**Conclusions**

Neuroinflammation has been linked to neurodegenerative conditions as well as in brain injury. Clinical evidence has highlighted that brain and CSF levels of specific SPMs are reduced in patients with Alzheimer's disease. Furthermore, emerging preclinical animal and cell culture studies have shown that specific SPMs can impact neurodegenerative conditions such as Alzheimer's and Parkinson's disease, as well as in cognitive and neurological response to surgery and injury.


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Metagenics Institute

# SPM Emerging Area

## Inflammation resolution and neurological conditions

### Research Highlights

- Neuroinflammation is a driving factor in neurodegeneration and the adverse response to brain injury.[1-5]
- Specialized pro-resolving mediators (SPMs) are a group of lipid mediators derived from polyunsaturated fatty acids that actively coordinate the resolution of inflammation.[6]
- Individuals with Alzheimer's disease have been shown to have reduced levels of SPMs in brain tissue. Within this patient group, higher levels of specific SPMs in cerebrospinal fluid (CSF) have been linked with better cognitive function scores.[7-9]
- Emerging preclinical research in animal and cell models has demonstrated that specific SPMs:
  - o Increased clearance of amyloid beta (Aβ) and improved pathology in models of Alzheimer's disease.[9-11]
  - o Reduced behavioral defects and neuroinflammation in models of Parkinson's disease.[12]
  - o Provided protection against blood-brain barrier (BBB) opening and memory and cognitive dysfunction postsurgery.[13,14]
  - o Reduced infarct size and improved neurological function postischemic stroke.[15-19]
  - o Reduced edema and improved neurological function posthemorrhagic stroke.[20,21]
  - o Reduced inflammation and recovery in models of brain and spinal cord injury.[22-24]

### Rationale for targeting inflammation for management of neurological conditions

**Raised inflammatory markers predict future cognitive decline**

- Inflammation is considered a catalyst for cognitive decline. Raised circulating inflammation markers have been shown to predict cognitive decline that presents decades later.[25]
- The brain receives signals from the periphery about inflammation and infection. Mediators of systemic inflammation can gain access to the brain via blood flow. These inflammatory mediators can impact the phenotype of microglia, the resident immune cells in the brain.[26]

**Unresolved neuroinflammation is one driver of neurological dysfunction**

- Microglia can become activated and secrete proinflammatory signals such as cytokines, chemokines, and reactive oxygen species.[1,4,27]
- These proinflammatory factors drive neurodegeneration through various mechanisms such as promoting mitochondrial dysfunction, activating programmed cell death pathways, and demyelination.[1]
- Examples of neuroinflammation promoting disease pathology or reducing neurological function include:
  - o Alzheimer's disease
    Aβ is inefficiently cleared by microglia, resulting in increased Aβ aggregation into plaques and activation of microglia. This microglial activation results in the further production of proinflammatory cytokines, which further impair neuronal function.[2]

    Hyperphosphorylation of tau, a cellular structural protein, has also been linked to microglial activation.[2,3]
  - o Parkinson's disease
    Aggregated alpha-synuclein, a protein that misfolds in Parkinson's disease leading to accumulation of large masses, can induce proinflammatory responses from microglia, resulting in increased neuronal cell death.[2]
  - o Brain injury
    Regions remote from the primary injury site have also been shown to suffer from inflammation-induced damage, and growing evidence suggests that an inflammatory microenvironment contributes to the progression of the injury.[4]
  - o Brain hemorrhage
    Neuroinflammation has been implicated as a key mediator of injury propagation and behavioral deficits following aneurysmal subarachnoid hemorrhage.[5]

**What are SPMs?**

- Specialized pro-resolving mediators (SPMs) are a group of lipid mediators that function as "resolution agonists," actively coordinate the resolution of inflammation, and promote healing and return to homestasis.[6]
- Several groups of SPMs have been identified including resolvins (Rvs), lipoxins (LXs), maresins (MaRs), protectins (PDs), and neuroprotectins (NPDs), which work together to bring about the resolution of the inflammatory cascade and return the tissue to homeostasis.[6]
- *In vitro* RvD1 and RvE1 have been shown to reduce inflammatory cytokine release from activated microglial cells,[28] highlighting their potential for neuroinflammation management.
- Given the link between neurological conditions and neuroinflammation, assessing the impact of SPMs and proresolving therapies is a promising area of research.

**In people with Alzheimer's disease, SPM levels are reduced and linked to cognitive function**

- In one study, levels of the SPMs LXA4 and RvD1 were significantly lower in hippocampal tissue of the patients with Alzheimer's disease compared with tissue collected from individuals without dementia (Figure 1A).[7]
- In tissue from the hippocampus and temporal lobe collected postmortem, levels of the SPM NPD1 were significantly lower in patients with Alzheimer's disease, compared with tissue collected from age-matched individuals without dementia (Figure 1B).[8]
- In the entorhinal cortex (an area affected early in disease progression) of patients with Alzheimer's disease, levels of SPMs (MaR1, PD1 and RvD5) were lower compared with age-matched individuals without dementia. Levels of the proinflammatory mediator prostaglandin (PG) D2 were higher in the group with Alzheimer's disease (Figure 1C).[9]
- In groups of patients with Alzheimer's disease and mild cognitive impairment and a group without objective impairment, higher concentrations of the SPM LXA4 in CSF were associated with higher cognitive function scores assessed by the Mini-Mental State Examination (MMSE).[7]

