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REVIEW ARTICLE

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Targeting Nicotinamide Phosphoribosyltransferase as a Potential Therapeutic Strategy to Restore Adult Neurogenesis

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SUMMARY

Adult neurogenesis is the process of generating new neurons throughout life in the olfactory bulb and hippocampus of most mammalian species, which is closely related to aging and disease. Nicotinamide phosphoribosyltransferase (NAMPT), also an adipokine known as visfatin, is the rate-limiting enzyme for mammalian nicotinamide adenine dinucleotide (NAD) salvage synthesis by generating nicotinamide mononucleotide (NMN) from nicotinamide. Recent findings from our laboratory and other laboratories have provided much evidence that NAMPT might serve as a therapeutic target to restore adult neurogenesis. NAMPT-mediated NAD biosynthesis in neural stem/progenitor cells is important for their proliferation, self-renewal, and formation of oligodendrocytes *in vivo* and *in vitro*. Therapeutic interventions by the administration of NMN, NAD, or recombinant NAMPT are effective for restoring adult neurogenesis in several neurological diseases. We summarize adult neurogenesis in aging, ischemic stroke, traumatic brain injury, and neurodegenerative disease and review the advances of targeting NAMPT in restoring neurogenesis. Specifically, we provide emphasis on the P7C3 family, a class of proneurogenic compounds that are potential NAMPT activators, which might shed light on future drug development in neurogenesis restoration.

Adult Neurogenesis in Aging and Disease

With decades of effort, the existence of lifelong neurogenesis in animals and humans has been demonstrated [1–3]. Adult neurogenesis in the mammalian brain is limited to certain areas rather than spread widely, as shown by evidence that new neurons in rodents are continuously generated by the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG) and the subventricular zone (SVZ) of the lateral ventricles where new neurons migrate into the olfactory bulb and differentiate into olfactory neurons [4,5]. Although neurogenesis exists in the human SGZ of the hippocampal DG, there is very limited postnatal neurogenesis in the human olfactory bulb [6–8]. The newborn neurons dividing from neural stem/progenitor cells (NSPCs) are important for replacing gradual neuron loss and maintaining specific function throughout life. How do new neurons exert their functions to maintain neurogenic niches and how is this process linked to human disorders? Considerable progress has been made in deciphering the role of neurogenesis in aging and disease.

Adult Neurogenesis in Aging

Aging leads to the physiological breakdown of health and significant functional decline. The integration of adult-born neurons into the circuitry of the adult hippocampus plays a role in learning and memory. In mice, the number of proliferating NSPCs in the SGZ is nearly completely absent by 24 months of age [9–11]. Aging attenuates the proliferation of the SVZ neural precursors, and the aged SVZ cells lose their capacity to proliferate and to be recruited by the lesion [12]. The loss of active horizontal neural stem cells (NSCs) in aged mice correlates with reduced neurogenesis [11]. In addition, a recent study reported that aging could increase microglial proliferation and neutrophil infiltration and inhibit SVZ cell proliferation and migration of neuroblasts in the cerebral ischemia model of middle-aged mice, indicating that

stroke-induced neurogenesis is reduced in aged mice [13]. Therefore, the regulation of adult neurogenesis as a therapeutic strategy to compensate for the defects of aging is very relevant.

Adult Neurogenesis in Cerebral Ischemia and Traumatic Brain Injury

Neurogenesis persists in the adult mammalian brain. Successive studies have shown that neurogenesis involves the body's intrinsic defense system to resist impairment by cerebral ischemia. After focal cerebral ischemia in rats, nascent neurons were increased in two neuroproliferative regions—the SGZ of the DG and the rostral SVZ [14]. Later, a study found newborn neurons in the ischemic penumbra surrounding cerebral cortical infarcts in patients with stroke, suggesting that stroke-induced compensatory neurogenesis may contribute to postischemic recovery and represent a target for stroke therapy [15]. What is responsible for ischemia-induced neurogenesis? A recent study found that early immature neuronal death in the DG following transient forebrain ischemia/reperfusion in mice could trigger cerebral ischemia-induced neurogenesis in the DG through microglia-derived insulin-like growth factor-1 [16].

