Intracranial injections and animal models: towards understanding and treating human disease

The use of laboratory animals helped us to better understand a myriad of biological processes in health and disease and enabled the development of therapies that effectively cure, or ameliorate life conditions of, millions of people every day. Laboratory animals are currently used in biomedical research to model pathological processes, symptoms, and progression of diseases that afflict humankind, and to test drugs and other therapeutic strategies with the hope of resolving illnesses or slowing down the advancement of clinical conditions.

Animal models of human disease can be created via genetic manipulations, when mutations that cause the conditions in humans are introduced in the animals and lead to comparable illnesses. They can also originate from injection of toxic compounds that damage tissues or specific populations of cells, as is the case with experimental models of neurodegenerative diseases, such as Parkinson’s disease and Huntington’s disease.

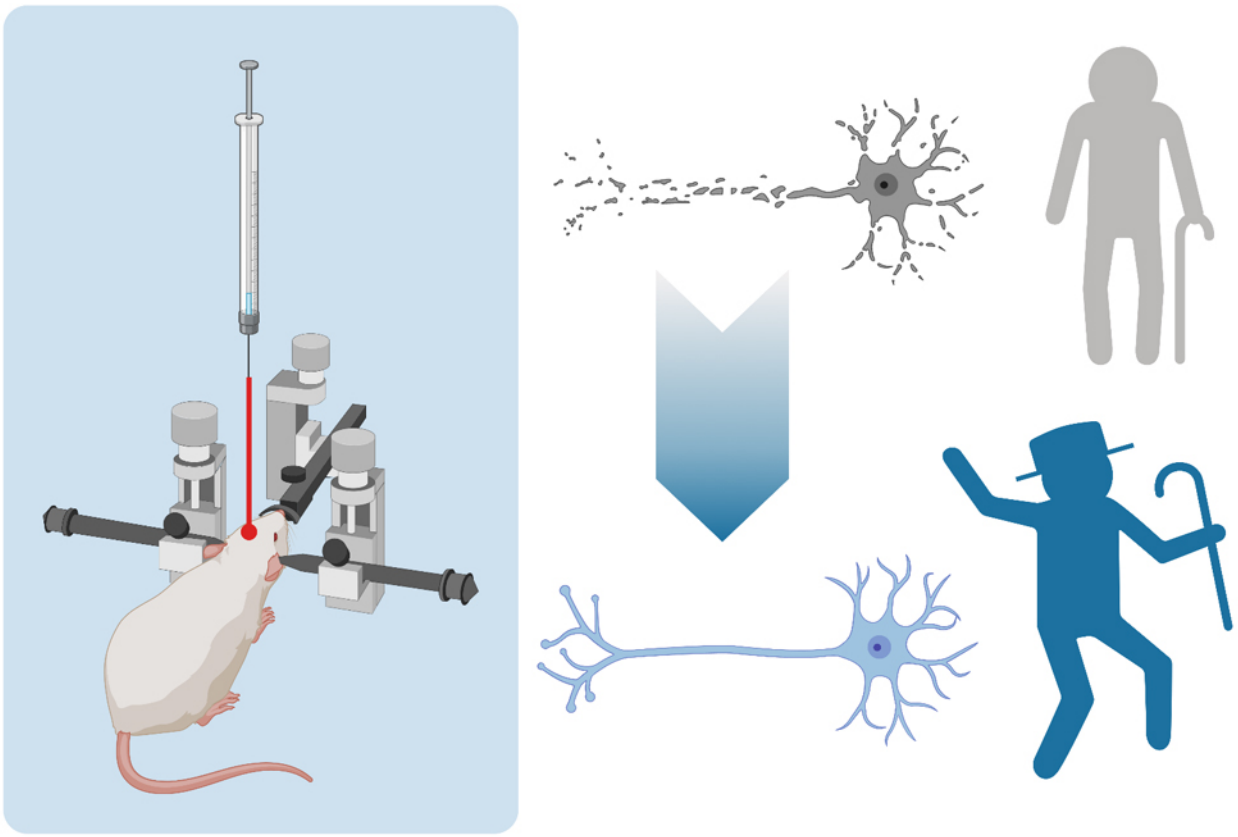

Fig. 1. Intracranial injection to the mouse brain is performed using a stereotactic frame to deliver substances correctly and reproducibly. The ultimate aim of experiments involving the delivery of compounds to the animal's brain is to better understand the pathological processes and resolve the

neurological condition.
The figure was created with BioRender.com.

With the establishment of a working disease model that ideally mirrors pathophysiology and clinical manifestations of the human counterpart, the researcher is now able to test whether a therapeutic agent can reverse the damage and provide relief from the symptoms. Administration of compounds can occur at the systemic level, when the drug is injected intravenously or administered orally. It can also be dispensed directly into the affected tissue, whenever the damage is localized to a restricted region. In the case of neurological conditions, delivery of therapies to the nervous system is complicated by the presence of a barrier between blood and brain that strictly regulates what substances are admitted into the brain tissue. Thus, when drugs are unable to cross this barrier, their administration needs to occur through a surgical intervention that allows careful placement of a needle through the skull and into the brain tissue.

This article is addressed to researchers who are certified for working with laboratory animals and have experience with basic handling. It provides them with detailed protocols on how to perform intracranial deliveries of compounds to the rodent brain. Two procedures are covered: one that can be used whenever a single injection is sufficient, and another one when sustained administration over time is better indicated.

The procedures highlighted here are versatile, they can be flexibly adapted to different research questions and employed to either produce animal models of disease or to deliver compounds to test their therapeutic prospective.

Both procedures are well tolerated, although the use of a sustained delivery system will cause slightly more damage to the area that is being infused, because of the larger size of the needle utilized. Nevertheless, the infusion system is recommended over repeated injections, whenever administration of multiple doses is necessary, because it will prevent the strain that comes with putting the animal through recurring operations.

The protocol describes how to reliably target the region of interest with the use of stereotactic coordinates deduced from a brain atlas and the adoption of a stereotactic frame, which is used to hold stable and maneuver the injection needle. These provisions will ensure correct targeting of the area and reproducibility of the surgery.

The article also includes general instructions for the use of analgesia and anesthesia but warrants to tailor pre- and post-operative care to the specific disease model utilized. It is also recommended to communicate with the local veterinary unit to ensure that best practices are followed, and the animals are not subjected to unnecessary discomfort and suffering.

Overall, the article aims to deliver exhaustive instructions to implement a well-tolerated and reproducible procedure for manipulating brain activity and discovering new therapies to treat a wide range of neurological disorders.

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