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Opinion

Could dexmedetomidine be repurposed as a glymphatic enhancer?

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Cerebrospinal fluid (CSF) flows through the central nervous system (CNS) via the glymphatic pathway to clear the interstitium of metabolic waste. In preclinical studies, glymphatic fluid flow rate increases with low central noradrenergic tone and slow-wave activity during natural sleep and general anesthesia. By contrast, sleep deprivation reduces glymphatic clearance and leads to intracerebral accumulation of metabolic waste, suggesting an underlying mechanism linking sleep disturbances with neurodegenerative diseases. The selective α_2-adrenergic agonist dexmedetomidine is a sedative drug that induces slow waves in the electroencephalogram, suppresses central noradrenergic tone, and preserves glymphatic outflow. As recently developed dexmedetomidine formulations enable self-administration, we suggest that dexmedetomidine could serve as a sedative-hypnotic drug to enhance clearance of harmful waste from the brain of those vulnerable to neurodegeneration.

Highlights

The brain clears itself of harmful metabolic waste through the glymphatic system to several egress routes, including the meningeal lymphatic vessels, and onward to cervical lymph nodes.

In rodents, glymphatic flow declines in the awake state and increases with slow-wave activity in electroencephalography during non-rapid eye movement (NREM) sleep.

Declining glymphatic function could be an underlying link between chronic sleep disturbance and neurodegeneration.

Dexmedetomidine is a widely used and studied sedative agent that promotes NREM sleep in humans. Further, it has neuroprotective and anti-neuroinflammatory properties. In rodents, dexmedetomidine enhances the glymphatic clearance of intraparenchymal tracers from the rodent brain.

Due to its mechanisms of action, safety, and ease of use through several noninvasive administration routes, dexmedetomidine should be studied as a self-administered sedative-hypnotic drug in outpatient care. It may be the best available sedative glymphatic enhancer and may prove to attenuate neurodegeneration in long-term use.

Enhanced glymphatic function potentially alleviates neurodegeneration

Aging is associated with disturbances of sleep architecture, which can set the stage for a variety of neurodegenerative disorders [1]. Recent findings on the **glymphatic system** (see Glossary) suggest a causal relationship between chronically disturbed sleep and neurodegenerative diseases [2]. According to the glymphatic concept, **CSF** flows directionally along an anatomically defined pathway through the brain parenchyma to clear the brain of amyloid-β and other metabolic waste products that accumulate during wakefulness and contribute to neurodegenerative diseases (Figure 1).

CSF accesses deep structures in the rodent brain along the periarterial spaces **(periarterial CSF influx)** and moves through the brain parenchyma facilitated by arterial pulsation [3,4] and supported by the astroglial **aquaporin 4 (AQP4)** water channels [5]. In this scenario, metabolic waste within the interstitial fluid (ISF) is drained along perivenous spaces **(ISF efflux)** and finds egress from the CNS through several outflow routes, including **meningeal lymphatic vessels**, perineural sheaths, and nasal lymphatic vessels. Glymphatic CSF flow is suppressed by the awake state and activated by certain anesthetic agents and during intervals of slow-wave activity in electroencephalography (EEG) that are characteristic of the restorative **non-rapid eye movement (NREM)** sleep phase [6,7]. Preclinical studies indicate that reduced noradrenergic signaling associated with sleep and anesthesia enables enhanced fluid flow through the extracellular space [7,8]. Due to its reliance on the glial astrocytes and a clearance function resembling that of the lymphatics, the system was named the glymphatic (glial–lymphatic) system (Figure 1) [3].

Using contrast-enhanced magnetic resonance imaging (MRI), Eide and Ringstad demonstrated that MRI contrast agent injected into the human CSF space exhibited a similar dynamic

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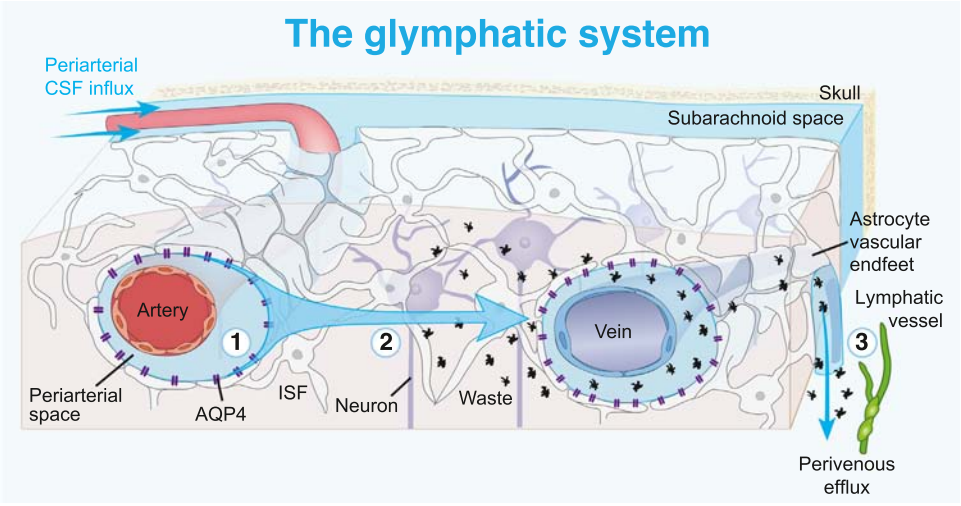