Similarly, traumatic brain injury (TBI) enhances neurogenesis in the rodent hippocampus and stimulates an increase in proliferation of endogenous NSPCs to heal itself after injury [17–19].

Adult Neurogenesis in Neurodegenerative Disease

Neurodegenerative disease is accompanied with the progressive loss of neuronal structure and function, which is associated with brain networks and chronic disease [20–22]. In recent decades, it is widely accepted that alterations in neurogenesis are closely associated with monogenic and sporadic neurodegenerative diseases. Aggrieved adult neurogenesis in neurodegenerative diseases fails to retain existing neurons and loses the endogenous repair mechanism for cell renewal and differentiation into distinct functional neurons.

Substantial alterations of neurogenesis in human patients suffering from Alzheimer's disease (AD), Huntingdon's disease (HD), and/or other cognitive impaired diseases were observed in different studies [23–25]. Patients with AD have a smaller hippocampal volume, which is associated with cognitive deficits [26]. A reduction of dopaminergic neurons in the SVZ is the hallmark of Parkinson's disease (PD). The number of neural precursor cells in the SVZ and olfactory bulb is reduced in postmortem brains of patients with PD [27]. Dopamine treatment could increase the proliferation of SVZ-derived cells in *in vitro* adult SVZ cultures [28]. In addition, α-synuclein, a protein abundantly expressed in the human brain, has been reported as a key protein in PD, AD, Lewy body disease, and other neurodegenerative diseases [29,30]. α-Synuclein knockdown mice showed increased new neurons in the hippocampal DG, whereas elevated endogenous α-synuclein levels could decrease dendrite length and impair dendrite branching [31]. Recently, using a ^{14}C retrospective birth dating approach, which could determine the time point when DNA was synthesized and cells were born and then deduce the age of cells in the cortex of human brain [24,32], it was revealed that the extent of striatal neurogenesis is significantly reduced in patients with HD [33].

Except for the studies mentioned above, stem cell-based therapies for neurogenesis-associated disorders have been shown in experimental animal models with neuroprotection [34–37]. Although many efforts have been made to elucidate the relationship between neurogenesis and human disorders, concerted efforts are needed to narrow the gap between animal models and humans. Exploring novel approaches, applying the approaches to humans with no or less toxicity and side effects, and breaking the limitations of obtaining data from surgical specimens and/or postmortem tissue samples are urgently needed. Historical breakthroughs have been made using patient-derived or genome-edited pluripotent stem cells and induced pluripotent stem cells (iPSCs), which provide a better understanding of the cellular physiological and pathological mechanisms and shed light on further decisions of therapeutic interventions.

Nicotinamide Phosphoribosyltransferase in Neurogenesis

The Characteristics and Functions of NAMPT

Nicotinamide phosphoribosyltransferase (NAMPT) enzymatic activity was reported in 1957 with the property of catalyzing nicotinamide mononucleotide (NMN) synthesis [38]. Decades later, the NAMPT gene was recorded in GenBank by an article published in 1990 as one of a set of putative lymphocyte G0/G1 switch genes [39]. Interestingly, a cytokine named pre-B-cell colony-enhancing factor (PBEF) [40], which enhances the effect of stem cell factor and IL-7 on pre-B-cell colony formation, was described in 1994 and was shown to be equivalent to NAMPT in 2001 and 2002 [41,42]. In 2005, NAMPT was reported as a visceral fat-derived adipokine and renamed visfatin. NAMPT is expressed in both the nucleus and cytoplasm, and its expression is regulated by circadian locomotor output cycles protein kaput (CLOCK) and aryl hydrocarbon receptor translocator-like protein 1 (BMAL1), which is related to circadian rhythmicity and circadian oscillation of nicotinamide adenine dinucleotide (NAD) levels *in vivo* [43,44]. In addition to intracellular NAMPT, NAMPT can be secreted into the extracellular space in some types of cells, and both intracellular and extracellular forms of the protein have NAMPT enzymatic activity [45–47]. The wide distribution of NAMPT suggests its pleiotropic functions in physiology and pathophysiology [48–51].

