AN ADAPTIVE FRAMEWORK FOR PARTURITION AND PREDATION PAIN

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ABSTRACT

Two of the pain situations that have been studied by Giancarlo Carli are parturition pain and the pain that accompanies immobility responses to a predator attack. An adaptive approach to these situations makes predictions about the level of analgesia or hyperalgesia that should lead to dampened or exaggerated pain responses in different contexts. In primates, there is evidence for significant pain during parturition in the form of writhing, stretching, and grimacing, but most cases feature little or no vocalizations. The prevalence of nighttime births in human and non-human primates is thought to be in part an adaptation to reduce predation, a situation where loud vocalizations would be counterproductive. Immobility responses after a predatory attack should also feature dampened pain responses. In line with this prediction, opiate analgesia has been demonstrated in immobilized rabbits. Other examples of adaptive responses to pain are given from the recent literature, including resistance to scorpion venom in grasshopper mice and socially induced analgesia to biting flies in deer mice.

Key words: pain, adaptation, evolution, parturition, death feigning, tonic immobility

If plants, through the evolution of capsaicin and menthol, can manipulate the pain responses of animals, it is logical to suppose that animals, which have the advantage of a nervous system, should also be able to do so. Capsaicin stimulates the heat receptors of mammals (Caterina et al., 1997; but not of birds, Jordt & Julius, 2002) so that animals avoid the fruit that contains it, while menthol does the same thing for leaves by stimulating mammalian cold receptors (Bautista et al., 2007). In these cases, animal responses have evolved according to the interests of plants. In general, however, we might expect they would evolve according to the interests of the animal experiencing the discomfort and pain and against the interests of the animal causing it.

Adaptive approaches to the study of pain are an important addition to traditional neuroscience approaches (Amit & Galina, 1986; Kavaliers, 1988). Adaptive views seek to (1) identify situations where pain varies in natural settings, (2) pinpoint the mechanisms behind the variation using behavioural experiments in captivity, (3) identify the neural mechanisms of the variation, as well as (4) the genetic differences that underlie them. The behavioural paradigms used in these studies go beyond the standard lab protocols of tail pinching, foot heating, and subcutaneous formalin injection and aim for increased ecological validity. The best examples of this approach come from studies of resistance to scorpion

toxins in grasshopper mice (Rowe et al., 2011), as well as analgesia produced in deer mice by natural stressors such as exposure to predators (Kavaliers, 1990) or parasitized mates (Kavaliers & Colwell, 1995) or attacks from dominant conspecifics (Teskey & Kavaliers, 1991) and biting flies (Colwell & Kavaliers, 1992).

The adaptive approach can be used on many types of pain. Two of the pain situations that Giancarlo Carli has worked on during his long research career, parturition pain and the pain that accompanies immobility responses to a predator attack, have been addressed with an integration of methods from neuroscience and behavioural ecology. In this paper, I first review this work, on which I have collaborated, and then give a series of examples from the recent literature using the adaptive framework.

Viewed in adaptive terms, behavioural responses to predation and parturition pain should vary according to the advantages the animal might incur in either dampening or exaggerating the external manifestation of pain (Amit & Galina, 1986). As these behavioural responses are strongly determined by the internal sensations, genetics, and neurophysiology of pain, the predictions should also apply to these levels. For instance, vocalizations, jumping, and writhing are among the most obvious behavioural responses to painful situations in mammals. One can expect these responses to be modulated according to their context as well as their effect on others. This adaptive logic is similar to the one that has been applied to other prey defences, such as the stotting of gazelles (Fitzgibbon & Fanshawe, 1988) and the tail flashing of deer (Caro et al., 1995), which varies as a predator pursuit deterrent according to context.

Injury resulting from a predator attack should lead to very different responses if the predator has a biting hold on its prey (the prey should jump and writhe), if the prey shows extensive bleeding from a life-threatening wound (double up), if the prey is alone versus close to kin (vocalize), or if the predator has moved away from its prey after immobilizing it (stay immobile). The simplest way to modulate these responses would be to change pain thresholds in the appropriate direction via either analgesia or hyperalgesia.

Parturition is also thought to be painful in many eutherian mammals, but presumably not in monotremes or marsupials, who respectively bear eggs and undeveloped foetuses. Because brain growth, contrary to that of the rest of the body, occurs to a large extent in the embryo, eutherian species selected for large brain size (simian primates, elephants, Carnivora, and Odontocete cetaceans) might have to deal with significant levels of parturition pain. A female giving birth is very vulnerable, but risks for her are likely to be very different if she is a small, frequently hunted primate like a vervet monkey or a large predatory mammal like a polar bear or a killer whale. Behavioural manifestations of parturition pain should logically follow these varying risks, as should internal mechanisms. For example, the vocalizations that normally accompany the levels of pain that are thought to be present during parturition may place some animals at much greater risk than others.