Figure 1. Overview of the glymphatic system. (1) Cerebrospinal fluid (CSF) enters the brain along perivascular spaces driven by arterial pulsations and enters the extracellular space supported by the aquaporin 4 (AQP4) water channels located in astrocytic endfeet. As the AQP4 are mainly permeable to water [71], larger molecules contained in the CSF are surmised to enter the brain parenchyma through gaps between astrocytic endfeet [3]. However, the mechanism facilitating the entry of CSF tracers into the brain are not fully understood [24]. (2) CSF mixes with the interstitial fluid and metabolic waste products, such as amyloid-β, in the brain parenchyma. This mixed fluid flows directionally and faster than expected based on simple diffusion processes toward perivenous spaces and white matter tracts (blue arrows) [3]. (3) Metabolic waste exits along perivenous spaces to be egressed from the central nervous system through several outflow routes. Deficiencies in glymphatic clearance of metabolic waste products are surmised to contribute to aging-related neurodegeneration and neurodegenerative diseases, while enhancing glymphatic clearance might prevent or delay the progression of neurodegeneration [2]. Abbreviation: ISF, interstitial fluid.

distribution of contrast enhancement as seen in rodents [9]. Fultz and colleagues found that slow-wave activity in EEG correlates with both cerebral blood flow and CSF flow in the fourth ventricle of healthy volunteers [10], whereas Helakari and colleagues showed a positive correlation between human slow-wave sleep and the brain pulsations that likely drive glymphatic CSF flow [11]. Further, cortical clearance of MRI contrast agent declined following acute and chronic sleep deprivation in humans [12,13]. Finally, a preprint at the time of writing suggests that pial arteries and astrocytes pulsate during NREM sleep, thus leading to a reduction in their diameter that potentially facilitates fluid flow through the periarterial space and brain parenchyma [14]. These findings imply that the pulsatile movement of CSF is linked to slow-wave sleep, whereas sleep disturbances result in inadequate CSF flow, which might ultimately contribute to neurodegeneration due to reduced clearance of metabolic waste such as amyloid-β and tau from the brain [2].

Anesthetic agents vary in terms of their effects on the movement of CSF tracers in the brain, probably due to their differing effects on EEG slow-wave delta power, noradrenergic signaling, and vasomotor effects [4,6,15,16]. Dexmedetomidine is an α_2-adrenergic agonist sedative that is widely used in perioperative and intensive care settings, and additionally displays neuroprotective and anti-inflammatory properties. In rodents, glymphatic influx of CSF tracer from the intrathecal space into the brain parenchyma increased under anesthetic regimens that reduced noradrenergic signaling and increased slow-wave delta power [6,7,15,17]. In particular, combining the α_2-adrenergic agonist dexmedetomidine with isoflurane significantly promoted glymphatic influx of CSF tracers while simultaneously increasing delta power in the EEG compared with isoflurane only [6,15]. Further, hippocampal clearance of an MRI tracer increased under isoflurane–dexmedetomidine anesthesia compared with isoflurane only [15]. Taken together, these findings suggest that α_2-

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adrenergic agonists such as dexmedetomidine could potentially serve as glymphatic enhancers to remove toxic products of metabolic activity, including amyloid-β [8,15,18].

Given that sleep disturbances are a considerable public health problem [19] and are strongly associated with preclinical and clinical stages of neurodegenerative disease [1], enhancing sleep with drugs that facilitate the removal of metabolic waste is an appealing therapeutic concept [20]. The recent finding that dexmedetomidine acts as a glymphatic enhancer suggests that dexmedetomidine could retard the progression of neurodegenerative disease in long-term use, particularly considering that dexmedetomidine has several other neuroprotective effects and furthermore manages the agitation and **delirium** frequently encountered in individuals suffering from neurodegenerative diseases [21,22]. In this opinion article, we put forward the suggestion that dexmedetomidine should be studied as a self-administered sedative-hypnotic drug for sleep problems to moderate the risk for neurodegenerative diseases, thus expanding its current uses. We shall first discuss the pharmacological characteristics of dexmedetomidine that make it a glymphatic enhancer. We then review the other neuroprotective and antidelirium effects of dexmedetomidine and discuss its novel extravascular routes of administration and safety aspects. Finally, we touch upon how dexmedetomidine could serve to enhance glymphatic CSF flow so as to attenuate the progression of neurodegenerative diseases.

We acknowledge that some molecular mechanisms of the glymphatic concept are still debated (see reviews by Mestre *et al.* [23] and Hladky and Barrand [24]) and that many questions thus remain open (discussed in Box 1). While these debates mostly relate to methodological disagreements, we argue that they are not highly relevant for the proposed novel repurposing of dexmedetomidine, which is an existing drug widely used already in clinical practice. The clinical literature has confirmed the key components of the glymphatic concept in humans and the many beneficial and neuroprotective effects of dexmedetomidine have similarly been demonstrated in various contexts and by various authors.

