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Abstract

Impairment of the main noradrenergic nucleus of the human brain, the *Locus coeruleus* (LC), which has been discovered in 1784, represents one of defining factors of neurodegenerative diseases progression. Projections of LC neurones release noradrenaline/norepinephrine, which stimulates astrocytes, homeostatic neuroglial cells enriched with adrenergic receptors. There is a direct correlation between the reduction of noradrenergic innervations and cognitive decline associated with ageing and neurodegenerative diseases. It is, therefore, hypothesised that the resilience of LC neurones to degeneration influences the neural reserve that in turn determines cognitive decline. Deficits in the noradrenergic innervation of the brain might be reversed or restrained by increasing the activity of existing LC neurones, transplanting noradrenergic neurones, and/or using drugs that mimic the activity of noradrenaline on astroglia. Here these strategies are discussed with the aim to understand how astrocytes integrate neuronal network activity in the brain information processing in health and disease.

Key words: Cytoplasmic Excitability, Astrocytes, Neurodegeneration, Noradrenaline, Norepinephrine, Second Messengers, Metabolic Excitability, Aerobic Glycolysis, Vesicles

Abbreviations:

AD – Alzheimer's disease
ARs – adrenergic receptors
BBB - blood-brain barrier
cAMP - cyclic adenosine monophosphate
COMT - catechol-O-methyltransferase
COX2 - cyclooxygenase-2
CNS - central nervous system
iNOS - inducible nitrite oxidase
LC - locus coeruleus
MAO - monoamineoxidase
MCP1 - monocyte chemoattractant protein-1
MS – multiple sclerosis
NA – noradrenaline (norepinephrine)
PD – Parkinson's disease
TH – tyrosine hydroxylase
TNF-α – tumour necrosis factor α

Structure and function of *Locus coeruleus*: the brain noradrenergic system

In his book *Thinking, Fast and Slow* Nobel Laureate Daniel Kahneman offers a useful definition for two main kinds of thinking associated with cognition: the first is fast and automatic, requires no effort, and has no sense of control, whereas the second, *slow* mode of thinking requires the effortful allocation of attention and concentration, and it is this *slow* mode that is mainly impaired in neurodegenerative disorders. Slow thinking is associated with the activity of the CNS noradrenergic system deriving from the brainstem nucleus *Locus coeruleus* (LC), discovered in 1784 by Félix Vicq-d'Azyr [1], a neuroanatomist, the last physician of Queen Marie Antoinette, although the name "locus coeruleus" was coined in 1812 [2, 3].

This small nucleus is located near the fourth ventricle (Fig. 1), and it is composed of neuromelanin-containing neurones. This neuromelanin gives a dark colour to the LC and hence this nucleus was also known as the *nucleus pigmentosus pontis* [4], which means "heavily pigmented nucleus of the pons". Neuromelanin is formed by the polymerisation of noradrenaline (NA) precursors. In adult humans the LC comprises around 50,000 neurones [5]. In 1959, activity of monoamine oxidase was described in the rodent LC, in 1964 monoamines were detected in LC neurones and in 1970 the noradrenergic neuronal projections to the central nervous system (CNS) were discovered [2]. It is generally acknowledged that LC is the prime source delivering ~70% of all NA in the CNS [6-8].

Diffuse innervation by projections of LC neurones reaches practically all parts of the brain and the spinal cord [9]. The majority of axons arising from the LC terminate in the neocortex and hippocampus [10-12]. Excitation of LC neurones leads to an almost simultaneous activation of neural networks across many CNS regions. This may be considered an anatomical basis for a functional “reset” for multiple brain networks [13, 14], since it allows spatially synchronous activation of many brain areas simultaneously, providing a reset mechanism.