Nicotinamide adenine dinucleotide is a ubiquitous coenzyme involved in biochemical reactions and serves as a substrate for NAD-dependent enzymes, such as poly-ADP-ribose polymerases, sirtuins (SIRTs), and CD38 [52,53]. There are two ways to synthesize NAD: *de novo* synthesis from tryptophan and the salvage pathway from nicotinamide (NAM), nicotinamide riboside, and nicotinic acid (Figure 1). NAMPT is the rate-limiting enzyme for mammalian NAD salvage synthesis by generating NMN from NAM and 5′-phosphoribosyl-1-pyrophosphate, thereby influencing NAD-dependent enzymes and regulating cellular metabolism, mitochondrial biogenesis, and the adaptive response to inflammatory, oxidative, proteotoxic and genotoxic stresses [42,50,54–64].

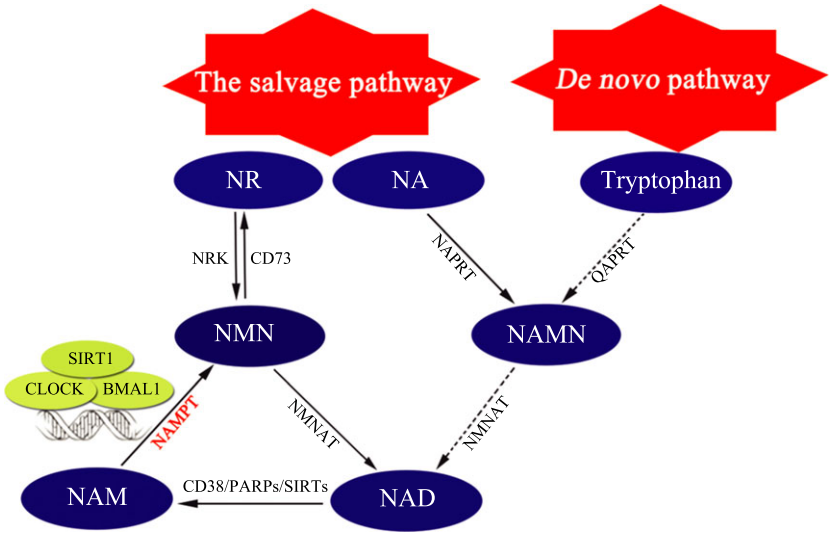

Figure 1 The nicotinamide adenine dinucleotide (NAD) biosynthetic pathways in mammals. There are two ways to maintain the cellular levels of NAD in mammals: the *de novo* pathway from tryptophan and the salvage pathway from NAM, NR, and NA with different catalyzing enzymes. NAMPT, the rate-limiting enzyme of NAD synthesis in the salvage pathway, can be bound and upregulated by the two major circadian regulators, BMAL1 and CLOCK, acting synergistically with SIRT1 [43,52–55,57–63]. BMAL1, aryl hydrocarbon receptor translocator-like protein 1; CLOCK, circadian locomotor output cycles protein kaput; NA, nicotinic acid; NAD, nicotinamide adenine dinucleotide; NAM, nicotinamide; NAMN, nicotinic acid mononucleotide; NAMPT, nicotinamide phosphoribosyltransferase; NAPRT, nicotinic acid phosphoribosyltransferase; NMN, nicotinamide mononucleotide; NMNAT, nicotinamide mononucleotide adenylyltransferase; NR, nicotinamide riboside; NRK, nicotinamide ribose kinase; PARPs, poly-ADP-ribose polymerases; QAPRT, quinolinate phosphoribosyltransferase; SIRTs, sirtuins.

Functions and Mechanisms of NAMPT in Restoring Neurogenesis

Nicotinamide adenine dinucleotide is an essential coenzyme involved in energy production and redox metabolism, which is closely related to mitochondrial energy metabolism. Recent studies showed that the energetic demands of stem cell proliferation and lineage fate decision require distinct metabolic programs [65], and the NAD level is very likely to connect the survival and function of stem cells. The NAMPT-driven salvage pathway plays a predominant role in maintaining the homeostasis of NAD levels. NAD depletion in brain tissue disrupts intracellular energy homeostasis and results in neural cell death [66]. Additionally, cell-autonomous NAMPT is the main source of NAD for NSPCs [67].

