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## METHODOLOGY

A pilot study have been conducted to test the effect of intranasal C3a administration on stroke recovery. Animals used included C3aR knockout mice (C3aR<sup>-/-</sup>), transgenic GFAP-C3a mice and wild-type (C3aR<sup>+/+</sup>) mice. Ischemia was induced using Photothrombotic stroke induction.

After 7 days till day 21 (short term study) or 28 (long term study), purified human C3a peptide at a concentration of 200nM was intranasally administered to awake, hand-restrained mice 20ml per dose, control mice received PBS, and the administration was randomized and blinded, with body temperature monitored for potential systemic responses. The evaluation of functional impairment in mice, subjected to intranasal C3a or PBS treatment, involved a modified cylinder test and a grid walking task to closely examine forepaw function. Treatment was initiated 7 days after stroke induction, and behavioral performance was monitored until Day 56 post-stroke.

## WHY C3A?

The C3a peptide has been demonstrated to enhance the formation of new connections among nerve cells in mouse brains, resulting in increased mobility compared to control groups. Another notable advantage is its potential to benefit most stroke patients, including those who fail to reach a hospital promptly or are unresponsive to clot-dissolving drugs (thrombolysis) or mechanical clot removal (thrombectomy) for various reasons.

## RESULTS

The activation of C3aR signalling positively influenced synapse numbers in the contralesional hemisphere, playing a crucial role in the post-stroke increase of presynaptic glutamatergic terminals, and possibly synapses, and this response is cortical region- and layer-specific. Signalling through C3aR positively regulated the expression of GAP43, a marker of axonal, presynaptic, and glial plasticity after focal ischaemic brain injury in both hemispheres.

Intranasal C3a stimulated neural plasticity in the peri-infarct cortex. C3a-treated mice, starting 7 days after stroke, exhibited enhanced neural plasticity with increased synapsin I and VGLUT1 expression, larger and denser synapsin I<sup>+</sup> puncta, and a 50% rise in GAP43<sup>+</sup> puncta density in the ipsilesional motor cortex, contributing to improved functional recovery.

Intranasal C3a led to a faster and sustained functional recovery. In the grid walking task and cylinder task, both groups showed recovery, but C3a-treated mice exhibited significantly fewer right foot faults at Days 14 and 56 post-stroke, indicating a quicker and more sustained functional improvement. C3a treated animals readily increased their affected paw usage between the treatment initiation and 4 weeks after the completion of the treatment.

## INTRODUCTION

The devastating impact of stroke, a sudden brain attack impacting millions, leaves a trail of disability and lost potential. While current interventions aim to salvage function, true tissue repair remains elusive. C3a, a molecule previously associated with inflammation, now revealed to orchestrate an unexpected ballet of brain repair after stroke. This research explores the mechanisms of C3a's action, its promising preclinical data from intranasal delivery, and charts the path towards potential clinical translation. Can C3a, once demonized, transcend its inflammatory past and become the hero of stroke recovery? Join us as we explore this scientific saga, where a glimmer of hope flickers on the horizon for stroke's countless victims.