Indeed, synchronous activation of LC projections [14], possibly reflected by γ waves on an electroencephalogram [13], is the hallmark of many fundamental LC-mediated activities including arousal and the sleep–wake cycle, cognitive control, emotional balance, attention and memory formation [9], which all require NA-mediated morphologic neuroplasticity [15-17]. The LC-derived NA and β-adrenergic receptors (β-ARs) have also been implicated in the physiological modulation of memory formation and retrieval [11, 18-20].

Noradrenergic LC neurones play an important role in the development of the CNS. It has been noted that LC axons are implicated in the differentiation of various parts of the brain, especially of the neocortex [7]. In rats this nucleus starts to form at 10 - 13 days of gestation [21], well before the emergence of neurones in the LC target brain areas, such as the cerebral cortex [7]. In the human brain LC nucleus appears as a separate structure between 9 to 12 weeks of gestation with efferent fibres projecting to the cortex [7, 22]. Given the morphologic presence of LC axon termini in the cortex, it is likely that NA, released from these terminals, regulates (perhaps as a growth factor) formation of the cortex [23]. Axons releasing NA emerge in the lower stratum of cortical marginal zone where the tangential axons of Cajal-Retzius cells extend and ramify. Cajal-Retzius cells of the marginal zone provide principal migratory cues for cells born later in development, thus contributing to the lamination of the cortex [24, 25]. Therefore, Cajal-Retzius neurones may be the targets of the early NA input [26], and indeed about 20 to 30 % of Cajal-Retzius neurones respond with cytosolic Ca^{2+} signals to an application of NA [27]. Ablation of the NA system after birth decreases the number of Cajal-Retzius cells, revealing a more direct role for NA in the development and regulation of cerebral cortex stratification [28].

Why is the NA-mediated coordination of cerebral cortex development required? While we are still far from understanding the complexity of this process, one possible reason may reflect (at least in part) the universal problem of regulating growing tissue mass, which hinders cell-to-cell signalling. In a growing mass of tissue distances between cells become far greater than those reachable by diffusion-based signalling [29]. To overcome this obstacle two mechanisms, represented by convection- and conductive-based signalling have emerged in evolution. In the first case substances in the extracellular milieu are delivered from the source to targets by the bulk flow. Cerebrospinal fluid flux varies diurnally (at least in mouse): at night the perivascular glymphatic tunnels [30] are widened, facilitating the removal of waste

products from the extracellular space during sleep [31]. Cerebrospinal fluid flux is sensitive to activation of adrenergic receptors, since administration of a mixture of AR antagonists (prazosin, atipamezole, and propranolol, each at 2 mM) into the cisterna magna affected the convective flow of fluorescent markers [31]. At the same time, this flow may be affected by dynamic changes in astroglial morphology, which is sensitive to β-ARs and consequential changes in cytosolic cyclic adenosine monophosphate (cAMP) [32-34]. In the second case, a conductive electrical mechanism represented by propagating action potentials along the canvas of branching neuronal axons mediates tissue coordination, which includes operation of LC projections [7] that widely innervate brain structures [9].

In addition to the cell-to-cell signalling logistics, enlarging tissue mass is accompanied by an energy challenge. Cell division and rapid morphologic changes are associated with high energy consumption. A special form of metabolic adaptation, the aerobic glycolysis, has evolved to meet this physiological demand. Aerobic glycolysis is a form of non-oxidative utilization of glucose that takes place in tissues even in the presence of adequate levels of oxygen; this process is also known as “the Warburg effect” [35]. In neurodevelopment, increased aerobic glycolysis is essential to generate intermediates to be utilized for biosynthetic pathways. This form of metabolism is an inefficient way to generate ATP, however it secures the production of synthesis intermediates such as lipids, nucleic and amino acids [36]. These building blocks of cellular structures are needed for cell division and for cellular shape adaptations, the processes defining the developing brain [37] as well as the cognitive processing in the adult [15, 16]. This metabolic strategy is essential for rapid generation of the biomass, also a characteristic of cancer cells [38], being thus a universal property of tissue growth and remodelling.