In the brain, NAMPT has uniquely strong expression in the hippocampus where adult neurogenesis exists [68,69]. NAMPT is mainly expressed in neurons and in NSCs *in vitro* and *in vivo*, with less expression in glial cells [67–69]. Accordingly, NAMPT is particularly important for the proliferation, self-renewal, and differentiation of NSPCs. Using adult NSPC-specific inducible NAMPT knockout mice, Stein et al. [67] reported that the inactivation of NAMPT in the adult Nestin$^+$ population impaired NSPC proliferation and self-renewal. Acute deletion of NAMPT in hippocampal neurospheres significantly reduced NAD levels in NSPCs and stalled the cells in the G1 phase of the cell cycle. Chronic ablation of NAMPT in hippocampal neurospheres abrogated oligodendrogenesis, and *in vivo* ablation of NAMPT in the adult Nestin$^+$ population reduced NSPC-mediated oligodendrogenesis upon insult.

Nicotinamide phosphoribosyltransferase is a key protein in the defense mechanisms of organisms and plays a critical role in metabolic homeostasis and survival [66]. The NAMPT–NAD–SIRT cascade has been demonstrated as a strong endogenous defense system [66]. NAMPT may contribute to the survival of NSPCs under energy depletion, genotoxic stress, and other insults. In addition, NAMPT may be beneficial for neurogenesis in paracrine and endocrine manners. NAMPT can be secreted by several types of neural cells [45–47] and can cross the blood–brain barrier by unknown mechanisms [46]. In adipocyte-specific NAMPT knockout and knock-in mice, adipocyte-derived NAMPT showed remote action on brain hypothalamic NAD–SIRT1 signaling and physical activity [70]. Our studies also revealed that NAMPT can regulate vascular function in paracrine and endocrine manners [71,72].

How NAMPT regulates proliferation, differentiation, and self-renewal of NSPCs is not fully understood. Current studies showed that the proliferative and prodifferentiation effects of NAMPT–NAD axis on NSPCs require several SIRTs [47,67]. In an *in vitro* model, studies using NMN and siRNA-mediated knockdown of SIRT1-7 revealed that SIRT1 and SIRT2 contribute to NSC proliferation, whereas SIRT1, SIRT2, and SIRT6 contribute to NSC differentiation [47]. In addition, another study showed that NAMPT is vital in oligodendrocytic lineage fate decisions via a mechanism mediated by SIRT1 and SIRT2 [67]. They also suggested the involvement of transcriptional upregulation of cyclins E and A and their upstream regulator E2F1 during NAMPT-mediated NSPC proliferation [67]. Up to now, the mechanism by which NAMPT promotes NSPC self-renewal remains unidentified.

Role of NAMPT in Aging-Associated Neurogenesis

Nicotinamide adenine dinucleotide and NAMPT levels are significantly decreased in diverse organs during aging [73]. Strikingly,

the reduction of NSPC proliferation, self-renewal, and insult-induced differentiation are observed during aging, concomitant with a decreased level of NAD and NAMPT in the hippocampus [67]. Long-term NMN administration combats age-related decline in NSPC functionality and maintains the NSPC pool [67]. Furthermore, age-related mitochondrial dysfunction can be corrected by NAD precursor supplementation [74]. Modulation of the NAD level improves mitochondrial function and prevents age-associated metabolic decline through the activation of the mitochondrial unfolded protein response and FOXO signaling, where the declining NAD level induces a pseudohypoxic state to disrupt nuclear–mitochondrial communication during aging [75,76].

In addition, the NAMPT–NAD axis connects to SIRT signaling, constituting a strong endogenous defense system against various stresses. The activation of SIRTs, which are NAD-dependent histone deacetylases, delays senescence and acts as a regulator of health span and life span [75,77]. Furthermore, SIRT activation has been proposed as a preventative and therapeutic measure against multiple age-associated disorders, including metabolic syndrome [78]. Furthermore, a study showed that SIRT1 delays aging by governing central circadian control to activate transcription of the two major circadian regulators, namely BMAL1 and CLOCK [77], acting synergistically to regulate the expression of the NAMPT gene.