Box 1. Brief introduction to the controversies regarding the glymphatic system

The mechanisms facilitating transport of water and solutes from the CSF into the extracellular space, including transport facilitated by AQP4 water channels, and the molecular mechanisms governing extracellular fluid flow are currently incompletely understood and debated [70]. The AQP4 are selectively permeable to water and to gaseous ammonia [71], such that most compounds in the CSF must traverse to the extracellular space by alternative, possibly paracellular, routes [72]. AQP4 is abundant in the astrocytic endfeet, where its polarized expression changes in animal models of traumatic brain injury, aging, and Alzheimer's disease [3]. Furthermore, CNS edema can be prevented by targeting AQP4 translocation [73], although the effectiveness of currently proposed AQP4 inhibitors may be via AQP-independent mechanisms [70]. *In vitro*, deletion of AQP4 greatly reduced the osmotic permeability of astrocytes [74]. After one study questioned the importance of AQP4 for driving uptake of CSF tracers into the extracellular space [75], the significance of AQP4 for glymphatic transport in rodents was confirmed in a joint publication including data from five independent laboratories, and in another study tracking the movement of radiolabeled water injected into the rodent CSF space *in vivo* [5,76].

It is notoriously difficult to study fluid flow in the brain, particularly in the extracellular space. The observations of glymphatic transport suggest that one of the key functions of natural slow-wave sleep is to actively export metabolic waste products from brain faster than is possible by simple diffusion. Parenchymal transport at speeds exceeding diffusion have been reported in anesthetized rodents already before the glymphatic system was described. For example, Cserr and colleagues reported convective efflux of large molecules from the interstitial fluid, and Groothuis and colleagues demonstrated that anesthetic agents modulated the rate of metabolite efflux [3,24]. Lately, human brain studies have reported that intrathecally injected magnetic resonance imaging contrast agent moves faster than expected by simple diffusion [77,78].

Several studies conducted in rodents suggest that dexmedetomidine and also xylazine, an α_2-adrenergic agonist used in veterinary medicine, consistently promote the influx and efflux of tracers from the CNS *in vivo*, relative to isoflurane anesthesia or the awake state [6–8,15,17,79]. However, the molecular mechanisms underlying these observations remain largely unexplored. Dexmedetomidine reportedly reduces AQP4 expression and alleviates cerebral edema related to traumatic brain injury [80], but its effects on AQP4 have not, to our knowledge, been investigated in normal physiological conditions.

Glossary

Aquaporin 4 (AQP4): an aquaporin water channel isoform primarily expressed in the astrocytic perivascular endfeet that line the brain vasculature. As AQP4 channels facilitate the passage of water from perivascular spaces to the interstitial space, their normal expression and polarized localization are essential for optimal glymphatic function.

Arterial pulsatility index: a noninvasive method for assessing vascular resistance with the use of Doppler ultrasonography that is clinically used to assess vasomotor tone. Arterial pulsatility index is defined as the difference between the peak systolic flow and minimum diastolic flow velocity divided by the mean velocity recorded throughout the cardiac cycle.

Cerebrospinal fluid (CSF): a colorless fluid filling the ventricular system and the subarachnoid space surrounding the brain. CSF is produced mainly by the choroid plexus and has an ion concentration similar to that of blood plasma. CSF plays a role in providing buoyancy and mechanical protection to the central nervous system and acts as a sink for metabolic waste produced in the neuropil.

Delirium: a syndrome characterized by an acute disturbance in attention, awareness, and cognition caused by a medical condition that cannot be better explained by a pre-existing neurocognitive disorder.

GABAergic effects: effects following activation of γ-aminobutyric acid (GABA) receptors.

Glymphatic system: glymphatic (glial–lymphatic): astrocyte-mediated perivascular transport of CSF to clear metabolic waste from the interstitial space of the brain parenchyma primarily during non-rapid eye movement (NREM) sleep and other states of high slow-wave activity.

Interstitial fluid (ISF) efflux: outflow of ISF from the brain parenchyma toward CSF clearance sites. This directional clearance apparently occurs along perivenous spaces and white matter tracts and is mediated by a bulk flow mechanism that is highly dependent on arousal state, noradrenergic tone, and AQP4 expression.

Meningeal lymphatic vessels: lymphatic vessels within the dura mater tracking the venous sinuses and at the base of the skull. These vessels drain

Pharmacology of dexmedetomidine as a glymphatic enhancer

Dexmedetomidine (Figure 2, top left), the dextro-isomer of medetomidine, is a selective α_2-adrenergic agonist that is routinely used in procedural and intensive care sedation of adults [25]. The sedative and analgesic effects of dexmedetomidine are attributed to activation of presynaptic α_2-autoreceptors on noradrenaline fibers throughout the neuraxis [26]. The α_2-selectivity makes dexmedetomidine a superior sedative in comparison to less selective α_2-adrenergic agonists such as clonidine which are less sedating and display greater systemic hemodynamic effects [25].