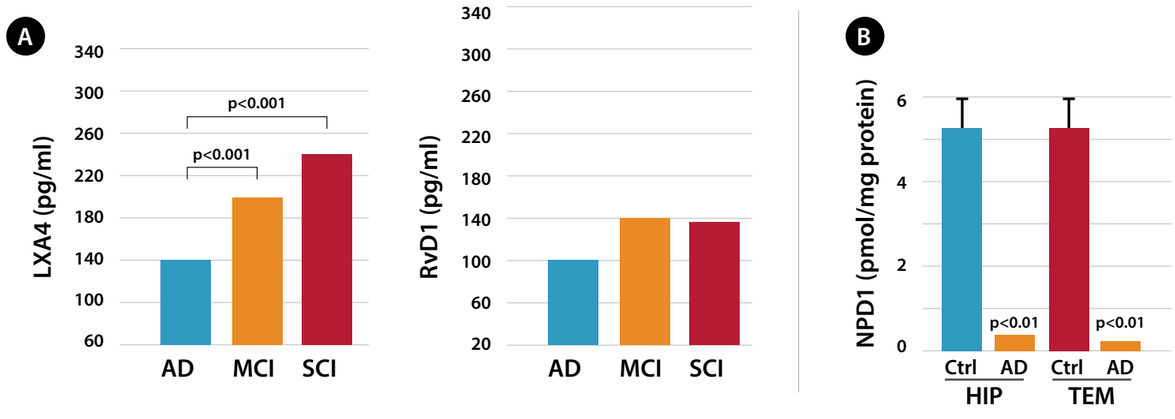
**Figure 1: Levels of SPMs are reduced in postmortem brain tissue of patients with Alzheimer's disease**

**A.** The SPMs LXA4 and RvD1 are reduced in patients with Alzheimer's disease in hippocamal tissue. Figures adapted from Wang X et al. 2015.[7]

**B.** The SPM NPD1 is reduced in hippocampus and temporal lobe of patients with Alzheimer's disease compared with age-matched controls. Figure adapted from Lukiw WJ et al. 2005.[8]

**C.** The SPMs RvD5, MaR1 and PD1 are reduced in entorhinal region in patients with Alzheimer's disease. Figures adapted from Zhu M et al. 2016.[9]

**AD:** Alzheimer's disease; **Ctrl:** control; **HIP:** hippocampus; **MCI:** mild cognitive impairment; **SCI:** subjective cognitive impairment; **TEM:** temporal lobe.




**Impact of SPMs in preclinical animal models of neurodegenerative conditions**

The preclinical evidence base supporting the impact of SPMs in a broad range of neurological condition is growing. Table 1 summarizes the data on SPMs in neurodegenerative diseases, as well as in several injury models.

**Table 1: Summary of SPM impact in preclinical animal and cell models of neurological conditions**

| Preclinical Model | SPM Investigated | Impact |
|---|---|---|
| Alzheimer's disease mouse models | RvE1,[10] LXA4[10] | • Reduced neuroinflammation |
| | MaR1,[9] RvD1,[9] LXA4[11] | • Reduced Aβ-induced inflammation in microglia, cortex, and hippocampus of mice |
| | RvE1[10], LXA4[10] | • Reduced Aβ pathology |
| | MaR[19] | • Stimulated uptake of Aβ by microglia |
| Parkinson's disease (inflammation-induced) rat model | RvD2[12] | • Prevented behavioral deficits and neuroinflammation |
| Postoperative cognitive decline (orthopedic surgery mouse models) | MaR1[13] | • Prevented BBB opening following surgery |
| | MaR1,[13] RvD1[14] | • Protected against postsurgery memory and cognitive impairment |
| Ischemic stroke (rodent models of brain ischemia reperfusion injury) | LXA4,[15,19] MaR1[16,17] | • Reduced infarct size |
| | LXA4,[15,18] MaR1[16,17] | • Reduced inflammatory marker expression |
| | LXA4,[15,18] MaR1[16,17] | • Improved neurological function |
| | RvD2[29] | • Reduced neuronal and endothelial cell death |
| | LXA4[18] | • Reduced hippocampal damage |
| Hemorrhagic stroke (rodent model of subarachnoid hemorrhage) | LXA4[20] | • Reduced brain water content (edema) 24 hours after the event<br>• Improved scores on tests of neurological function 21 days after the event |
| | LXA4[20] | • Improved neurological function postevent |
| | LXA4[21] | • Prevented endothelial dysfunction |
| Brain injury (mouse models) | LXA4[22] | • Reduced BBB permeability post-TBI<br>• Attenuated brain edema post-TBI<br>• Reduced TBI-induced lesion volume |
| | RvD1[24] | • Promoted functional recovery after focal brain injury<br>• Reduced neuronal cell death in remote brain regions |
| Spinal cord injury (mouse model) | MaR1[23] | • Accelerated inflammation resolution<br>• Improved locomotor recovery<br>• Reduced secondary injury progression |

RvE1, resolvin E1; RvD1, resolvin D1; RvD2, resolvin D2; MaR1, maresin 1; LXA4, lipoxin A4; Aβ, amyloid beta; TBI, traumatic brain injury; BBB, blood-brain barrier