AN INTERNATIONAL ORGANIZATION DEDICATED TO PROTECTING THE RIGHTS OF ALL ANIMALS

PETA

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Richard J. Hodes, M.D.
Director
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Via e-mail: hodesr@31.nia.nih.gov

Dear Dr. Hodes,

On behalf of People for the Ethical Treatment of Animals (PETA) and our more than 6.5 million members and supporters worldwide, I am writing to share several ethical and scientific concerns regarding the National Institute on Aging's (NIA) new initiative to increase its use of marmoset monkeys to study Alzheimer's disease (AD)—and to ask that you reconsider this strategy.

As you know, the failure rate for new AD treatments developed from preclinical animal experimentation is exorbitantly high.[1,2] Previous NIA endeavors to "improve" animal "models" of AD, including the development of multiple transgenic animals, have also failed to replicate the human disease faithfully and to translate into human treatments.[3,4] The most important information gleaned from decades of expensive and harmful studies is that using animals to study AD cannot predict human efficacy or toxicity, and treatments developed using animals will consistently fail to translate into treatments for humans with AD. We urge NIA to initiate the transition from animal experimentation to human-based, human-relevant methods for Alzheimer's research, rather than spending millions of dollars subjecting tens of thousands of marmosets and other primates to harmful, wasteful experimentation.

AD Is Unique to Humans

AD is unique to humans, with variable and interacting cognitive and neurological symptoms,[5,6,7] variable age of onset and progression rate,[8,9,10,11] and numerous genetic,[12,13,14,15] environmental,[16,17,18,19] and epigenetic[20,21,22] contributors. The heterogeneous etiology and symptomatology of AD in humans is impossible to recapitulate or measure adequately in a laboratory setting. Experiments designed to study AD in animals, including those using primates and/or transgenic animals, artificially simulate only one or two symptoms, failing to induce or measure critical components of the disease, including the neuronal loss, neurofibrillary tangles, tauopathy, rapid cognitive decline, and dementia observed in human patients.[23,24,25,26,27]

Simulating Alzheimer's-Like Symptoms in Primates Involves Invasive and Harmful Procedures

To simulate individual Alzheimer's-like symptoms in primates, experimenters induce long-term neuropathology using invasive methods, including intracranial injection of amyloid-beta fibrils,[28,29,30] deliberate exposure to toxins,[31,32] and lesion-induced neural degeneration.[33] The proposed NIA initiative to induce AD

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symptoms in marmosets will not only increase the number of primates subjected to these invasive and harmful procedures but also prompt additional ethically questionable experimentation on primates, including unestablished and often deadly gene-editing procedures.[34]

Marmosets Are Particularly Sensitive and Vulnerable

Primates, including marmosets, are highly intelligent, complex, social animals. Those held captive in laboratories and subjected to experimental procedures exhibit signs of extreme distress, including pacing, rocking, head-twisting, and eating their own feces. Highly traumatized primates will bite their own flesh, pull out their own hair, and engage in other forms of severe self-mutilation.[35,36,37,38] Current standards for social housing and enrichment do not meet marmosets' need to problem-solve, forage, climb, and engage in complex social interactions, including caring for their offspring.[39] The lack of mental and social stimulation, as well as exposure to common laboratory procedures, leads to chronic stress that affects primates not only psychologically but also physiologically. It is well documented that primates in laboratories display aberrant immune system functioning, including increased stress-related hormones, dysregulation of the hypothalamic-pituitary-adrenal axis, and depressed immune system functioning.[40] Additionally, marmosets are prone to bone disease[41] as well as a condition known as "marmoset wasting disease," a systemic inflammatory disorder that leads to weight loss, diarrhea, alopecia, weakness, intestinal inflammation, paralysis, and death.[42]

In a recent National Academies of Sciences, Engineering, and Medicine workshop dedicated to discussing the care, use, and welfare of marmosets in biomedical experiments, experts drew the following conclusion:

> [Marmosets] have unique requirements in terms of housing, feeding, social interactions, and other facets, many of which remain poorly understood. There is no standardized diet for captive marmosets, and there are very few people who have expertise in working with them. Marmosets in captivity are susceptible to a range of diseases and are particularly prone to Marmoset Wasting Syndrome, which is not one disease but a perplexing composite of multiple conditions and etiologies that could be due to poor nutrition, stress, infection, or a combination of these factors. Their breeding and parenting behavior is also poorly understood, and although marmosets are easier to handle than tamarins (as they tend to be less easily stressed and are more easily habituated to handling), their multiple births can lead to poor parenting performance.[43]

The current lack of knowledge regarding the provision of standard care for marmosets is concerning, particularly given that the proposed NIA initiative will not only increase the number of marmosets in unprepared laboratories but also introduce unprecedented gene-editing procedures for these already at-risk primates.

Compromised Data

The negative effects of laboratory life on marmosets' mental and physical health are not just ethically unacceptable; they also introduce several confounds into experimental data. The altered immune system functioning in primates in laboratories and the additional systemic inflammation found in captive marmosets are particularly concerning, given the role of immune system modulation in AD neuropathology.[44,45,46] Coupled with the fundamental species differences in

gene expression and protein function,[47] immune system functioning,[48] neurodevelopment,[49,50] neuroanatomy,[51,52] age-related changes in hormone production,[53] and age-related neurodegeneration,[54,55] the proposed experiments in marmosets cannot fully or accurately represent human AD, and treatments derived from these experiments will fail to be effective in human patients.

Conclusion

For ethical and scientific reasons, emerging research methods designed to prevent and treat AD should undergo a transition away from animal experiments and toward the use of modern research tools. *In vivo* imaging in humans with AD or at risk for developing the condition and postmortem analysis of brain tissues from patients with AD are helping researchers understand the genetic, environmental, and neurobiological underpinnings of the disease.[56,57,58,59] Cutting-edge technology, including AD-derived induced pluripotent stem cell models,[60] 3-dimensional cell-culture models,[61,62] systems-level biological computational modeling,[63,64] and quantitative systems pharmacological modeling,[65,66] are being used not only as more accurate and detailed models of AD but also, currently, to test drug efficacy and safety.

It is critical that the NIA support research that promises the greatest possible benefit to humans with the least possible harm to animals. We urge NIA to reconsider investing valuable financial and scientific resources into harmful experiments with marmosets and instead to direct these resources toward clinically relevant, human-based research strategies.

Thank you for your consideration of our concerns. May we please meet with you to discuss them further?

Sincerely,

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