In humans, dexmedetomidine induces natural sleep-like sedation from which the individual can be aroused [27]. In fact, dexmedetomidine sedation resembles the deep recovery sleep following sleep deprivation, with respect to increases in the duration of certain deep sleep stages, namely, NREM sleep stages 2 and 3 high on slow-wave activity in EEG (Table S1 in the supplemental information online) [25]. Indeed, several dexmedetomidine trials conducted in critically ill patients have demonstrated improvements in subjective and objectively measured quality and quantity of sleep [28]. Given that sleep disorders involving sleep fragmentation and sleep–wake cycle disruption are prominent features of many neurodegenerative diseases such as Alzheimer's disease [1], dexmedetomidine might be a beneficial sleep-restoring sedative drug for these patients.

Targeting sleep is particularly interesting in patients suffering from neurodegeneration, insofar as recent preclinical and human studies suggest a causal relationship between deteriorated sleep,

CSF solute to extracranial deep cervical lymph nodes.

Non-rapid eye movement (NREM) sleep: a restorative phase of sleep that is divided into three stages, N1, N2, and N3, with N3 being the deepest state of sleep associated with high slow-wave activity. NREM sleep episodes are followed by a rapid eye movement (REM) sleep phase that is associated with high brain activity.

Periarterial CSF influx: entry of CSF into the brain in perivascular spaces that surround cerebral arteries and arterioles. Arterial pulsation drives CSF bulk flow into the brain in parallel with blood flow. Mixing of CSF with ISF is dramatically enhanced by sleep and anesthetics that increase slow delta wave activity, for example, α_2-adrenoceptor agonists. This CSF–ISF exchange process has also been shown to be highly dependent on localized AQP4 expression at the astrocytic endfeet.

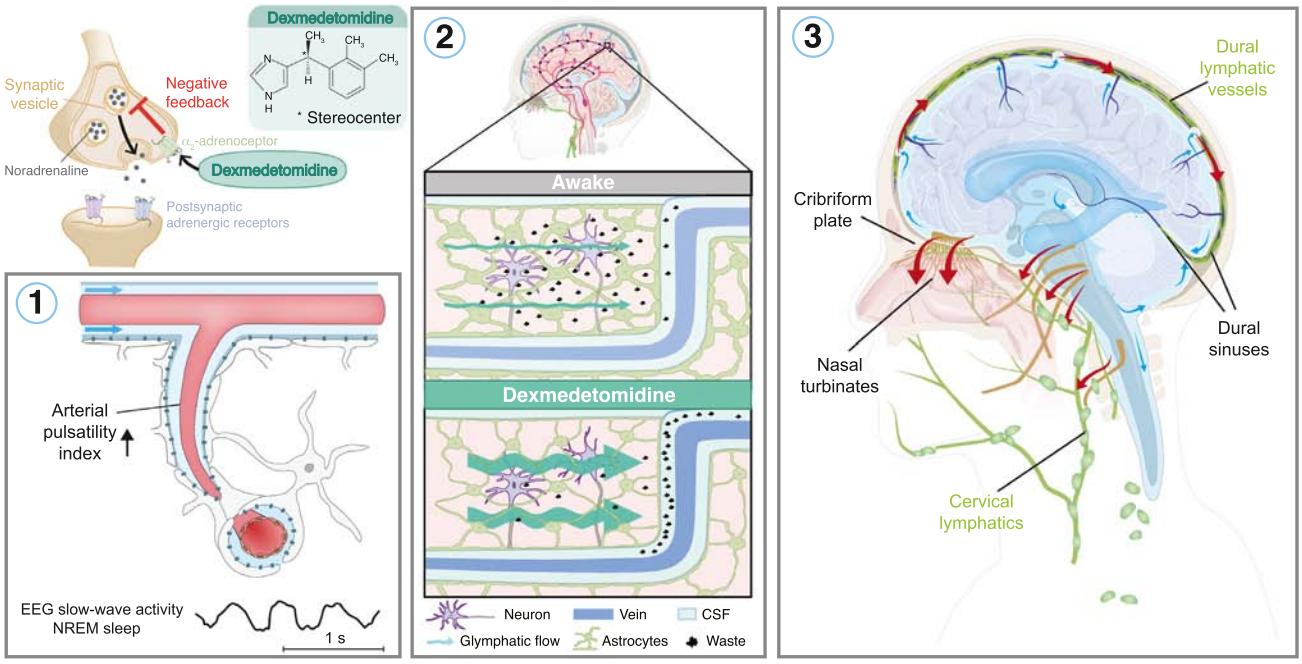

Figure 2. Proposed mechanisms for dexmedetomidine as a glymphatic enhancer. The sedative and analgesic effects of dexmedetomidine are mainly due to activation of presynaptic α_2-adrenergic receptors resulting in reduced noradrenergic tonus in brain (top left) [26]. The effects of dexmedetomidine on the key components of glymphatic flow and brain clearance (presented in Figure 1 are as follows: (1) an increase in arterial pulsatility index (Tables S1 and S2 in the supplemental information online) and an increase in periarterial cerebrospinal fluid influx due to oscillations in arterial and astrocytic volumes induced during slow-wave activity in the electroencephalogram during non-rapid eye movement (NREM) sleep [14]; (2) shrinkage in astrocytic size due to reduction in central noradrenergic signaling which leads to an increase in volume of the extracellular space enabling the flow of fluid and its solutes through the brain parenchyma (see [14] and Table 1); and (3) preservation of high activity of lymphatic outflow routes [3,44]. Abbreviations: CSF, cerebrospinal fluid; EEG, electroencephalography.

