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Cortisol: often not the best indicator of stress and poor welfare

The definitions of the term stress are often confusing and should not be linked to cortisol, which is a valuable welfare indicator, but context is needed to interpret it.

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The glucocorticoid cortisol is produced in many mammals, such as primates, carnivores and ungulates, and in other animals. Corticosterone has the same function, being produced in rodents and many birds, including poultry, so reference to cortisol below generally applies to corticosterone as well. The hypothalamic–pituitary–interrenal response of fish that experience adversity involves interrenal tissue whose cell functions are very similar to those of the mammalian adrenal gland. Maximal concentrations of cortisol are produced in a trout when it is removed from water and hence deprived of oxygen.

Cortisol in positive and negative situations

A key, adaptive function of the glucocorticoids is to make energy available in emergency situations, and in some other situations where it is needed, but they have other important roles. The majority of cells in the human body have receptors for cortisol and glucocorticoids reach every organ, thus cortisol has a broad variety of effects, including effects on metabolic, cardiovascular, and immune responses. There is a daily fluctuation in the secretion of cortisol and hence in plasma cortisol concentration, beginning in humans with a distinct sharp rise of cortisol at the time of waking, followed by a steady decline over the course of the day, with the lowest levels in the early morning hours. The cortisol facilitates effective learning, via the functioning of the hippocampus, and maintains other normal functions in the body (Broom & Zanella, 2004). Hippocampal cells actively take up cortisol in vitro. Extreme adversity can suppress the daily cortisol cycle in humans (Kivlighan *et al.*, 2008) and lead to less effective hippocampal function and hence worse learning ability and memory.

The facilitation of learning is clearly a positive function, as is the increase in cortisol during courtship, mating and exertion to obtain food. Whilst cortisol has an adaptive function for the individual when it is produced in response to perceived danger, pain or difficulty to control interactions with the environment, these situations are negative and there may be some substantial negative consequences of the cortisol, as described below. Cortisol has roles in both positive and negative situations so it is erroneous to consider it to be always or generally harmful to the individual.

The meanings of stress and welfare

For most people, stress implies the effects of a challenge to the individual that disrupts homeostasis resulting in adverse effects. It is not just a stimulus that activates energy-releasing control mechanisms. Stimuli whose effects are beneficial would not be called stressors by most people. Also, situations that activate the hypothalamic–pituitary–adrenal cortical axis as part of a brief emergency response, but whose effects are useful to the individual, would not be called stressors by most of the public.

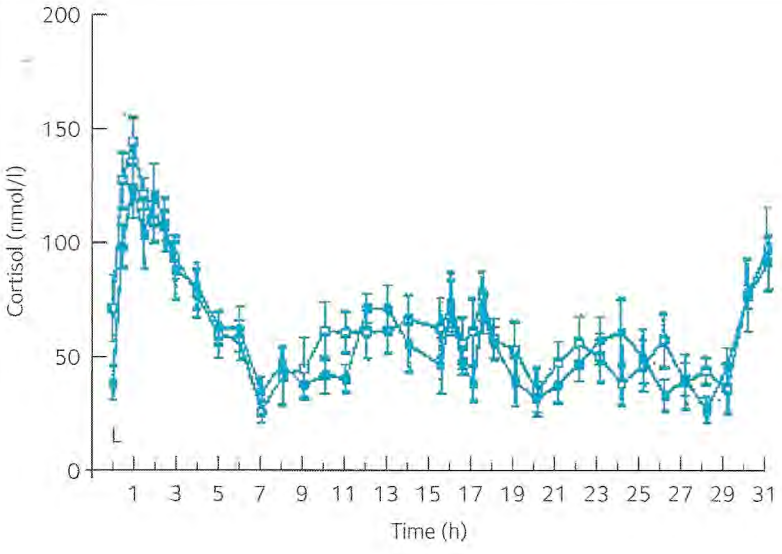

Figure 1. The concentration of cortisol in blood plasma was measured in two groups of catheterised sheep, after a period of adaptation to the catheters, during a commercial 31 hour journey. The basal concentration was close to 50 nmoles per litre. There was a one hour stationary period at 15 hours.

'The context in which changes in cortisol occur is essential information for interpretation of the physiological data'

The writings of Selye, although stimulating useful research, have been scientifically confusing in relation to the use of the term stress. A definition of stress that is in line with the general public usage of the word is: stress is an environmental effect on an individual which overtaxes its control systems and results in adverse consequences, eventually reduced fitness (Broom & Johnson, 1993; Broom, 2014). According to this definition, there is no good stress and effects that are called good stress should be called stimulation. During the development of individuals, stimuli that result from situations that are somewhat difficult for that individual can be useful experience but these are best not referred to as being stressful. This definition is similar to that of Lazarus (2006) who said that stress refers to a situation in which demands are perceived to exceed one's personal resources. However, whilst this definition depends on perception, it is better for the definition to depend on function and to apply to all animals.

Scientists and legislators now use animal welfare as a term that is a scientific concept describing a potentially measurable quality of a living animal at a particular time. The welfare of an individual is its state as regards its attempts to cope with its environment. Welfare can be measured scientifically and varies over a range from very good to very poor. Welfare will be poor if there is difficulty in coping or failure to cope. There are various coping strategies with behavioural, physiological, immunological and other components that are coordinated from the brain. Feelings, such as pain, fear and the various forms of pleasure, are often part of a coping strategy and feelings are a key part of welfare. Coping with pathology is necessary if welfare is to be good so health is an important part of welfare. There is a clear relationship between stress and welfare in that, whenever there is stress, welfare will be poor. However, welfare could be temporarily poor without any long-lasting adverse effect, so this would be poor welfare without stress (Broom & Johnson, 1993).