In the brain aerobic glycolysis contributes to various functional tasks related to the activation of LC neurones and is associated with the production of L-lactate in astrocytes. Astroglial production of L-lactate is up-regulated during exercise, arousal and alerting with sensory stimulation as well as in some pathophysiological states. The upregulation of aerobic glycolysis likely involves the activation of LC neurones [39], which respond to L-lactate, generated by astroglia when NA activates ARs on astroglial plasma membrane, with elevated firing, i.e. discharge of action potentials [40]. Such communication may likely exist also between LC axon termini and nearby astroglia, since transcranial direct current stimulation also evokes NA-dependent activation of astroglia [41].

Noradrenergic LC neurones are constitutively active – they fire action potentials even when synaptic activity is inhibited [42]; this continuous activity has to be supported by adequate energy provision. Indeed, energy delivery is maintained by dense vascularisation of the LC nucleus [43], supporting the notion that LC neurones are metabolically demanding. The exposure of LC neurones to blood vessels is impressive. A single LC neurone, with a soma diameter of 45 μm, is associated with a length of 20 meters of capillary wall [44]. In general, abundantly vascularised tissues represent a relatively high risk in regard to their exposure to circulating toxic substances, and therefore LC neurones exposure to blood circulation renders them vulnerable to toxic agents even if these are present at very low concentrations and even if they exhibit poor blood brain barrier (BBB) permeability. In addition, toxins may be entering LC axons in sufficient quantities through blood, with subsequent retrograde transport to cell bodies [44, 45]. Moreover, LC neurones can also get exposed to the cerebrospinal fluid molecules involving tanycytes [46], specialized ependymal cells located nearby the nucleus in the floor of the fourth ventricle, and this may additionally represent a source that affects LC neuronal viability, making these neurones sensitive to toxins and viruses present in the cerebrospinal fluid [47].

In summary, LC is highly vulnerable to stress due to abundant vascularisation, which exposes the nucleus to environmental burdens; death of LC neurones facilitates the development of neurological and neurodegenerative disorders, including Alzheimer's (AD), Parkinson's (PD) and other diseases [6, 45, 48, 49]. The slow age-dependent demise of LC leads to reduced levels of NA throughout the brain [6], with subsequent impairment of NA-mediated stimulation of cells that express ARs. An important target for NA are astrocytes, since the density of ARs in these cells appears to be higher than in neuronal processes [50]. Hence, reduced NA innervation that follows LC degeneration is reflected in impaired function of astroglia.

Adrenergic astroglial excitation and neurodegeneration

Astrocytes are morphologically and functionally heterogeneous cells primarily responsible for homeostasis of the CNS. These functions were recently reviewed [51], and include regulation of synaptic formation, control of connectivity of synapses, integration and synchronization of neuronal networks and the maintenance of BBB integrity [52-70]. Importantly, astrocytes are also the fundamental defensive elements of the nervous tissue; insults to the brain or spinal cord trigger reactive astrogliosis, which spatially contains damaged area, while also facilitating post-damage regeneration of neural tissue [54, 62, 64]; in certain context astrogliosis can be maladaptive and neurotoxic [71]. Astrocytes, also designated gliocrine cells [72], are part of the glymphatic system, which is responsible for waste removal [30]; this system is an important element of the brain organ homeostasis.

The release of NA from LC neurones stimulates astroglial ARs, leading to an increase in cytosolic free Ca^{2+} ($[Ca^{2+}]_i$) [73, 74] and cAMP [32], via α- and β-ARs, respectively Almost all astrocytes in the cortex of awake mice generate synchronous $[Ca^{2+}]_i$ signals in response to stimulation of α-ARs following the release of NA from LC neuornes [75-77], while $[Ca^{2+}]_i$ does not change in neighbouring neurones [78]. This is consistent with the view that the density of ARs (especially β-ARs) in astroglial processes is much higher than in neuronal dendrites [50]. Activation of second messengers signalling cascades in astrocytes stimulates multiple effector mechanisms (Fig. 2), including numerous metabolic pathways, changes in cell morphology, vesicular release of gliosignalling molecules etc. [63, 72, 79]. Vesicle trafficking also contributes to the plasmalemmal delivery of receptors and transporters that determine the signalling landscape of astrocytes, as well as to regulation of cell shape and glycolytic metabolism [32, 67, 72, 80-82].

