

Oral presentation

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## Cerebrospinal fluid transport across the cribriform plate into extracranial lymphatics in rats: development and quantification

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### Background

The notion that cerebrospinal fluid (CSF) absorption occurs mainly through the arachnoid granulations and villi is being challenged by studies that support a major role for the lymphatic circulation in CSF transport. An important pathway by which CSF is removed from the cranium is movement through the cribriform plate in association with the olfactory nerves. CSF is then absorbed directly into lymphatics located in the submucosa of the olfactory epithelium. In this report, (A) we determined the time during development at which the CSF compartment and extracranial lymphatic vessels connect anatomically in neonatal rats and (B) we investigated an indirect method to quantify this transport in adult rats.

### Materials and methods

In a total of 115 Fisher 344 rats, CSF-lymphatic connections were investigated using the silastic material Microfil or a soluble Evan's blue-protein complex injected into the subarachnoid space. We examined animals at E21 (birth at 21 days), and postnatal days P1-P9, P12, P13, P15, P22 and adults. To quantify this transport in adult animals,  $^{125}\text{I}$ -human serum albumin (HSA) was injected into the lateral ventricles of ~200 gm animals using a stereotactic device. After 10 (n = 7), 20 (n = 7), 40 (n = 4) and 60 minutes (n = 8), the animals were sacrificed. Angled coronal tissue sections were cut from the head region anterior to

the cribriform plate to sample the olfactory turbinates and various other tissues were excised.

### Results

Associations between the CSF compartment and extracranial lymphatic vessels were not obvious until about a week after birth, a period during which CSF secretion is markedly up-regulated in this species. After injection of tracer into the subarachnoid compartment, the highest concentrations of  $^{125}\text{I}$ -HSA were observed in the middle olfactory turbinates with peak concentrations achieved 20 minutes after injection. At this point, the recoveries of injected  $^{125}\text{I}$ -HSA (percent injected/gm tissue) were (mean  $\pm$  SE) 29.1  $\pm$  7.2% middle turbinates, 3.8  $\pm$  1.2% blood, 0.1  $\pm$  0.04% skeletal muscle, 0.6  $\pm$  0.2% spleen, 1.4  $\pm$  0.5% liver, 1.0  $\pm$  0.3% kidney and 0.2  $\pm$  0.1% tail.

### Conclusion

These data suggest that the ability of extracranial lymphatic vessels to absorb CSF develops around the time that significant volumes of CSF are being produced by the choroid plexus. The rapid movement of the CSF tracer into the olfactory turbinates supports further a role for lymphatics in CSF absorption and provides the basis of a method to investigate the potential for impaired absorption in various CSF disorders.