CSF flow, and neurodegeneration [2]. Dexmedetomidine possibly promotes the transport of fluid and molecules in the periarterial space through a direct effect on arteries and through vasomotor changes occurring during NREM sleep [14] (Figure 2 part 1 and Table 2S in the supplemental information online). In rodents, arterial pulsation seems to be the main driver of CSF tracer transport in periarterial spaces, as observed through an imaging window inserted in the skull [4]. In support of that finding, CSF flow was impeded by hypertension-induced arterial stiffening in spontaneously hypertensive rats and in mice with elevation of blood pressure upon systemic administration of angiotensin II [4,29]. Imaging the much larger human brain with high frequency magnetic resonance encephalography (MREG) showed that heart rate and respiration drive brain pulsations and probably also CSF movement [30,31].

Although the effects of dexmedetomidine on cerebral arteries are incompletely understood, multiple human studies have demonstrated that dexmedetomidine augments the **arterial pulsatility index** (Table 2S in the supplemental information online). Studies suggesting that dexmedetomidine indeed induces cerebral vasoconstriction [32,33] have raised the concern that dexmedetomidine might induce cerebral ischemia or aggravate delayed cerebral ischemia after subarachnoid hemorrhage. However, recent preclinical studies indicate that dexmedetomidine appears to be safe and might even be neuroprotective in these contexts [34–36]. Increases in the pulsatility index and vasoconstriction could potentially facilitate CSF influx into the brain through an enlarged perivascular space.

While enlarged perivascular space promotes influx of fluid in the periarterial space, dexmedetomidine likely promotes the transport of fluid and molecules through the brain parenchyma owing to suppression of central noradrenergic tone, which reduces resistance to parenchymal flow of compounds and fluid in the extracellular space (Figure 2 part 2). In preclinical studies, high central noradrenergic tone resulted in decreased extracellular space, while local application of adrenergic antagonists (prazosin, atipamezole, and propranolol) on the cerebral cortex, anesthesia with a systemic α_2-adrenergic agonist (i.e., the veterinary α_2-agonist xylazine in combination with ketamine), or simply deep natural sleep, all increased extracellular space volume, thus opening the extracellular space for fluid flow through the brain parenchyma and increasing the efflux of intraparenchymal compounds from the brain (Table 1) [8,37].

Finally, dexmedetomidine may be favorable for restoring glymphatic function due to preservation of an outflow route for metabolic waste (Figure 2 part 3). In particular, solutes from the CNS drain directly into the perineural CSF spaces, nasal lymphatic tissue, and the meningeal lymphatic vessels, ultimately arriving in cervical lymph nodes [38,39]. The importance of the meningeal lymphatic vessels as a downstream draining route of the glymphatic system was shown by ablation of the meningeal lymphatic vessels, which lead to reduced perivascular influx of CSF macromolecules into the brain parenchyma and concomitantly reduced clearance of macromolecules from the brain, which ultimately resulted in cognitive impairment in rodents [40]. The meningeal lymphatic vessels have only recently been visualized in humans by imaging the movement of intrathecally injected contrast agent with MRI [41–43]. Those studies confirmed that meningeal lymphatic vessels indeed exist in humans [41], that intrathecal contrast agent drains into cervical lymph nodes [42], and that drainage of parenchymal contrast agent deteriorates with age, linking the function of meningeal lymphatic vessels with aging-related neurodegeneration [43].

Interestingly, the function of lymphatic vessels is differentially affected by different anesthetic regimens. While the volatile anesthetic isoflurane significantly reduced solute transport speeds in peripheral lymphatic vessels, medetomidine (the racemic mixture of levo- and dexmedetomidine) combined with ketamine preserved lymphatic function [44].

Table 1. The role of noradrenergic tone on extracellular space volume fraction in preclinical studies[a]

Study	Subjects	*n*	Study drugs	ECS measurement method	Outcome
Xie *et al.*, 2013 [7]	Mice	10	Ketamine, xylazine[b], and a mixture of adrenergic receptor antagonists (prazosin, atipamezole, and propranolol)	Real-time tetramethylammonium iontophoretic measurement	- Compared with the awake state, ECS volume fraction was increased during natural sleep, ketamine/xylazine[b] anesthesia, and after local administration of adrenergic antagonists
Sherpa *et al.*, 2016 [37]	Rats	4	Isoprenaline	Real-time tetramethylammonium iontophoretic measurement	- Compared with the awake state, application of the β-adrenergic receptor agonist isoprenaline resulted in increased astrocytic volume and decreased the ECS volume fraction
Zhao *et al.*, 2020 [8]	Rats	18	Isoflurane, dexmedetomidine, pentobarbital sodium, noradrenaline, and a mixture of adrenergic antagonists (prazosin, atipamezole, and propranolol)	Contrast-enhanced MRI	- Local administration of adrenergic antagonists increased ECS diffusion and drainage of Gd-DTPA whereas local noradrenaline reduced them - Compared with anesthesia under intravenous dexmedetomidine or pentobarbital sodium, inhaled isoflurane decreased ECS volume fraction and restricted diffusion of Gd-DTPA in ECS
Zhao *et al.*, 2021 [69]	Rats	12	Propofol and isoflurane	Contrast-enhanced MRI	- Compared with anesthesia under isoflurane, propofol resulted in larger ECS fraction and faster drainage of Gd-DTPA