What are the consequences of reduced levels of NA in the CNS that may occur during ageing and neurodegeneration? Age-dependent degeneration of LC likely impairs NA-mediated astroglial cytoplasmic (Ca^{2+}) excitability which may facilitate cognitive decline [6, 49]. Accordingly, preventing the loss of LC neurones may, in principle, slow-down neurodegeneration [48, 49]. It is thought that LC demise and noradrenergic dysfunction begin several years prior to the appearance of clinical symptoms of AD [83-86]. Degradation of LC is associated with idiopathic Parkinson's disease (PD), and perhaps is a common feature of all types of neurodegeneration in aged population [8].

The concept of cognitive reserve defines the degree of functional impairment in response to brain pathology, i.e., a similar extent of brain damage may in different subjects result in different cognitive outcomes [87]. This is likely due to acquired functional compensation prior to injury, due to exposure to sensory-rich environment, which could be defined as "cognitive fitness" and likely involves NA-mediated mechanisms. The cognitive reserve has

two components: the *neural reserve*, represented by neural networks predating pathology, and *neural compensation*, which reflects upon the defensive reaction mounted in response to pathology. Incidentally both components are regulated by noradrenergic innervation and involve astroglia. The "*neural reserve"* has been tested in longitudinal clinical-pathological study [49]. In this study cognition status of 165 patients was monitored annually by 19 cognitive tests. Upon death, brain autopsy and uniform neuropathological examination was performed to evaluate the neuronal density in LC and other brainstem nuclei. The results revealed that a higher density of LC neurones is correlated to a lower loss of cognitive function, hence indicating that neural reserve is represented by noradrenergic innervation. The neuroglial compensation, which is very much linked to glial reactivity and reactive astrogliosis in particular, is similarly regulated by noradrenaline [88]. In other words, the rate of LC neurone loss determines the rapidity of cognitive decline manifestation. Therefore, the key question is how to prevent neurone demise in LC and perhaps other brainstem nuclei during the lifetime.

Astroglia-based strategies to slow-down neurodegeneration

During normal aging, LC noradrenergic neurones are impaired, and it is estimated that up to 25% of those neurones, responsible for ~50% of brain NA levels, are being lost in elderly (>90 years age) [89]. Several possibilities exist to reverse the deficient noradrenergic transmission during neurodegeneration. We highlight three possible approaches: (i) exposing the subjects and animals to enriched sensory environment or to electrical stimulation; (ii) transplanting noradrenergic neurones into the brain; and (iii) applying drugs that elevate NA and or act in a signal in a similar manner as agonists of ARs on astroglia, although via different receptors.

Enriched sensory environment and electrical stimulation

Exposing the subjects to an enriched sensory environment (which stimulates LC neurones and astroglia) is perhaps the most straightforward approach to functionally recruit the LC neurones. When exposed to NA, astrocytes *in vitro* attain stellate morphology [90], which depends on an optimal increase in cytosolic levels of cAMP [32]. In a mouse model of AD, astroglial atrophy develops in some brain areas, and that this can be reversed by exposing the animals to an environment enriched with sensory stimuli [91-93]. While the mechanism of these morphological changes is unclear, it is possible that the enriched environment may act through activation of LC neurones; the enhanced activity of these neurones may underlie an increased power of the γ oscillations of the electroencephalogram [13]. Indeed, it was tested experimentally whether behavioural experience affects γ-oscillations; the results revealed that the power of hippocampal Θ-associated γ-oscillations recorded under urethane anaesthesia tended to be greater in rats reared in an enriched environment than those reared in an isolated condition [94]. Therefore, activation of LC neurones by exposing subjects to the enriched sensory environment is a possible strategy.

