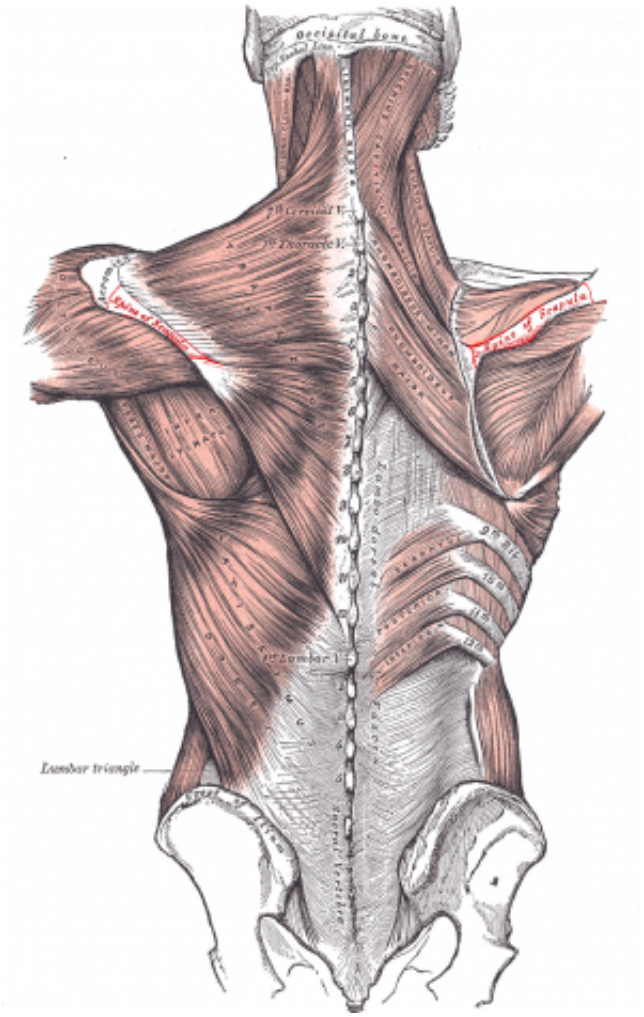
A strong saline solution can boost the delivery of morphine and other drugs to the spinal cord

May 3 2022



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The glymphatic system enables the flow of cerebrospinal fluid to the brain tissue, particularly during sleep, enabling the fluid to cleanse the tissue and carry accumulated metabolites with it towards the bloodstream during waking hours. Previously, it has been observed that the function of the glymphatic system can be modulated with drugs. This makes it an interesting target for drug development, especially regarding Alzheimer's disease and other degenerative brain diseases associated with the accumulation of metabolic products in the brain.

In addition to its general role in the clearance of the central nervous system, the glymphatic system may also be relevant to the entry into the brain of drugs that affect the central nervous system. The blood-brain barrier protects the brain from exogenous compounds, which is why many orally administered drugs do not reach the brain. Instead, special routes of administration are needed, such as direct administration to the cerebrospinal fluid.

Previously, drugs administered to the cerebrospinal fluid have been thought to be distributed to the brain and the spinal cord primarily by slow diffusion. However, the glymphatic model challenges this assumption. It has already been observed in laboratory animal models that certain drugs that activate the glymphatic system, such as the intensive care sedative dexmedetomidine, can boost the brain access of drugs administered to cerebrospinal fluid.

Surprisingly, a strong saline solution and other hypertonic solutions administered to the bloodstream accelerate the glymphatic influx of cerebrospinal fluid at the brain level. Hypertonic solutions, such as strong saline solutions and the sugar alcohol mannitol, among others, are used to reduce intracranial pressure in intensive care patients.

In the recently completed study, researchers from the University of Helsinki investigated how the glymphatic system and hypertonic

solutions could be put to use when administering pharmaceutical agents directly to cerebrospinal fluid in the lower back, with the spinal cord as the target for the drug. The study was published in the *Journal of Controlled Release*.

Morphine concentration in the spinal cord quadrupled and pain relief intensified

As a model drug, the researchers used the opioid morphine, which is used, for example, to treat postoperative pain and severe cancer pain. The spinal cord is among the most important sites of action for morphine, which provides effective pain relief when administered locally to cerebrospinal fluid.

The researchers simulated a typical patient-care situation in a rat model, administering morphine directly to cerebrospinal fluid in the lumbar area, after which the rats received a hypertonic saline solution. The study revealed that the combination of two different techniques multiplied the morphine concentration in the spinal cord.

"Opioids are administered directly to lumbar cerebrospinal fluid, primarily in the case of non-urgent surgeries and the treatment of cancer pain, whereas hypertonic solutions are used in emergencies where vital functions are threatened. In fact, it's interesting to see that by combining the two methods used in fairly different patient groups you can almost quadruple the morphine concentration in the spinal cord and enhance pain relief," says Doctoral Researcher Kim Blomqvist from the University of Helsinki.

It is likely that the method can be studied fairly quickly in humans as well, as both techniques are already in clinical use. According to the researchers, the combination of the two techniques should also be

investigated with other pharmaceutical agents administered directly to cerebrospinal fluid, of which many are in development.

More information: Kim J. Blomqvist et al, Systemic hypertonic saline enhances glymphatic spinal cord delivery of lumbar intrathecal morphine, *Journal of Controlled Release* (2022). DOI: 10.1016/j.jconrel.2022.03.022