

## Aquaculture and Fish Welfare: Evidences for Fish Nociception

Carla Patrícia Bejo Wolkers\*, Anette Hoffmann

Department of Physiology, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto-SP, Brazil

\*Corresponding author: Dr. Carla Patrícia Bejo Wolkers, Department of Physiology, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto-SP, Brazil, Tel: +55 16 36023332; E-mail address: carlawolkers@yahoo.com.br

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The prominent increase in the use of fish as animal model for behavioral, pharmacological and physiological studies, as well as in aquaculture production chains, raises important questions about the welfare of these animals and the possibility of suffering. However, the occurrence of pain in basal vertebrates such as fish is a controversial issue, even in the scientific community. While some authors suggest that the lack of specialized brain structures, such as the neocortex, prevent fish from feeling pain [1], a number of recent studies have demystified this view, pointing out that teleost fish are able to detect and respond to noxious stimuli of different sensory modalities. These studies have shown that fish have nociceptors with similar characteristics to the nociceptors found in mammals, which are capable of detecting potentially painful stimuli [2,3]. In addition, several species of fish, such as piauçu (*Leporinus macrocephalus*) [4,5], tilapia (*Oreochromis niloticus*) [6] and rainbow trout (*Onchorhynchus mykiss*) [7,8], which are commonly used species in fish farms, have shown behavioral and physiological changes in response to the application of noxious stimuli of different natures. These responses suggest the possibility of the perception of these stimuli as aversive and potentially painful.

The existence of a functional opioid system that modulates behavioral and physiological responses triggered by noxious stimulation has also been described in teleost fish. In addition to having all the major types of opioid receptors present in vertebrates (delta, kappa and mu) with protein structures similar to mammalian receptors [9,10,11], the injection of exogenous opioid substances, such as morphine [3,7] and tramadol [12], inhibit the behavioral and physiological responses triggered by the application of noxious stimuli, suggesting that these drugs can promote analgesia in fish, as observed in mammals. Recent studies have demonstrated that different types of external

stressors, such as social subordination [13], the exposure to conspecific alarm substances [4] and restraint [5], inhibit nociceptive responses in fish, suggesting the activation of an endogenous antinociceptive system. The antinociceptive system, which is activated by stressful situations in fish, appears to be modulated by endogenous opioid substances because pre-treatment with naloxone, a non-selective opioid antagonist, blocks the antinociception induced by the conspecific alarm substance [4] and 3min of restraint stress [5].

Although information on nociceptive processing by fish brain is still incipient, electrophysiological studies demonstrate the presence of neuronal activity, measured by evoked potentials, on telencephalon [14,15], spinal cord, cerebellum and optic tectum [14] after noxious stimulation of skin, suggesting the existence of a nociceptive pathway from the periphery to the higher central nervous system of fish.

However, despite the growing number of studies addressing this issue, the demonstration of pain in fish is a difficult task because pain is considered a complex sensory experience that involves not only the perception of an aversive stimulus but also cognitive and emotional processes [16], which is often difficult to evaluate in animal models. Regarding emotionality, some studies point to the presence of benzodiazepine receptors [17,18] and to the anxiolytic-like effects of benzodiazepine drugs [19] and of the selective serotonin reuptake inhibitor fluoxetine [20] in teleosts. Furthermore, the restraint stress-induced antinociception is inhibited by the application of benzodiazepine midazolam in a specific telencephalic region, the dorsomedial telencephalon, suggesting that this region is related to the nociceptive processing in fish and can be part of its endogenous antinociceptive system [21]. Thus, although it is not yet possible to state definitively that fish

are sensitive to pain, it is important that the possibility of suffering should be considered when defining management practices that are used in aquaculture, particularly when a procedure can result in potentially painful tissue damage.

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