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Review

Role of thyroid hormones in different aspects of nervous system regeneration in vertebrates

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ABSTRACT

Spontaneous functional recovery from injury in the adult human nervous system is rare and trying to improve recovery remains a clinical challenge. Nervous system regeneration is a complicated sequence of events involving cell death or survival, cell proliferation, axon extension and remyelination, and finally reinnervation and functional recovery. Successful recovery depends on the cell-specific and time-dependent activation and repression of a wide variety of growth factors and guidance molecules. Thyroid hormones (THs), well known for their regulatory role in neurodevelopment, have recently emerged as important modulators of neuroregeneration. This review focuses on the endogenous changes in the proteins regulating TH availability and action in different cell types of the adult mammalian nervous system during regeneration as well as the impact of TH supplementation on the consecutive steps in this process. It also addresses possible differences in TH involvement between different vertebrate classes, early or late developmental stages and peripheral or central nervous system. The available data show that THs are able to stimulate many signaling pathways necessary for successful neurogeneration. They however also suggest that supplementation with T_4 and/or T_3 may have beneficial or detrimental influences depending on the dose and more importantly on the specific phase of the regeneration process.

1. Introduction

Regeneration of body parts in an adult animal is a remarkable phenomenon occurring in many invertebrates and in some vertebrates such as urodeles. During vertebrate evolution however, regeneration became limited and was almost completely lost in very complex organs such as the mammalian brain (Tanaka and Ferretti, 2009). Damage to the postnatal nervous system (NS) in humans commonly leads to long term deficiencies. While surgery holds promises for healing damaged nerves from minor bruises and compressions, successful recovery from major trauma and neurodegenerative diseases remains a challenge. Comparative research of the organisms and organ systems that normally recover from injury with those where recovery is rare should provide us with a deeper understanding about the fate-determining molecules involved in the process. As such we can compare regeneration in peripheral nervous system (PNS) versus central nervous system (CNS), young animals versus adult ones and anamniotes versus amniotes.

For a successful regeneration to occur, the NS goes through four consecutive phases: (1) an immediate phase with cell death and/or survival mechanisms elicited in response to injury; (2) a cell proliferation phase where new neurons and glial cells are formed; (3) an axon extension and remyelination phase where the injured/new neuron (re)grows the severed axon and myelination is established to ensure the viability of the axon; (4) the target reinnervation phase in which the axons form synaptic contacts with the target tissue and functional recovery is established. The potential for NS regeneration therefore depends on the characteristics and interaction of neurons and glia as well as other surrounding cells. CNS regeneration in adult amniotes is indeed thought to be hampered both by the intrinsic neuronal maturation properties and the presence of an inhibitory environment (Avci et al., 2012). The glia in CNS consists mainly of oligodendrocytes (OLs), astrocytes and microglia while Schwann cells (SCs) and macrophages (non-resident cells that infiltrate during injury) are the main non-neuronal cells present in PNS. This differential distribution of non-neuronal cells across the NS certainly influences the capacity of regeneration (Gaudet et al., 2011).

In an attempt to identify the key regulators acting on neuronal and non-neuronal cells during regeneration, numerous candidate molecules have surfaced, among them the thyroid hormones (THs). THs have been known for long to critically modulate various

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aspects of NS development, and TH-mediated maturation processes are accompanied by loss of regenerative ability of the CNS both in mammals and postmetamorphic frogs (Avci et al., 2012; Gibbs et al., 2011). THs have only recently emerged as essential modulators of regeneration following injury and during neurodegenerative diseases. A literature survey suggests that THs can have beneficial or detrimental effects depending on the time, location and type of NS damage. For instance, in case of multiple sclerosis (MS) in humans, a decrease in cellular TH levels leads to worsening of the condition (Zych-Twardowska and Wajgt, 2001) whereas in Alzheimer's disease (AD) higher circulating TH levels are associated with atrophy (Kalmijn et al., 2000). The present review focuses on the comparison of CNS versus PNS regeneration following injury in adult mammals, summarizing the effects of THs observed in various cell types during the subsequent phases of the regeneration process. This information is compared with data on the influence of TH treatment on NS remodeling/regeneration in fish and amphibians during and after metamorphosis. This approach should help to find out to what extent differences in the response to TH signaling could be involved in shifting the balance from facilitating to inhibiting NS regeneration and vice versa.

2. TH regulation & action

THs are secreted by the thyroid gland into the blood stream. The majority of plasma THs consists of the less active thyroxine (T_4) while the more active form, 3,5,3′-triiodothyronine (T_3), is less abundant (Hulbert, 2000). Upon reaching the target cell, THs are transferred into the cytoplasm by transmembrane TH-specific transporters (Arjona et al., 2011; Friesema et al., 2003; Muzzio et al., 2014; Nakao et al., 2006; Visser et al., 2011) (see Fig. 1). The deiodinases present in the cell soma control the ratio of different forms of THs. In the NS, T_4 is converted to T_3 mainly by the deiodinase type 2 enzyme (D2) while T_4 and T_3 are converted by the deiodinase type 3 enzyme (D3) to rT_3 and T_2 respectively (see Fig. 1). Type 1 deiodinase (D1) can either activate or inactivate THs, but is only expressed at low levels in the NS (Bianco and Kim, 2006). The expression of deiodinases can change according to TH availability in a kind of feedback system. D2 is upregulated in hypothyroid conditions in an attempt to restore normal T_3 levels inside the cells, while D3 expression is increased during thyrotoxicosis (Bianco and Kim, 2006). The heterogeneous distribution of TH transporters and deiodinases across the NS ensures that cellular concentrations of THs can vary from one cell type to another and from one region to another according to the actual needs (Dentice and Salvatore, 2011).