Role of NAMPT in Stroke-Associated Neurogenesis

The relationship between NAMPT and cerebral ischemia has been elucidated in detail [66,79]. NAMPT is a therapeutic target of ischemic stroke, including neuroprotection in acute phase, neovascularization in subacute phase, and neurorestoration in chronic phase [66].

Upon ischemic insult, NAMPT has been shown to support the neurorestoration. Recently, our group demonstrated that the NAMPT–NAD cascade promotes regenerative neurogenesis after ischemic stroke [47]. Compared to wild-type mice, NAMPT transgenic mice shows elevated brain NAD level, enhanced number of NSCs, improved neural functional recovery, increased survival rate, and accelerated body weight gain after MCAO, which are not observed in H247A mutant-NAMPT transgenic mice due to the loss of NAD biosynthetic activity, providing evidence for proneurogenic effects of the NAMPT–NAD cascade [47]. Delayed administration of NMN for 7 days with the first dose at 12 hours post-MCAO, which cannot confer neuroprotection in acute phase, still reduces MCAO-induced death rate during the first week, improves the neuronal recovery, and increases postischemic neurogenesis in the SVZ and DG of MCAO mice [47]. NMN and NAD promote NSC proliferation and differentiation in cultured NSC neurospheres, where NAMPT inhibitor FK866 induces converse effect [47]. Additionally, NAMPT may participate in poststroke synaptic plasticity [66].

Except for the benefits from NAMPT-induced neurogenesis in stroke, NAMPT also confers neuroprotection to reduce OGD-induced injury in neurons [45,46,69,80–82], improves ischemic brain damage, and increases myelinated fibers in the striatum and corpus callosum in the experimental MCAO model [69,83–87]. Moreover, NAMPT indirectly provides a positive microenvironment for neurogenesis by enhancing neovascularization in endothelial cells, vascular smooth cells, and endothelial progenitor cells [88–90]. Our studies have demonstrated that the NAMPT–NAD cascade improves the mobilization and functions of endothelial progenitor cells and promotes the growth of vascular smooth muscle cells [71,91]. Moreover, an increase in newly formed blood vessels was found in the brain's penumbra zone after MCAO in NAMPT transgenic mice, and increased cerebral blood flow at 7 and 14 days was detected in ischemic brain area [89].

With regard to the above-mentioned positive effects of NAMPT in restoring neurogenesis, targeting NAMPT can be applied as a powerful strategy to treat neurogenesis-associated disorders. Although novel NAMPT inhibitors have been discovered recently [92–94], there is no report about NAMPT activators, except for a recent study demonstrating that P7C3 chemicals activate the NAMPT–NAD pathway [95]. Hence, exploring novel NAMPT activators as candidates to treat neurological diseases is quite essential.

P7C3 Neuroprotective Chemicals as Potential NAMPT Activators

The deficiency of effective proneurogenic and neuroprotective drugs to treat neurogenesis-associated disorders, including AD, PD, HD, TBI, and amyotrophic lateral sclerosis as well as age-related cognitive decline, needs to be resolved. Surprisingly, a recent study reported that the administration of active P7C3 chemicals could result in a rebound in the intracellular levels of NAD and protect cultured cells from doxorubicin-mediated toxicity caused by NAD depletion [95]. The evidence showed that P7C3 could bind NAMPT and function by enhancing the activity of the rate-limiting enzyme in the salvage pathway of NAD synthesis [95], suggesting the potential role of the P7C3 family as NAMPT activators.

The Characteristics of Compound P7C3 and Its Derivatives

McKnight's group initially discovered neuroprotective chemicals using an unbiased *in vivo* screen [96]. The authors screened 1000 druglike compounds and found eight compounds with enhanced neuron formation in the SVZ of the DG [96]. Among the compounds, P7C3, an aminopropyl carbazole chemical, has the highest potential of favorable pharmacological properties, with better absorption, distribution, metabolism, and excretion characteristics, and has an appropriate half-life, rate of clearance, and bioavailability [96]. Moreover, P7C3 is orally bioavailable and readily able to cross the blood–brain barrier and is nontoxic at doses several folds higher than the efficacious dose [96].