One intriguing feature of parturition on both human and non-human primates is the fact that it most often occurs at night (Jolly, 1972). One plausible function for nighttime delivery is that it decreases exposure of vulnerable females to predation. If darkness offers visual concealment and eating of the afterbirth contributes to olfactory concealment, it would make sense if the loud vocalizations that often accompany pain in other situations were inhibited during parturition. Lefebvre and Carli (1985, 1986) tested this idea with a review of all cases (88 individuals in 29 species, 13 in the field and 75 in captivity) they could find on primate parturition. Mild or severe discomfort, in the form of straining,

stretching, arching, grimacing, writhing, shaking, doubling up, eye closure, and restlessness was reported in 69 cases. Silence and moderate level vocalizations were reported in 21 and 43 cases, respectively. Loud vocalizations occurred in only 6 cases. The trends therefore suggest that, during primate parturition, visible pain responses are seldom accompanied by the loud cries manifested by animals in other situations (Carli & Monti, 1987). In contrast, injuries encountered during intraspecific aggression are accompanied by very loud screams (e.g. Yamada and Nakamichi, 2006, a juvenile bitten by an adult male). In rats, vocalizations that are emitted during attacks by dominants and electric shocks (van der Poel & Miczek, 1991) are absent during parturition, despite the presence of straining and stretching behaviours that are strongly reduced by epidural morphine (Catheline et al., 2006) and can thus be seen as symptoms of pain. In an intriguing follow-up on the known nighttime bias of births in humans, Harkness and Gijsbers (1989) report that stress and pain levels are lower for nighttime births than they are for daytime births. They suggest this might derive from the anti-predator advantage of nighttime parturition.

A similar situation might occur during immobility responses to a predator attack. Many prev species show a form of 'death feigning' when attacked by a predator, the most famous being the 'playing possum' shown by the Virginia opossum Didelphis marsupialis (Gabrielsen & Smith, 1985). The immobility is thought to minimize prey movement cues likely to stimulate predator attack. In the lab, the prey species most often studied are chicken, quail, and rabbits, and the predator attack is simulated by a human forcefully restraining the animal. The prey's response is operationalized by the time it takes to right itself after ceasing to struggle, following the blocking of the normal righting reflex when the prey is maintained on its back. Researchers in physiology and comparative psychology have also called this response 'animal hypnosis' and 'tonic immobility'. The duration of immobility varies according to many factors, but the fact that it is increased by experimental manipulations of fear (Gallup, 1977) and decreased by the habituation brought on by repeated elicitation (Lefebvre & Sabourin, 1977a, b) are consistent with an interpretation based on passive predator avoidance. As further evidence for this function, Jöngren et al. (2010) have shown that measures of tonic immobility in red junglefowl load on the same principal components as responses to a ground predator (a moving stuffed pine marten), and to a lesser extent responses to an aerial predator (flying hawk model). Jöngren and colleagues (2010) have also identified 13 genetic loci that differ between individuals that show more versus less tonic immobility.

According to an adaptive framework, if the response most likely to lead to survival after an attack is writhing, jumping, and loud vocalization, so that the predator is startled and loses its grip, the most efficient mechanism to achieve this should be intense pain. If, on the contrary, the best response is immobility, a decrease in pain would be ideal. In line with this prediction, Carli and collaborators were the first to show that pain appears to be reduced during 'death feigning' (Carli, 1975; Carli et al., 1976, 1977) and that the mechanism for this reduction might be opiate analgesia (Carli et al., 1981; reviewed by Porro & Carli, 1988). These results have since been extended to other species (Leite-Panissi et al., 2001; Miranda et al., 2006) and progress has been made on identifying the mechanisms of both immobility and its accompanying analgesia (Menescal-de-Oliveira & Hoffmann, 1993).

The adaptive framework can also provide insights into other types of pain. For example, Weary and Fraser (1995) point out that adaptive variation in pain should be taken into account in interpreting the behaviours of stressed animals. Pigs, for instance, are well known

for their loud cries when handled, a baseline against which the increased screams of males when castrated need to be titrated (Weary et al., 1998). Recent work by the Kavaliers and Mogil research groups also suggests that social context plays a role in pain responses. Here, it is not so much the broadcasting of pain via loud vocalizations and writhing that appears to have been selected, but the ability of observers to detect pain in the social cues given off by conspecifics. These cues may not be deliberately broadcast (Danchin et al., 2004), but they are available to animals that observe them in others. Kavaliers and colleagues (2005) have shown that pre-exposure to biting flies leads to defensive burrowing and analgesia in both the bitten mouse and in familiar conspecifics that have witnessed either the biting or the subsequent defensive burrowing of the victim. Pain does not have to be broadcast by vocalizations, but can be picked up by observational information given by reliable facial (Langford et al., 2010) and postural (e.g. writhing; Langford et al., 2006) indicators of pain.

An elegant example of the way an adaptive framework to pain can integrate multiple levels of explanation is the work of Rowe and collaborators on resistance to scorpion toxins in grasshopper mice. Grasshopper mice (genus *Onychomys*) are predatory rodents that eat several kinds of insects, including scorpions. Young grasshopper mice show symptoms of pain when stung by *Centruroides* scorpions, but they improve their predatory skills with age and are resistant to the paralysing and often lethal effects that the scorpion venom has on other rodents (Rowe & Rowe, 2006, 2008). Grasshopper mouse resistance appears to be specific to *Centruroides* toxins: house mice respond much more strongly to scorpion venom than do grasshopper mice, but both show the same response to formalin injection (Rowe et al., 2011). The scorpion venom binds Na, 1.7, a Na+ channel expressed in mammalian pain-sensing neurons; genetic studies have identified four amino acid substitutions at highly conserved positions in grasshopper mice Na, 1.7 that differ from orthologs in other rodents (Rowe et al., 2011).

Studies of this type that identify the evolutionary ecology of a pain response, its behavioural characteristics, neurophysiological mechanisms, and genetic background are not only valuable for their intellectual elegance. A complete, integrative understanding of the way evolution has led to analgesia in a specialized case like the grasshopper mouse might yield general insights applicable to less specialized situations. Finding out how evolution has solved specific problems in a few species may save researchers a lot of work in figuring out the general rules that they can apply to other species, including humans.

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