Electrical stimulation of the brain can be used to a similar effect. Transcranial direct current stimulation (tDCS), which is an application of constant, weak-intensity electrical current to the brain through the skull, could be used for this purpose. In humans, current intensity of 1–2 mA, applied for 10 - 30 minutes has been used with positive effects including memory enhancements, accelerated motor function rehabilitation, alleviation of depressive symptoms, and slower progression of neurodegeneration in AD patients [95, 96]. The mechanism of action of tDCS has been revealed only recently; it was shown that tDCS induces widespread increase in astroglial $[Ca^{2+}]_i$ which is inhibited by ablation of noradrenergic neurones or

blockade of α_1-ARs, suggesting that tDCS triggers NA release in the cortex [41]. Therefore, enhanced NA signalling contributes to long-term neural plasticity through astroglia.

Transplantation of noradrenergic cells

Intra-brain transplantation of noradrenergic cells represents the second strategy. Destruction of LC neurones could be compensated by their replacement, as has been attempted in the past by implanting a solid tissue block of foetal LC tissue into the third ventricle of aged rats, which lead to significant improvements in working memory [97]. In addition to grafts, injections of noradrenergic cell suspensions were used for treating neurological conditions, including epilepsy [97-100]. However, to test whether the strategy of replacing noradrenergic neurones is feasible, an animal model is needed in which LC is selectively lesioned. The rat ablation model consists of LC neurone-selective destruction by an injection of the immunotoxin, the anti-dopamine-β-hydroxylase-saporin [101]. Saporin is a potent ribosome-inactivating lectin [102], whereas specific monoclonal antibody against dopamine-β-hydroxylase, a NA-synthetic enzyme, also expressed on the surface on noradrenergic neurones [103, 104]. This model results in noradrenergic dysfunction [105], which imitates clinical findings [49], and therefore it is also a suitable animal model for neurodegeneration. It was further tested, whether in such an animal model behavioural deficits emerge and whether these changes may be reversed by transplantation of noradrenergic neurones. A recent study demonstrated that noradrenergic innervation contributes to the regulation of hippocampus-dependent spatial learning and memory [106]. Rats that were exposed to selective immunolesioning of hippocampal noradrenergic afferents at post-natal day 4 were subjected, four days later, to the bilateral intra-hippocampal implantation of LC noradrenergic neuroblasts. Then, from 4 weeks onwards to about 9 months post-surgery, sensory-motor and spatial navigation abilities were evaluated, followed by post-mortem tissue analyses. Three groups of animals were studied: untreated or vehicle-treated controls, immunotoxin-treated animals and animals immunotoxin-treated and subsequently grafted with noradrenergic neurones. All these groups exhibited normal sensory-motor function and were equally efficient in the reference memory version of the water maze task, whereas working memory abilities were seen consistently impaired in the immunotoxin-treated rats only. Notably, the noradrenergic re-innervation promoted by the grafted progenitors reinstated a fairly normal working memory, suggesting a primary role for LC noradrenergic inputs in the maintenance of specific aspects of hippocampus-based memory functions [106]. These studies indicate that cell transplantation of noradrenergic neurones may be a strategy to be employed, however the complexity of such a procedure is significant and thus a challenge.

Drugs that elevate NA and/or activate NA-dependent second messengers

The third strategy to mitigate neurodegeneration due to deficient LC innervation, is to apply drugs that elevate the levels of NA thus mimicking the action of NA, specifically on astroglia, the main site of aerobic glycolysis [80] and cholesterol synthesis [107] in the CNS. In other words, these drugs aim to maintain a sufficient level of astroglial noradrenergic excitation. In addition to elevating levels of NA, a valid strategy is also to activate second messenger pathways as are activated by ARs, but through mechanisms independent of ARs.