To further evaluate the properties of P7C3, several more derivatives of P7C3 were designed in an *in vivo* structure activity relationship study to assess its proneurogenic activity [96]. The single derivative of P7C3 (P7C3-A20), replacing the hydroxyl group at the chiral center of the linker with fluorine, exhibits better proneurogenic activity compared to the parent compound [96]. In the follow-up study, (-)-P7C3-S243 was designed with improved

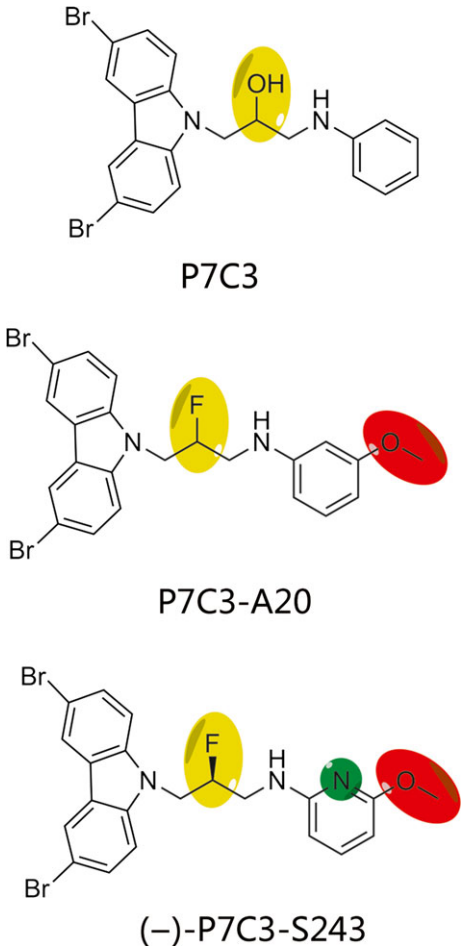

Figure 2 The structures of P7C3 and two active analogs, P7C3-A20 and (-)-P7C3-S243. Parts with yellow, green, and red colors represent modified sites compared to P7C3 [96,97].

druglike properties compared to previously reported compounds, replacing the aniline moiety of P7C3-A20 with an alternative heterocycle [97] (Figure 2). All of the analogs display no observed toxicity, no binding of the hERG channel whose dysfunction causes cardiac toxicity, good blood/brain distribution, oral availability, and excellent metabolic stability in mice, rats, and cell culture [97,98]. P7C3 and its more active analogs, namely P7C3-A20 and (-)-P7C3-S243, have been employed in almost all functional studies to date (Table 1). Based on the aminopropyl carbazole scaffold, Yoon et al. [99] also synthesized a series of aminopropyl carbazole derivatives (compounds 1–26) and screened them in cultured NSCs to assess their biological activity. Among the compounds, compound 9 is safe, is nontoxic to NSCs, and increases the viability of NSCs better than P7C3-A20 [99].

Proneurogenic and Neuroprotective Effects of the P7C3 Family

Prolonged P7C3 administration in adult mice enhances hippocampal neuron formation with no abundance of hippocampal

Table 1 Overview of the proneurogenic and neuroprotective effects of the P7C3 family