THs mainly signal via nuclear TH receptors (TRs). Vertebrates have two TR subtypes, TRα and TRβ, encoded by two genes, *thra* and *thrb*. For each gene, posttranscriptional splicing generates multiple isoforms that vary among the different vertebrate classes (Darras et al., 2011; Flamant and Gauthier, 2013). Of the wide range of mammalian TRs only TRα1, TRβ1 and TRβ2 are transcriptionally active (Cheng et al., 2010). The expression pattern of these receptors in the NS varies between regions/cell types and also according to developmental stage (Flamant and Gauthier, 2013). Besides nuclear TRs, THs also recognize a transmembrane integrin receptor, αVβ3, as well as cytoplasmic TR variants through which they exert non-genomic effects (see Fig. 1) (Cheng et al., 2010). Thus, in order to decipher the effect of THs on regeneration, it is important to monitor changes in the expression of TH transporters, deiodinases and TRs in specific cell types during the process. Table 1 summarizes the present knowledge on the presence of different deiodinases and TRs in the different cell types of the adult rodent NS and documented changes during regeneration.

3. Effects of THs on cell survival

Rupture or severe injury of an axon is followed by atrophy of the axon from the injury site up to the innervated tissue/cell. In the CNS this is generally accompanied by death of the neuronal cell body too, while the cell body of severed axons in the PNS mostly survives (Kaselis and Šatkauskas, 2013). Axon damage also induces massive loss of OLs in the CNS and the spontaneous formation of new OLs is limited (Almad et al., 2011; McTigue et al., 2001). The SCs in the PNS have a striking regenerative capacity. Surviving SCs spontaneously undergo dedifferentiation and proliferation to reestablish the SC population (Arthur-Farraj et al., 2012). This drew researchers to investigate the factors that can help in the survival of neurons and other cells in the NS.

Neurotrophins like brain derived neurotrophic factor (BDNF), neurotrophic factor 3 (NT-3), NT-4 and glial derived neurotrophic factor (GDNF) are crucial for cell survival and neurite outgrowth (Kaselis and Šatkauskas, 2013), especially during development. While mature cells may be less dependent on these factors, they may need them again upon injury as shown very clearly for BDNF (Shulga and Rivera, 2013). Both BDNF and NT-3 are TH-dependent; they are reduced in hypothyroid and increased in hyperthyroid developing brain (Shulga and Rivera, 2013). Following injury of the adult NS, BDNF mRNA levels are reduced in PNS as well as CNS (Gonzalez et al., 2005; Lipska et al., 2001; Shulga et al., 2009). The TH-dependent regulation of BDNF in adult brain seems however complex and context dependent as shown by experiments in organotypic hippocampal slices (Shulga et al., 2009). In this model, T_4 administration suppressed BDNF mRNA expression in control slices while the same concentration of T_4 upregulated the reduced BDNF mRNA levels in lesioned slices and increased cell survival as well, indicating that the traumatized neurons had re-acquired some immature-like characteristics (Shulga et al., 2009; Shulga and Rivera, 2013). However, it has been shown in rats and humans that severe CNS injury can lead to a condition called non-thyroidal illness syndrome or low T_3 syndrome, strongly reducing circulating T_3 levels. Therefore the massive cell death in CNS following major injury may occur in part due to the absence of a protective, TH-mediated upregulation of BDNF (Shulga and Rivera, 2013) while this is less a problem for PNS injury.

TH administration after injury can rescue cells from dying in both PNS and CNS, as evident from the survival of sensory neurons in dorsal root ganglia (DRG) after sciatic nerve injury (Schenker et al., 2003), hippocampal injury (Shulga et al., 2009) and white matter damage (Hung et al., 2013). It is however important to note that the TH-dependent upregulation of BDNF in injured CNS is non-monotonic and the protective effect of THs against cell death may disappear at high doses (Shulga et al., 2009). This would agree with a study in adult zebra finch where a high dose of T_4 led to increased neuronal cell death, particularly in regions that showed naturally occurring neuronal turnover (Tekumalla et al., 2002). This limitation should certainly be taken into account when considering the possibility of TH treatment for CNS injury.

4. Effects of THs on cell proliferation

Adult neurogenesis relies on the presence of neural stem cells (NSCs) which are found mainly in the ventricular/subventricular zone (VZ/SVZ) of the vertebrate brain (Brus et al., 2013; Kishimoto et al., 2012; Maden et al., 2013). In adult fish, amphibians and reptiles, these NSCs are thought to continue proliferating throughout the brain. In mammals, spontaneous proliferation only occurs in the subgranular zone of the hippocampus and the SVZ of the olfactory bulbs (Maden et al., 2013). THs seem to regulate NSC