more sophisticated brain than animals; 80% of the human brain is dedicated to the neocortex and particularly the pre-frontal areas, the regions considered the site of thought. By virtue of its construction, this brain is sensitive not only to self-preservation fears as in animals, but also to more complex psychological situations, which we label as ‘emotions’. In the comprehensive history taking of medical students in Amsterdam, ‘emotions’ were the reported triggers of VVS in one-half of the cases; the remaining 50% of triggers were situational (e.g. standing, alcohol intake) or physical experience (e.g. warmth, illness).

In general terms, emotions may be divided into different types that include strong fear, deep disgust, intense joy, pain, and blood phobia. Each of these ‘emotions’ can be considered individually.

Intense fear, disgust, or joy

Although not commonly reported, VVS can occur during or immediately after intense joy, as it can in conjunction with strong fear or disgust. Further, fear of an impending danger may be a trigger even when nothing imminently threatens the person. This virtual peril could be the consequence of a very unpleasant sight or situation. These types of VVS are evidently the result of a major psychological activity that is unlikely to occur in other vertebrates with less sophisticated brains. Furthermore, emotion-induced VVS differs from psychogenic pseudosyncope in humans, in which there is no measurable fall in heart rate or blood pressure and consciousness is preserved.

Real fear, joy, or disgust (as distinguished from the ‘virtual’ variety) can trigger conditions that appear similar to the fear situations observed in animals. However, for reasons discussed above the vasovagal reaction is among the most common resulting in physiological changes; furthermore, when it occurs in individuals who are in the upright position, given the gravitational stress, the blood supply to the brain may decrease sufficiently so that syncope occurs.

Intense pain

Pain, when severe or considered as such, is a frequent trigger of VVS. Some localizations of pain, for example abdominal, are particularly prone to cause VVS. In these circumstances activation of the PNS is usually readily apparent. In animals, except in the case of massive haemorrhage as is also true in humans, vasovagal reaction during pain or injury has not been observed.

Blood phobia

As reported in the Amsterdam study, blood exposure phobia is a common VVS trigger particularly in females (13% vs. 3% in males). Bienvenu and Eaton concluded that over 3% of the US population (4.4% of women and 1.8% of men) suffers from clinically significant blood phobia. They found a similar proportion of blood phobia between 0.5% and 1% in males and in females over 50 years. In younger females the proportion was significantly higher, around 3.5%. To explain this observation they proposed the ‘paleolithic-threat hypothesis’. In brief, in this evolutionary period, research has documented extensive Homo sapiens intragroup warfare; a predominant cause of death was wounding by a sharp object. As expressed by Bracha ‘it is unlikely that most non-combatants (females and pre-pubertal children) could outrun a young male adversary. Hence, the
few non-combatants who inherited the polymorphism for the “paradoxical” fainting response to the first sight of a sharp object or blood now possess a survival advantage.

Once again VVS, whatever its explanation is, seems specific to humans. Animals may experience vasovagal reactions during haemorrhage but they need a loss of around 30% of their total blood volume to start ‘fainting’.26

Finally, although all animals have self-preservation reactions, only Homo sapiens react ‘frequently’ with syncope due to the previously described surge of SNS activity followed by abrupt withdrawal of sympathetic activity and activation of PNS activity. This seeming excessive susceptibility to VVS may be accounted for by certain of the explanations provided above.

Bracha et al. hypothesized with their Paleolithic theory that VVS could have some self-preservation utility. In this regard, one might hypothesize that if Homo sapiens had been subject to the risks of serious VVS-related trauma for several millions years, then one would have predicted that the species would also have acquired adaptive processes to at least limit such a disadvantage. Therefore, it can be speculated that persistence of this condition has some usefulness.

What could be the potential advantages for humans to be frequent vasovagal fainters?