Year	Studied chemical	Experimental model	Proneurogenic and neuroprotective effect
2010 [96]	P7C3 and its analogs	NPAS3$^{-/-}$ mouse model of neurological malfunctions	Enhance neuron formation in the SGZ of the DG
		U2OS cell model of calcium-induced mitochondrial dissolution	Rescue NPAS3$^{-/-}$-induced loss of hippocampal neurogenesis
		Aged rat	Ameliorate cognitive decline in aged rat
2012 [102]	P7C3	MPTP-mediated mouse model of PD	Protect mature neurons in the mouse brain region outside of hippocampus
	P7C3-A20	MPP^{+}-mediated worm model of PD	Protect substantia nigra dopaminergic neurons from cell death
2012 [109]	P7C3	G93A-SOD1 mutant mouse model of ALS	Protect ventral horn spinal cord motor neurons from cell death
	P7C3-A20		
2013 [99]	Compound 9	Cultured rat cortical NSCs	Induce neurogenesis to enhance neuronal differentiation and inhibit astrocytogenesis
2014 [108]	P7C3	Depression-prone ghrelin receptor-null mouse model	Increase proliferating DG cell survival and mature neuron formation
	P7C3-A20		Augment hippocampal neurogenesis following focal ablation of hippocampal stem cells
2014 [104]	P7C3-A20	Moderate fluid percussion brain injury rat model of TBI	Increase proliferating neurons and improve cognitive function after TBI
2014 [97]	(-)-P7C3-S243	Mouse model of hippocampal neurogenesis	Protect developing neurons in hippocampal neurogenesis
		MPTP-mediated mouse model of PD	Protect mature neurons within the substantia nigra in PD
2014 [105]	(-)-P7C3-S243	Blast-mediated rodent model of TBI	Block brain axonal degeneration and preserve learning, memory, and motor coordination
2015 [106]	P7C3	Rat model of nerve crush injury	Enhance neuron survival, axonal regeneration and prevent microglia proliferation
2015 [107]	P7C3	Ts65Dn mouse model of DS	Increase hippocampal neurogenesis in Ts65Dn mice
2015 [103]	Compound 1	Cultured rat cortical NSCs	Enhance neurogenesis by increasing final cell division

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; DG, dentate gyrus; DS, Down syndrome; MPP, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NAD, nicotinamide adenine dinucleotide; NPAS3, PAS domain protein 3; NSCs, neural stem cells; PD, Parkinson's disease; SGZ, subgranular zone; TBI, traumatic brain injury.

astrocytes or oligodendrocytes, protecting newborn neurons from cell death during a month-long differentiation instead of increasing cell proliferation [96]. Mice with the loss of the gene encoding the neuronal PAS domain protein 3 (NPAS3) have impaired adult neurogenesis with 3-fold increased cleaved caspase-3-positive (apoptotic) cells in the SGZ, display severe attenuation in dendritic branching and spine density in the DG granular neurons, and have aberrant hyperexcitability of synaptic transmission in the outer molecular layer of the DG and in the CA1 region of the hippocampus compared to wild-type littermates [96,100,101]. Prolonged administration of P7C3 normalizes the elevated levels of hippocampal apoptosis and corrects the deficits in the DG of NPAS3$^{-/-}$ mice but has no effects in the CA1 region of the hippocampus [96]. The administration of P7C3 or its active analogs could protect against mitochondrial dissolution induced by calcium ionophore A23187 and preserve mitochondrial membrane integrity in cultured U2OS cells [96]. Furthermore, P7C3 enhances hippocampal neurogenesis, ameliorates cognitive decline, prevents weight loss in terminally aged rats [96], and shows protection of mature neurons in brain region outside of the hippocampus [102]. Yoon et al. [99] demonstrated that compound 9 could induce neurogenesis and inhibit astrocytogenesis in cultured rat cortical NSCs. Compound 1 was identified to enhance neurogenesis by increasing final cell division to generate neurons during NSC differentiation [103]. Due to the proneurogenic and neuroprotective activity of P7C3 compounds, substantial studies are needed to focus on exploring its role in neurological disease.

In the mouse model of TBI, both proneurogenic and neuroprotective effects account for the anti-TBI effects of P7C3 compounds. Administration P7C3-A20 initially at 30 min postsurgery for 7 days decreases contusion volume, blocks mature cortical neuron death, increases the generation of new hippocampal neurons in the DG, and improves functional neurological outcome at 1 and 4 weeks after TBI [104]. Similarly, long-term administration of (-)-P7C3-S243 blocks widespread axonal degeneration and preserves learning, memory, and motor coordination in TBI mice, given the hypotheses that the protective effects may be regulated by activating NAMPT [105]. Moreover, the administration of P7C3 doubles motor and sensory neuron survival after sciatic nerve crush injury, promotes axon regeneration, enhances behavioral and muscle functional recovery, and reverses pathological mobilization of spinal microglia following neonatal nerve injury, suggesting the potential application of the P7C3 family in nerve injury-related diseases [106].