The depletion of brain NA is considered to affect astrocytes in AD and PD, as in these conditions LC nucleus is disintegrated, a state associated with reduced levels of NA in the CNS [6]. Indeed, ageing and ageing-related disorders, such as AD and PD, are characterized by a subclinical chronic inflammatory status and it has been considered that existing neuropathology can be exacerbated by systemic inflammation instigated by a spread of pro-

inflammatory cytokines across the BBB. This was recently studied by monitoring activation of microglia and astroglia in animals with intact and chemically ablated LC. Lipopolysaccharide was injected systemically and the results revealed that the activation of both microglia and astrocytes was aggravated, if LC was experimentally disintegrated [108].

The second-messenger systems mediated by Ca^{2+} and cAMP in astrocytes operate in different time-domains [109], which may distinctly modulate downstream processes [110]. Whether this is the case also in other glial cells, needs to be determined. Activation of ARs on glial cells can elicit potent anti-inflammatory actions, which help limit neuro-inflammatory events throughout the CNS [6, 108].

The anti-neuroinflammatory action of NA that was considered in the past to be the target for therapy in AD, where β-amyloid accumulates and induces events consistent with an inflammatory response mediated by microglia and astrocytes, including the transcription factor NFκB, expression of pro-inflammatory cytokines and activation of phagocytotic activity [111]. Phagocytic activity was analysed in more detail in astrocytes in relation to sleep deprivation and transport of cholesterol [112, 113], both processes associated with neuroinflammation. Under normal conditions anti-neuroinflammatory molecules, including neuropeptides and transmitters, such as NA, are maintained at high levels during inflammatory processes and thus limiting the neuroinflammatory response via ARs on glial cells.

In particular, the inflammatory status is significantly attenuated via activation of β-AR. Neuroinflammation induced by lipopolysaccharide or with pro-inflammatory cytokines was inhibited by activating β-AR. Moreover, exposure of glial cells to β-amyloid, which can induce the expression of cytokines, including tumour necrosis factor -α, monocyte chemoattractant protein-1, inducible nitrite oxidase, and cyclooxygenase-2, were all significantly reduced by co-application of NA [114]. Moreover, treatments with drugs that elevate NA levels *in vivo* can reduce toxin-induced inflammatory status in the CNS [115], endotoxin-mediated inflammation [116], or neuroinflammation induced by application of β-amyloid [114, 117]. Moreover, one such agent is antagonist for α_2-ARs, which blocks these receptors, also known as α_2-autoreceptors, since they are located at the presynaptic membrane and mediate the inhibition of release of NA from LC neurones via the activation of a G_i-protein second messenger pathway. Treatment of adult rats with 5-fluoro-methoxyidazoxan, an α_2-ARs antagonist, reduced neuroinflammation following intra-parenchymal injection of aggregated Aβ. The NA levels could be also elevated by using NA reuptake inhibitors such as atomoxetine and reboxetine, to exert anti-inflammatory action *in vivo* [118-120]. Furthermore, levels of NA can be elevated by inhibiting the degrading enzymes of NA, the monoamine oxidases (MAOs), predominantly expressed in astroglia [121-124] and catechol-O-methyltransferase (COMT) [125]. Levels of MAO mRNA were increased in AD patients vs. controls [126], while variants in the MAO genes are risk factor to develop AD [127]. Inhibitors of COMT have been used for many years to reduce levodopa breakdown during treatment of Parkinson's disease [128]; and recently it was shown that dinitrocatechol, a BBB-permeable COMT antagonist, was beneficial in the experimental autoimmune encephalomyelitis (EAE) mouse model of multiple sclerosis (MS) [129].