[a]Abbreviations: ECS, extracellular space; Gd-DTPA, MRI contrast agent (gadolinium diethylenetriamine penta-acetic acid).
[b]Xylazine is an α_2-adrenergic agonist used in veterinary medicine.

In addition to central effects, dexmedetomidine influences peripheral arteries in a dose-dependent manner. Low concentrations of dexmedetomidine induce peripheral vasodilation through central reduction in sympathetic tone, whereas high concentrations of dexmedetomidine induce peripheral vasoconstriction through activation of peripheral α_{2B}-adrenergic receptors [45]. Peripheral vasodilation and vasoconstriction frequently induce reflex hypotension or hypertension, respectively [45]. These systemic adverse effects are mainly a concern with intravenous administration of dexmedetomidine, as discussed in the section 'Safety aspects'.

Neuroprotective, anti-inflammatory, and antidelirium effects

Neurodegenerative diseases, such as Alzheimer's disease, are characterized by neuroinflammation and intracerebral accumulation of protein aggregates [46]. However, their pathogenesis remains incompletely understood and highly debated. One general explanation for neurodegenerative processes is that intracerebral accumulation of metabolic waste stems from insufficient clearance of interstitial peptides or proteins, which in turn induce neuroinflammation or toxicity [2].

Interestingly, preclinical studies have described neuroprotective and anti-inflammatory effects of dexmedetomidine in a variety of animal models of neurological disease states, suggesting that dexmedetomidine displays a variety of neuroprotective effects in conditions such as hypoxic neuronal injury, ischemic-reperfusion injury, subarachnoid hemorrhage, post-traumatic brain injury, and epilepsy [47]. In rodents, dexmedetomidine attenuates neuroinflammation, neuroapoptosis, microglial activation, and neuroinflammatory responses to sleep deprivation [21,48]. In a meta-analysis of 67 studies, Wang and colleagues reported lower plasma levels of stress hormones (cortisol, noradrenaline, adrenaline), c-reactive protein (CRP), blood glucose, IL-6, and tumor necrosis factor α, and a beneficial immune cell response among patients who received intravenous dexmedetomidine perioperatively compared with control patients. These findings suggest that dexmedetomidine may mitigate stress and inflammation related to surgery while intensifying favorable immune responses [49].

Delirium is a multifactorial syndrome characterized by disturbances in attention, cognition, and consciousness. While the elderly are at high risk for developing delirium, the underlying mechanisms of delirium are incompletely understood [50]. Delirium is an independent predictor of mortality and increases the requirement for mechanical ventilation and hospital stay among critically ill patients [21]. Administration of dexmedetomidine as a perioperative adjunct or in sedation is associated with lower incidence of postoperative delirium and is used to support the sleep–wake cycle of intensive care patients [21]. Proposed antidelirium mechanisms of dexmedetomidine include reduction of surgical stress response and improvement in the quality of sleep [21]. Moreover, dexmedetomidine is devoid of direct **GABAergic** or anticholinergic effects, which might otherwise carry an increased risk of delirium [25]. Enhanced glymphatic clearance, evidenced by washout of intrahippocampal tracers, has been hypothesized to contribute to the antidelirium effects of dexmedetomidine [15]. Indeed, the accumulation of endogenous waste, such as lactate and amyloid-β, might well be a salient factor in the pathogenesis of delirium. That hypothesis is supported by the findings that inhalational anesthetic agents such as isoflurane increase the risk of delirium and prevent glymphatic CSF flow [6,7,15,17].

Novel extravascular routes of administration

Dexmedetomidine is currently approved only for intravenous administration with a recommended maximum infusion speed of 1.4 μg/kg/h in adults [25]. Novel administration routes now expand the use of dexmedetomidine outside of perioperative settings and intensive care units. Here, the intranasal, buccal, sublingual, and oral routes appear to be the most comfortable and feasible for self-administration [51–54] (see also ClinicalTrials.gov identifier NCT04251910[i]). In healthy volunteers, buccal dexmedetomidine (i.e., drug solution retained in the mouth for 5 min) had a high systemic bioavailability of 82% [54]. Promising preliminary results with respect to safety and reduction of dementia-associated agitation have recently been reported for a sublingual, orally dissolving dexmedetomidine (BXCL501) at 30 and 60 μg doses in a Phase 1b/2 study (ClinicalTrials.gov identifier NCT04251910[i], press release[ii]), although full publications or pharmacokinetic parameters of BXCL501 are not yet available. BXCL501 will now be studied for agitation in dementia in Phase 3 trials among patients in assisted living facilities or nursing homes. However, the drug is already FDA-approved for agitation related to schizophrenia or bipolar disorder I and II in adults (see section 'Safety aspects' for more details)[iii].