Down syndrome (DS) is a genetic disease with intellectual disability caused by the triplication of human chromosome 21. Eisch et al. [107] first discovered that patients with DS are marked by diminished adult hippocampal neurogenesis. Surprisingly, chronic P7C3 treatment has no effect on hippocampal neurogenesis in wild-type mice but is sufficient to restore the neurogenic deficits in Ts65Dn mice, an animal model with similar neuropathological features in patients with DS [107]. In addition, Walker et al. [108] found that P7C3 and its analogs exert an antidepressant-like effect in depression-prone ghrelin receptor-null mice exposed to chronic social defeat stress or caloric restriction by increasing hippocampal neurogenesis in which the ablation of hippocampal stem cells with radiation eliminates the antidepressant effect.

Moreover, P7C3 compounds show neuroprotective efficacy to prevent the death of existing mature neurons in neurodegenerative disease; however, no further studies were carried out on neurogenesis in the corresponding disease models. In the mouse model of PD, P7C3 blocks the cell death of dopaminergic neurons in the substantia nigra of adult mice, P7C3-A20 shows greater potency and efficacy, and an antihistaminergic drug Dimebon confers no protection [102]. Of note, (-)-P7C3-S243 is more efficacious than P7C3 and P7C3-A20 in the animal model of PD with almost complete protection [97]. In the mouse model of amyotrophic lateral sclerosis, P7C3 delays disease progression when administration is initiated substantially earlier than the expected time of symptom onset [109]. P7C3-A20 protects ventral horn spinal cord motor neurons from cell death, correlates with the preservation of motor function, and is efficacious when administered at disease onset, where Dimebon is also not active [109].

However, the effects of the P7C3 family on stroke remain unclear. Further studies need to be performed to explore the role of P7C3 compounds in functional recovery poststroke. In addition, there is no study reporting changes in the cellular or plasma NAMPT levels following P7C3 compound administration in any disease model, which may align with their effects on neuroprotection and neurorestoration. More efforts should be made to provide more evidence for P7C3 compounds as NAMPT activators, which will bring hope to patients suffering from neurological diseases.

Recent tremendous progress in techniques and methods has allowed the modeling of human diseases, including how to mimic hippocampal circuitry and neurogenesis in the adult brain. Successful generation of iPSCs from adult human dermal fibroblasts brings hope to novel experimental models [110]. Lancaster et al. [111] initially introduced a human pluripotent stem cell (hPSC)-derived three-dimensional (3D) organoid culture system to develop various discrete brain regions, termed cerebral organoids. Interestingly, cerebral organoids could recapitulate features of human cortical development, that is, characteristic progenitor zone organization with abundant outer radial glial stem cells. In addition, the authors also successfully modeled microcephaly using RNA interference and patient-specific iPSCs [111], suggesting a novel approach to study the human neurodevelopment process and model developmental diseases through the *in vitro* culture of cerebral organoids from hPSCs. Thus, we suggest that P7C3 compounds can be tested in the model of human patient-derived organoids to verify its reported neuroprotective and proneurogenic efficacy.

Conclusions

Adult neurogenesis continues to be a hot topic in the neuroscience field. Due to the intricate structure of the human brain, it is difficult to obtain a detailed process of adult neurogenesis and mimic the process of neurogenesis-associated human disorders. Future studies will aim to unveil the mysterious masks of those diseases and link new detection techniques to neurogenesis in normal or diseased human conditions. In addition, the proposed novel approach, namely 3D culture of organoids, can be used for drug testing to screen more effective and specific chemicals to restore adult neurogenesis. Current studies have provided much evidence supporting NAMPT as a potential therapeutic target to

restore adult neurogenesis. However, more efforts are still needed to fully clarify the mechanisms by which NAMPT regulates the neurogenesis, and its role in neurodegenerative diseases, such as AD and PD. On the other hand, mining NAMPT activators as a powerful therapy is extremely urgent. Meanwhile, the proneurogenic and neuroprotective effects of P7C3 compounds should be further demonstrated in humanized disease models before clinical trials. Finally, the mechanisms of action underlying P7C3 compounds in neurological diseases need to be further explored.

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Conflict of Interest

The authors declare no conflict of interests.

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