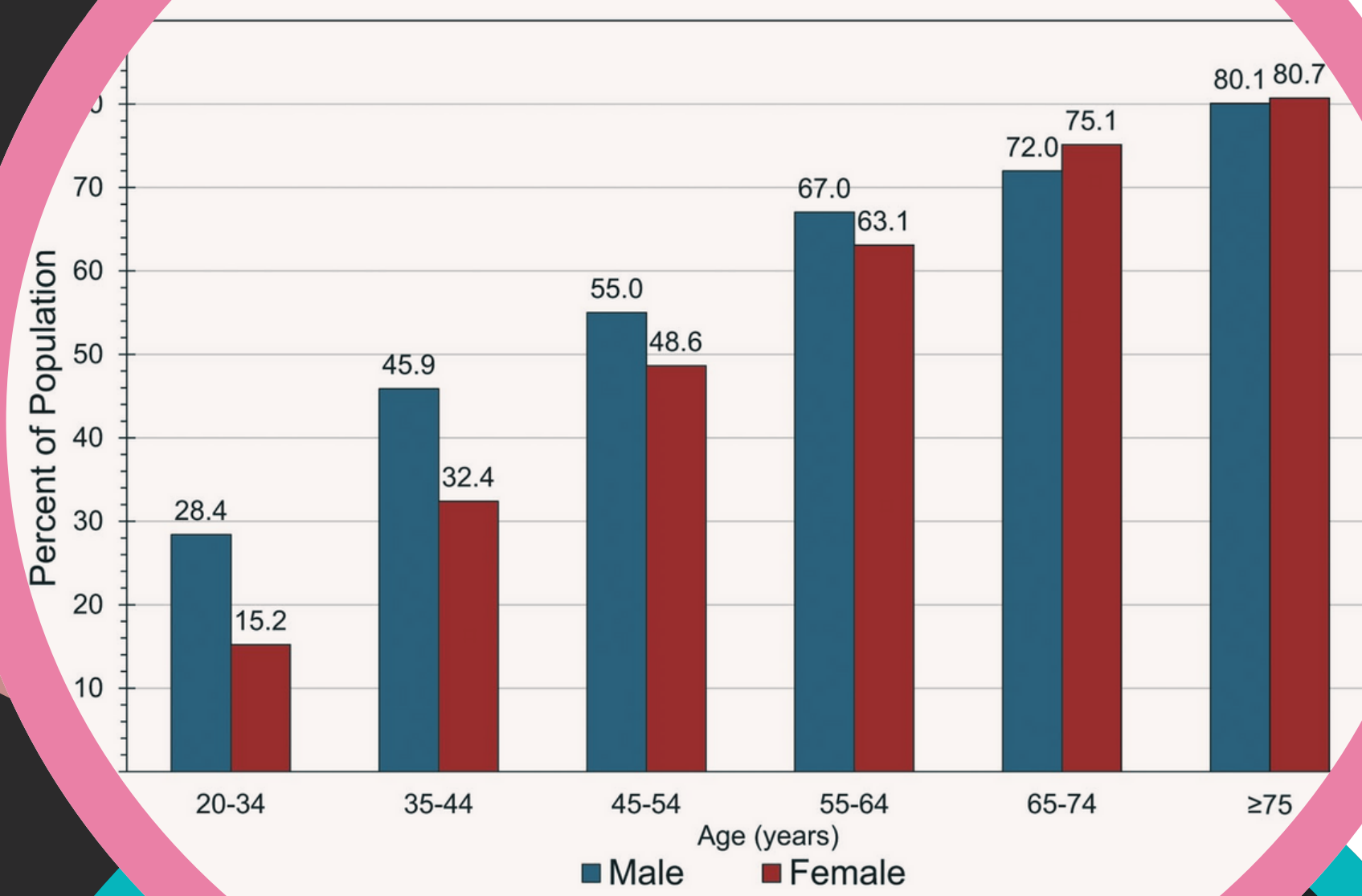
## PREVALENCE

Stroke is the second leading cause of death worldwide. According to the World Health Organization, an estimated 5.5 million people died from stroke in 2021.

Nearly 15 million people experience a stroke each year: This translates to roughly one stroke every four seconds globally.

Prevalence is increasing: Due to aging populations and lifestyle factors, the number of people living with stroke is expected to reach 131 million by 2047.

Stroke is a leading cause of disability: Around 50% of stroke survivors suffer some degree of long-term disability.



## LIMITATIONS

One key concern lies in the potential over-activation of the immune system, particularly in individuals with pre-existing inflammatory conditions, as its powerful systemic effects can spark unwanted inflammatory fires in other tissues.

Further research is crucial to fine-tune C3a dosage and delivery timing to ensure optimal benefit while minimizing risks.

## NANOTECHNOLOGY

Nanotechnology! Encasing C3a in tiny polymer or micelle carriers targets its delivery, maximizing healing while minimizing unwanted inflammation. It's like a brain-seeking missile, delivering precise relief! This nanotech twist unlocks C3a's potential for safer, more effective stroke therapy.)

## References:

1. Pekna, M., & Nilsson, O. (2019). Complement C3a treatment accelerates recovery after stroke via modulation of astrocyte reactivity and cortical connectivity. *Journal of Clinical Investigation*, 129(10), 2091-2103
2. Nilsson, O., & Pekna, M. (2022). Targeting Complement C3a Receptor to Improve Outcome After Ischemic Brain Injury. *Frontiers in Pharmacology*, 13(838809).
3. University of Gothenburg. (2019, January 30). Groundbreaking findings bring hope for faster and better recovery after stroke.