Intranasal dexmedetomidine may be administered to the nasal mucosa either as drops or through a nebulizer. Single dosing of dexmedetomidine hydrochloride had a bioavailability ranging from 41% to 65% and a rapid onset of action (30–45 min) [51–53]. Currently used intranasal dexmedetomidine formulations (100 μg/ml) markedly exceed the recommended maximum volumes (0.1–0.2 ml) for intranasal administration of drugs [55] and have a relatively short (3–4 h) duration of action [52,53]. Thus, development of dexmedetomidine formulations with longer duration of action and higher concentration is warranted.

A solid oral formulation of dexmedetomidine was recently introduced, which, however, undergoes high first-pass metabolism in the liver, resulting in low bioavailability of only 7–14% [56]. Clinical Phase 1 and 2 studies of oral dexmedetomidine nonetheless demonstrated its safety and efficacy in promoting deep sleep stages [57]. Compared with intranasal administration, oral dexmedetomidine has slower onset (50–60 min) and longer duration of action (10 h) [56,57]. Other potential but more rarely studied routes of administration include subcutaneous, intramuscular, rectal, transdermal, intrathecal, and epidural routes. Subcutaneous and intramuscular dexmedetomidine show high bioavailability of 80–100%. Although these routes of administration may be uncomfortable for self-administration [58], they can be advantageous in treating agitation

of uncooperative patients [59]. Particularly the subcutaneous route displays a favorable pharmacokinetic profile due to its long duration of action [58].

Safety aspects

The safety of intravenous dexmedetomidine has been studied extensively in children, adults, and elderly patients [25]. Compared with traditional analgesics and sedatives such as opioids, benzodiazepines, or propofol, dexmedetomidine has minimal effects on respiration [25,60]. Dexmedetomidine administered as an intravenous bolus has significant hemodynamic effects and is therefore contraindicated in individuals with structural heart disease or second- or third-degree atrioventricular block [25].

In healthy volunteers, therapeutic or higher plasma concentrations of dexmedetomidine decreased heart rate by up to 20%. This effect on heart rate and consequently on cardiac output results from a centrally mediated reduction in sympathetic tone, with concurrently increased vascular resistance by direct peripheral vasoconstrictive effects [45]. Thus, dexmedetomidine has biphasic effects on blood pressure, with low concentrations decreasing heart rate and blood pressure, whereas higher concentrations increase blood pressure [60]. However, we note that decreased heart rate is a normal phenomenon during physiological NREM sleep in healthy subjects [61].

Prolonged use of dexmedetomidine in critically ill patients may lead to tachyphylaxis and withdrawal symptoms including hypertension, tachycardia, diaphoresis, anxiety, and altered mental status [62]. However, increased risk of tachyphylaxis was reported among critically ill patients receiving dexmedetomidine continuously for at least 3 days with daily dosages of 13 μg/kg [62], greatly exceeding the doses suggested for intermittent sedation. There are no data on adverse effects, such as addiction or tolerance, in long-term use in an outpatient setting, which should be a high priority to investigate in prospective studies.

Among adults with bipolar disorder I or II, adverse effects occurred in 35% or 36% of patients taking 120 or 180 μg of sublingual dexmedetomidine, respectively, compared with only 18% in the placebo group, and no serious or severe adverse events were reported at either dose [63]. The most reported side effects were somnolence, dry mouth, hypotension, and dizziness. Hypotension was reported among 5–6% (six to eight patients out of 126) of treated patients and bradycardia in 2% of the treatment group, but in none from the placebo group [63]. When sedative doses of dexmedetomidine were given to healthy adults intranasally or subcutaneously, the hemodynamic changes were minor [53,58]. In general, extravascular dosing with dexmedetomidine has lesser hemodynamic effects compared with intravenous administration [53,58].

Target diseases for dexmedetomidine as a glymphatic enhancer

Changes in glymphatic CSF flow have been demonstrated in animal models of several chronic neurodegenerative diseases, including Alzheimer's disease, cerebrovascular disease, and glaucoma [20]. Recent neuroimaging studies have shown changes in CSF flow of patients suffering from various neurodegenerative diseases or sleep deprivation. For example, patients with normal pressure hydrocephalus exhibited delayed cortical clearance of MRI contrast agent [64] and reduced diffusivity of water along the perivascular spaces [65]. Interestingly, reduction of water diffusivity seems to correlate with cognitive decline [66]. Therefore, drugs with properties that enhance glymphatic clearance are positioned to attenuate neurodegeneration [2].