Potential ‘advantageous’ effects of VVS cannot be stated with certainty. However, one may speculate that certain advantages could exist:

**Psychological**

To lose consciousness has an evident consequence: events happening during this period are no longer experienced. Therefore, at least in terms of undesirable experiences, VVS could be considered a transitory means to escape from a momentarily intolerable world. However, the psychological benefit is insufficient in that it does not adequately account for all triggering situations, some of which are not intolerable at all (e.g. intense joy). Furthermore, the ‘escape’ is only transitory. In addition, the price being paid is relatively high, as losing consciousness induces potential for injuries that could be severe, as well as a defenselessness that could leave the fainter in jeopardy.27

**The brain self-preservation theory**

If a benefit from VVS is not convincing for the body as a whole due to the possibility of injuries, loss of postural tonus may be beneficial for brain perfusion. When a patient suffers VVS during head-up tilt testing (HUT), the simple maneuver of returning the table to the horizontal position permits prompt recovery of consciousness. Therefore, lying down has an immediate benefit for the brain: it restores better blood supply for an organ which has few energy reserves and for which preservation of blood flow is absolutely crucial.

One may speculate that if the human’s brain senses a decrease in blood supply below a certain limit, such as may occur with diversion of blood to skeletal muscles in the setting of fear or fright, it initiates a self-preservation reflex. In brief, following a period of heightened alertness or fear in which SNS is fully engaged, the cerebrum activates the PNS and/or inactivates the SNS, in order to create bradycardia and vasodilatation. This maneuver in turn decreases blood supply and leads to loss of both consciousness and postural tone; the former reduces energy consumption briefly while the latter (i.e. the fall to a gravitationally neutral position) immediately improves blood supply to the brain. In essence, this paradoxical response in human VVS is a self-preservation reaction of the brain to ultimately restore its blood supply. By this theory, the brain has become so important for humans that it could be speculated that it has been necessary for it to acquire its own self-preservation autonomy.

**Are there data to support this theory?**

Patients who experience the classic VVS pattern during HUT exhibit, a rapid and full compensatory reflex adaptation to upright position; during this phase there is haemodynamic stabilization without decrease in blood pressure but with a progressive increase in heart rate. However, a few seconds before loss of consciousness, an abrupt and major decrease in blood pressure with absolute (asystole) or relative bradycardia occurs.28 Micro-neurographic recordings as well as other pathophysiological observations suggest that these phenomena are the consequence of a sudden withdrawal of SNS tone and therefore an abrupt predominance of the vagal tone.

It has long been considered that the sudden change from SNS to PNS predominance is initiated by a reflex originating from the mechanoreceptors located in the cardiac ventricular cavities and reacting to the sudden decrease in preload and increased force of myocardial wall motion.30 It is believed that theseafferentmessages sent from the mechanoreceptors are interpreted by midbrain nuclei as indicating an undesirable myocardial wall stress, and thus the reflex initiates a decrease in heart rate and dilatation of systemic blood vessels (i.e. an attempt to reduce afterload). However, this theory has been strongly challenged.31,32

An alternative concept is the so-called ‘brain theory’: this view proposes that the initiation of the reflex occurs within the brain itself. When midbrain nuclei become aware that circulatory changes (e.g. marked drop in cerebral blood pressure) preclude maintaining sufficient blood supply to the brain they suddenly reverse their operational activity to a reaction in which salvage of brain blood supply becomes the main goal (i.e. loss of postural tone and assumption of a gravitationally neutral position). In support of this concept is the finding of Lagi et al.,33 who demonstrated during tilt-induced syncope that important changes in cerebral haemodynamics occur much earlier than the vasovagal reactions. Furthermore, the findings of van Dijk et al.34 illustrate that electroencephalographic slowing corresponds to onset of transient loss of consciousness in most VVS patients who faint while undergoing tilt-testing, and that the slowing appears to closely follow reduction of systemic pressure. Their overall observations support a cortical as well as mid-brain response to haemodynamic instability, and are consistent with the ‘brain theory’ of VVS.

**Conclusion**

In animals self-preservation is directed towards protection of the body through an escalation of behaviours depending on the severity and proximity to danger.
In humans self-preservation is directed not only to protection of the body through an escalation of behaviours, as is the case in animals, but also to protection of the brain’s functional integrity. Brain self-preservation, depending on the severity and nature of the threat, may be in some cases managed by the induction of VVS. Although seemingly a disadvantageous evolutionary adaptation, the faint, which by virtue of the loss of postural tone, causes the body to take on a gravitationally neutral position, and thereby provides a better chance of restoring brain blood supply and preserving brain function.

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