Another possibility to elevate levels in NA is to use vindeburnol, a derivative of vincamine, an alkaloid from the dwarf periwinkle (*Vinca minor*). It was shown that vindeburnol elevates the level of tyrosine hydroxylase (TH), the rate-limiting enzyme of catecholamine synthesis in the LC neurones [130, 131], leading to an increase in NA levels. The vindeburnol treatment of

5xFAD mice, a transgenic mouse model of AD [132], appears to reduce the β-amyloid burden associated with reduced LC damage [133]. However, the effects of vindeburnol on behavioural deficits in those mice were tested recently, revealing a reduced anxiety-like behaviour (time spent near the walls – thigmotaxis - as apposed in the open field) compared to wild-type littermates, indicated by reduced thigmotaxis which was increased by vindeburnol. Moreover, *in vivo* vindeburnol reduced β-amyloid burden in the hippocampus, and *in vitro* increased neutrophic factor expression and cAMP levels, pathways that can improve LC maturation and function [134].

The limitation of using NA re-uptake inhibitors, α_2-AR antagonists and metabolic inhibitors, is that endogenous NA levels need to be relatively high; however, these levels are reduced due to loss or damage to LC neurones during neurodegeneration. A further strategy to elevate NA is by using a NA precursor such as droxidopa [135], which is converted to NA by the enzyme DOPA decarboxylase also known as aromatic L-amino acid decarboxylase, also localised in neuroglia [136]. Several studies have shown that droxidopa can reduce clinical symptoms in the *in vivo* mouse models of MS [137] and in AD [114, 138].

While the aforementioned strategies are targeting mechanisms associated with determining the level of NA, the future drug discovery will have to focus more specifically into mechanisms that are targeting NA-mediated astroglial function, including aerobic glycolysis, cholesterol synthesis, cell morphology and secretion. Recently, a strategy modulating the metabolic response of astroglia by carbon monoxide was considered as one of such directions [110].

Conclusions

As mild cognitive decline is associated with changes in the modes of thinking, especially the slow, effortful type, rigorous neurobiology and pathobiology studies are needed to understand the cell- and tissue-based mechanisms in order to contain cognitive decline, likely the most important grand challenge, to be solved. Throughout recent years the noradrenergic hypothesis of neurodegeneration associated with ageing has gained recognition as several studies associated the severity of cognitive decline with a reduced number of Locus coeruleus neurones. Deficient release of NA is a prominent feature of aged and diseased brain. The NA acts through microglia and astroglia to coordinate and metabolically support neuronal networks, astrocytes likely represent a rate-limiting step in the complex homeostatic support of neural networks when the processes are related to aerobic glycolysis and cholesterol synthesis. When levels of NA are critically low, this failure translates into disease initiation/progression. In principle, strategies to be employed in reverting or at least slowing down the rate of neurodegeneration include approaches that augment the activity of existing LC neurones (recruiting neural reserve), transplanting noradrenergic neurons, and/or using drugs that elevate NA and mimic the activity of NA on astroglia.

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Conflicts of Interest

The authors declare no conflict of interest.

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Figure legends

Figure 1. The nucleus Locus coeruleus in the sagittal section of a human brain (marked by arrow).

Figure 2. Left panel: neurones from the Locus coeruleus (LC) project axons to most, if not all, areas of the brain and into the spinal cord as denoted by the arrows. LC nerve endings with varicosities (swellings on noradrenergic nerve terminals) diffusely overlay the tissue. About half of these terminals do not form tight contacts with target cells, resembling synapses [6]. Astrocytes are the main target of noradrenergic innervation in the adult brain. Activation of astroglial adrenergic receptors trigger intracellular signals mediated by Ca^{2+} or second messengers which control astroglial homeostatic cascades which contribute to the maintenance of cognitive reserve. Deficits in adrenergic innervation may disrupt astroglial function and exacerbate cognitive abnormalities.