Writings about the concepts of 'one health' and 'one welfare' emphasise that the meanings of scientific terms concerning humans and non-humans should be the same. However, human usage and definitions sometimes apply only to humans and there can be an erroneous assumption that some mechanisms are confined to humans. The distinction between physical and psychological stressors may involve the assumption that most non-human stress is solely physical. Dedovic *et al.*, (2009) suggest that a stressor facing a wild animal, with the anticipation of bodily injury, is physical while social evaluative threat would be considered psychological. It has been suggested that reactive stressors tend to implicate brainstem, specific hypothalamic nuclei and the bed nucleus of the stria terminalis, which all have direct connections to the paraventricular nucleus whilst anticipatory stressors, seem to engage limbic system regions. This is likely to be valid but does not differentiate non-human and human because the brain mechanisms are present in a range of species. A concept of the future and other aspects of sentience are evident from many non-human studies (Broom, 2014). Health, welfare and stress are the same concepts in humans and other sentient animals because most of the mechanisms are the same.

Cortisol as an indicator of stress and welfare

When humans and other animals are subjected to short-term problems, e.g. painful procedures, frightening situations such as being picked up or transported, or experiences that cannot be controlled, the increase in cortisol that usually occurs can be measured and used as an indicator of the extent of poor welfare. In some cases an experimenter can predict that there will be long-term harm so the individual can be said to be stressed. Cortisol concentration in blood and saliva and, later, the concentration of cortisol metabolites in urine, faeces and hair increases when a person hits their finger with a hammer, a rabbit is subjected to a temperature of 42°C, a calf is loaded onto a transport vehicle, a sheep is driven around bends so that balance is difficult, a pig is introduced to into a group of strangers, a salmon is pumped through a pipe, or a wild bird is brought into captivity. The increase can be assessed in relation to the basal cortisol concentration and the known maximum increase in such an animal. Provided that the sampling of, for example, blood is not itself the cause of any increase and the time taken for the cortisol increase to occur is taken into account, the magnitude of change gives useful information about the subject's welfare (Broom & Fraser, 2015).

An example of cortisol measurement giving useful information about animal welfare is shown in Figure 1. During a period of monitoring sheep during a road journey, the sheep showed a very marked increase in plasma cortisol from the baseline when they were loaded on to the vehicle. This occurred despite the fact that the staff concerned were experienced animal handlers and did not treat the animals roughly. The sheep had never before been on a vehicle and were clearly very disturbed by the loading. The response lasted for 5-6 hours. The cortisol concentration then dropped to close to the basal level as the sheep became accustomed to their new environment. It did not change during a one hour period when the vehicle was stationary. Most of the journey was on motorways, but the last 3 hours of the journey were on side roads with bends at intervals. The drivers drove just as they would with human passengers. However, a sheep standing on a moving vehicle has much more difficulty maintaining its balance than a human sitting in a seat. Cornering and acceleration caused problems for the sheep, so cortisol concentration increased. It is clear from studies over relatively short periods, like this one, that measurement of cortisol concentration can provide information about the welfare of animals and help in the formulation of advice about how to avoid welfare problems for the animals.

Long-term problems may be an accumulation of short-term difficulties in life, each of which is associated with cortisol production. Although this production of cortisol is essential for survival, after injury or various other problems, if it continues to be present it can break down the protein in muscle, inhibit the ongoing replacement of calcium in bone and produce myopathy, weakness, fatigue, and decalcification of bone (Melzack, 2001). Frequent, high levels of cortisol production may lead to neural degeneration of the hippocampus, amygdala, and pre-frontal cortex and suppression of immune system function (McEwen, 2007). People with Post-Traumatic Stress Disorder and other substantial long-term problems have hippocampal and other brain damage, some mediated via cortisol (Bremner, 1999). High plasma cortisol in elderly men is associated with lower cognitive ability (MacLullich *et al.*, 2005). Glucocorticoid effects on the immune system may include changes in the numbers of leucocytes, suppressing the activity of B-cells and cytotoxic T-cells and changing cytokine activity in ways which increase susceptibility to pathogens.These are clearly negative effects on the individual so frequent, high concentrations of cortisol are indicators of stress and poor welfare.

However, some environmental conditions, such as housing conditions that do not meet the individual's needs, may not lead to a change in cortisol concentration. Hence the absence of an increase in cortisol concentration does not indicate that there is no problem for the individual. Many chronic problems lead to attempts to cope not involving cortisol and to other negative effects so a range of welfare indicators is needed to identify that the individual has a problem. This is true of human and non-human subjects. Damage to the hippocampus and other regions of the brain, clearly an indicator of poor welfare, may be caused by high fat diet, alcohol, food restriction or sleep deprivation with no effects on cortisol. Abnormal behaviour, such as stereotypies or high levels of aggression, are sometimes a very useful indicator of poor welfare in situations where there is no elevated cortisol. Fluctuations in cortisol may provide no evidence of poor welfare because they are preparation for courtship or active food-finding. Hence the context in which changes in cortisol occur is essential information for interpretation of the physiological data (Broom & Fraser, 2015).

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