A recent Danish national cohort study found that long-term use of blood–brain barrier permeable ß-adrenergic antagonists for hypertension is associated with reduced risk of Alzheimer's disease

compared with nonpermeable ß-adrenergic antagonists. This finding suggests that chronic central noradrenergic blockade may attenuate the progression of Alzheimer's disease pathology [67]. If central noradrenergic blockade indeed is behind this phenomenon, dexmedetomidine that reduces noradrenaline release might have similar benefits as did the blood–brain barrier permeable ß-adrenergic antagonists.

Delirium and agitation are closely interrelated with dementia, although these connections are not fully understood. According to a recent meta-analysis including mainly postsurgical patients, the odds of developing dementia were nearly 12 times higher among delirious compared with nondelirious inpatients [22]. Similarly, agitation is a frequently encountered and challenging problem among demented patients. Fortunately, dementia-agitation might be amenable to treatment in the future with orally dissolving, patient-administered dexmedetomidine that is currently studied in clinical trials[ii].

Concluding remarks

We present a rationale for testing dexmedetomidine and by extension for developing other α_2-adrenoceptor agonist derivatives as sedative-hypnotic medication for outpatient care. We agree with the suggestion by Benveniste and colleagues that the benefits of dexmedetomidine in relieving intensive care delirium may partly be explained by enhanced glymphatic efflux carrying harmful compounds from the brain [15]. Although intravenous dexmedetomidine has been studied extensively in perioperative settings and among critically ill patients [25], there are no studies investigating the long-term use of dexmedetomidine. In this Opinion paper, we list outstanding issues calling for exploration of the safety, feasibility, and benefits of intranasal or oral dexmedetomidine (see Outstanding questions) and eagerly await the ongoing findings from trials investigating orally dissolving dexmedetomidine, BXCL501, in agitation related to dementia.

Due to their relatively short duration of action, oral or intranasal dexmedetomidine could be used as a hypnotic sleeping aid, as an alternative to short-acting benzodiazepines, or other hypnotics such as zolpidem. Other benefits of these administration routes include ease of use and minor hemodynamic effects [53,58]. However, we see a need for intranasal formulations containing a higher dexmedetomidine concentration and longer duration of action.

Benzodiazepines, the most frequently prescribed 'sleeping pills', reduce the amount of slow-wave sleep and are associated with an increased risk of dementia in long-term use [68]. In addition, their prolonged use is associated with tolerance and dependence, increased risk of falls and fractures, and even higher mortality [68]. Given that sleep disruption is strongly associated with neurodegenerative diseases as an early sign and a comorbidity [1], we hypothesize that dexmedetomidine could be superior to benzodiazepines in improving sleep quality, with possible benefits in slowing the progression of neurogenerative diseases. The trials of sublingual dexmedetomidine among patient populations suggest it could also be studied in healthy individuals as a self-administered sedative drug.

An accumulating body of evidence suggests that dexmedetomidine has several potentially neuroprotective effects acting on multiple systems. Dexmedetomidine enhances NREM sleep, reduces central noradrenergic signaling, neuroinflammation, and stress responses, and can simultaneously relieve agitation or delirium [21,49]. Moreover, recent preclinical findings indicate that dexmedetomidine improves glymphatic clearance of solutes from the brain [15]. This latter observation calls for targeted research aiming to improve sleep quality in individuals at risk or suffering from neurodegenerative disease. Novel alternatives to current ineffective treatment strategies are worth exploring in the face of the global burden of neurodegenerative diseases and sleep disorders [19].

Outstanding questions

Is dexmedetomidine a safe sedative with respect to hemodynamic, respiratory parameters, and potential adverse effects in daily or weekly long-term use?

How do the possible adverse effects of dexmedetomidine compare with other sedative-hypnotic drugs used in outpatient care (e.g., benzodiazepines)?

Is dexmedetomidine beneficial for sleep architecture, cognitive function, and neurological function in healthy volunteers, individuals with sleep disturbances, or patients suffering from neurodegenerative diseases?

In addition to promoting glymphatic function in preclinical study setups, does dexmedetomidine promote brain clearance of metabolic waste from the human brain? Could long-term use of dexmedetomidine slow cognitive decline among individuals at risk for developing Alzheimer's disease?

What might be the optimal target population for dexmedetomidine administration in the prevention of neurodegenerative diseases and what is the optimal administration route in potential outpatient care?

How are the quality of life and subjective sleep quality influenced by long-term dexmedetomidine use in healthy volunteers, in individuals with sleep disturbances, or in patients developing neurodegenerative diseases?

Does dexmedetomidine reduce the risk of delirium in intensive care by promoting glymphatic clearance, and which patients might particularly benefit from dexmedetomidine administration in intensive care settings?

How does dexmedetomidine influence astrocytic aquaporin 4 function in preclinical study setups?

How does dexmedetomidine influence the levels of stress hormones, inflammatory biomarkers, and immune response in long-term use?

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Resources

[i]https://clinicaltrials.gov/ct2/show/NCT04251910

[ii]https://ir.bioxceltherapeutics.com/news-releases/news-release-details/bioxcel-therapeutics-announces-fda-approval-igalmitm

[iii]www.igalmihcp.com

Supplemental information

Supplemental information associated with this article can be found online at https://doi.org/10.1016/j.tips.2022.09.007.

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