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Technical Sheet

Reducing Aggression in Mice

In the laboratory, mice interact with each other and with humans. When a concern about "aggression" in mice is raised, defining what is meant by aggression will help to clarify the issue. Are the mice aggressive when handled, jumpy, difficult to catch or too active? Or are the mice fighting, wounding or killing each other? In the first case, the aggression is problematic behavior toward humans, and in the second, the problem behavior is directed at conspecifics. Both concerns may occur in the same mice, but one type of behavior will often predominate.

A likely cause for difficulty of handling by humans is fear. The behavior of an animal during interactions with humans is dependent on its confidence in humans, and that confidence has to be developed through positive experiences. To better manage an animal's fear, acclimate it to handling before beginning procedures. In other species, the best acclimation results are seen when animals are regularly handled when young.[1, 2] Although not always practical due to the large numbers in use, mice can be acclimated to handling as adults.[3] If acclimation to handling is not practical, it may help to handle the animal with a method that allows for movement between cages, without directly manipulating the animal in a way that it finds aversive. For example, animals were more amenable to cage change when they were transferred by hand or cup rather than by grasping the tail.[3] To reduce overall stress for mice between handling episodes, provide them with nesting or burrowing material.[4]

Aggression, or agonistic behavior, is defined as behavior directed toward another that elicits an aggressive or defensive response by the recipient.[5] Examples include threatening postures, chasing, pinning, mounting and biting.[6] Mouse aggression in the laboratory is primarily, though not exclusively, a male problem. Aggression in male mice is a reason why female mice are frequently preferred as test subjects. Female mice can be aggressive toward each other and their mates, but this is usually related to defense of the nest and of pups.[7]

In the wild, male mice maintain a dominance hierarchy and patrol territories that they have scent marked.[8] One adult male mouse is the primary breeder in the territory and the others disperse or are subordinate.[8] Normal dominance behavior between males in the wild is usually mitigated by escape or appeasement (i.e., submissive behavior from the recipient). Wild mice do fight and they are injured, but they are rarely killed by other mice, especially after dominance hierarchies are established. In cages, dominance-related behavior can escalate from dominance to injury or killing because there is no way to escape an aggressive mouse who does not respect the signaling of a subordinate mouse to stop. Escape does not necessarily mean traveling great distances; it can be as simple as moving out of the sightline of the dominant animal.

An additional complication is that the established hierarchies are not apparent to humans. If there are ten mice in a cage, there is a dominant mouse and nine subordinate mice of varying ranks. If the mice are arbitrarily divided into two groups of five by humans, the animals grouped together may be more prone to fighting. Dominance hierarchies among mice can be despotic, in which one animal dominates and the others are all equally submissive, or linear, in which there are animals varying in dominance from alpha to omega within one cage. If the dominant mouse is removed, the subordinate mice establish another dominant by fighting amongst themselves.[9]

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Some mouse strains are defined by their aggressive nature. Aggressive strains in common use include SJL,[10] BALB/c,[11] and FVB.[12] Other strains have been selectively bred to be more or less aggressive in order to study aggression in mice, such as the SAL (short attack latency) and LAL (long attack latency) strains. Although some consider C57BL/6 mice to be aggressive, in general they are not when compared to other mouse strains. However, they may appear to be more aggressive because they are the most commonly used mouse strain in research and thus there are many of them to observe.

Strategies for mitigating conspecific aggression in the laboratory environment must include an understanding of the underlying drive of the agonistic interactions and means of amelioration compatible with the aims of the laboratory environment. Male mice in the laboratory fight over territory, resources and dominance rank.

Territories

Laboratory mice do not have territories to defend in the same fashion as their wild counterparts. Decreasing cage space to allow no space to defend reduces aggression in some strains.[13,14] However, this effect was notably absent in FVB mice.[13] Additionally, increasing housing density may not be practical or recommended from a sanitation, welfare or regulatory standpoint. Group sizes of five or less have been shown to have fewer agonistic incidents than larger group sizes,[15] but the effect of increasing cage size on this group dynamic is unknown.

As stated previously, mice patrol territories that they have scent marked. At cage change, those scent marks are disturbed. As a consequence, post-cage change aggression is seen in mice. This aggression peaks at 15 minutes post-change[16] and lasts at least 45 minutes.[17] The greatest level of aggression has been found in cages that undergo incomplete cleaning, such as the renewal of substrate only. Eliminating olfactory familiarity, as is accomplished through a complete cage change and not transferring familiar scented objects, appears to mitigate this aggression.[16-18] The only apparent exception to this is that the transfer of nesting material has been shown to mitigate aggression.[18] Thus, complete cage change with transfer of nesting material may help diminish post-cage cleaning increases in aggression.

Resources

In a cage, structural enrichment becomes the predominant feature and the dominant animal may use it as a marking post or a resource to be dominated. Structures that create ambush points, such as tunnels with single point of access or elevated structures from which dominant animals can waylay subordinates entering or exiting can exacerbate aggressive interactions. Removing enrichment resources that cause competition can also decrease aggression.[19-21] The possible exception to this is nesting material, which has been shown to decrease aggression and may also provide more flexible escape routes, mitigating also aggressive interactions.[16, 22-25] While in general this is our best recommendation, there is at least one report[26] of nesting material *increasing* aggression and shelters *decreasing* it, thus showing that response to enrichment is specific to genetic background and any intervention should be evaluated on a strain-by-strain basis before widespread implementation.

Dominance

Fighting sorts out the social hierarchy in groups of mice; generally once the social hierarchy has been established, additional fighting should not be necessary.[15] Therefore, maintaining males' weanling groups and preserving those familiar social contacts should sustain these stable social groups and decrease fighting.[15] While removing the dominant mouse will sometimes be an easy fix, this may also increase fighting among the other animals as a new dominant emerges.

Aggression in most strains of mice is exacerbated by solo housing.[5] Even separation from a group for 24 hours may induce changes in behavior. Single housing is not ideal, as mice have shown a preference for social conspecifics even in the context of aggression,[24, 27] but it may be the final option and (anecdotally) sometimes the only way to manage some strains after weaning.

Summary

Strategies for mitigating conspecific aggression include maintaining stable social groups from a young age with no periods of individual housing, elimination of enrichment items that may be a protected resource and the cleaning of olfactory stimuli in the cage, with the exception of transferring nesting material from the prior cage to the new one at the time of cage change.

Strategies for mitigating fear-driven aggression resulting in jumpiness or difficulty in handling include acclimation of the animals to human handling and research procedures, as well as decreasing the stress associated with handling through the use of transfer items such as tubes or cups rather than handling by the tail or scruff.

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