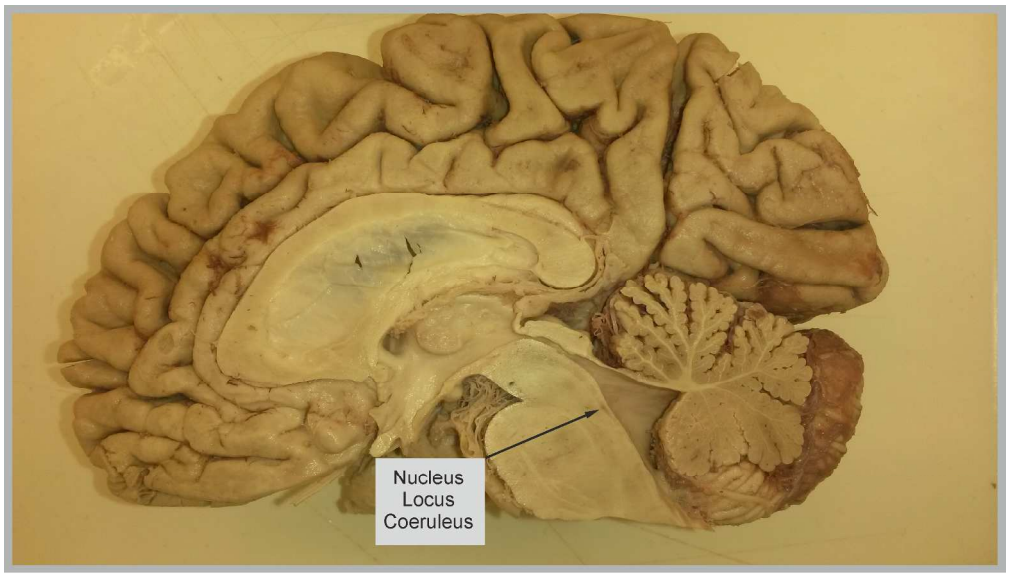

Figure 1

Figure 1

250x164mm (300 x 300 DPI)

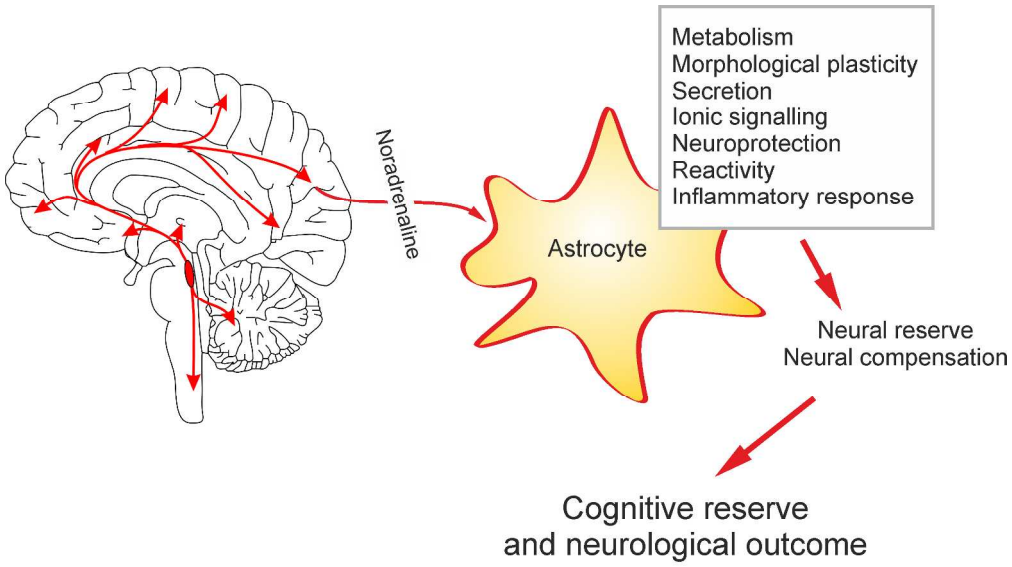

Figure 2

Figure 2

266x155mm (300 x 300 DPI)