Molecular neurochemistry of the lanthanides

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Abstract

Lanthanides, once termed rare-earth elements, are not as sparce in the environment as their traditional name suggests. Mean litospheric concentrations are in faccomparable to the physiologically fundamental elements such as iodine, cobalt and selenium. Recent advances in medical technology have resulted in accumulation of lanthanides presenting potential exposure to both our central and peripheral nervous systems. Extensive and detailed studies on these peculiar active metals in the context of their influence on neural functions are therefore urgently required. Almost all neurochemical effects of trivalent lanthanide ions appear to result from the similarity of their radii to the key signaling ion calcium. Lanthanides, especially La^{3+} and Gd^{3+} block different types of calcium, potassium and sodium channels in human and animal neurons, regulate neurotransmitter turnover and release, as well as synaptic activity. Lanthanides also act as modulators of several ionotropic receptors, e.g. GABA, NMDA, and kainate and can also affect numerous signaling mechanisms including NF-κB and apoptotic-related endoplasmic reticulum IRE1-XBP1, PERK and ATF6 pathways. Several lanthanide ions may cause oxidative neuronal injuries and functional impairment by promoting reactive oxygen species (ROS) production. However, cerium and yttrium oxides have some unique and promising neuroprotective properties, being able to decrease free radical cell injury and even alleviate motor impairment and cognitive function in animal models of multiple sclerosis and mild traumatic brain damage respectively. In conclusion, lanthanides affect various neurophysiological processes, altering a large spectrum of brain functions. Thus, a deeper understanding of their potential mechanistic roles during disease and as therapeutic agents requires urgent elucidation.

Key words: lanthanides, synaptic transmission, oxidative injury, neuroprotection

1. Introduction

Lanthanides, often named “rare earth elements” (REEs) are lustrous, silvery-white or goldish, relatively soft and plastic metals, whose atomic numbers range from 57 to 71 (Fig 1.). For almost a century lanthanides were considered intriguing laboratory curiosities. Sir William Crookes, an outstanding English chemist described them in 1887: ”…These elements perplex us in our researches, baffle us in our speculations and haunt us in our very dreams. They stretch like an unknown sea before us - mocking, mystifying and murmuring strange revelations and possibilities...” Because of their high chemical reactivity, lanthanides never exist in nature as pure elements, but only as sparsely distributed compounds that form rare minerals. Scandium and yttrium, also classified as REEs are not formal members of the lanthanide family, however due to their considerable chemical analogy to this group, they are usually described jointly. Importantly, the ionic radii of La^{3+}, Ce^{3+}, Pr^{3+}, Nd^{3+} and Gd^{3+} are comparable to that of Ca^{2+}, an ion that plays a crucial regulatory role in several cell functions (Pałasz and Czekaj 2000). This particular structural similarity determines the physiological and toxicological effects of soluble lanthanide salts (Xu et al. 2017;Gramowski et al. 2011).

Lanthanides were long considered biologically inert elements, not involved in biochemical pathways. However, a recent discovery of a unique bacterial PQQ-alcohol dehydrogenases that require lanthanides has shed an intriguing light on the physiological actions of these metals (Chistoserdova 2019, Wehrmann et al. 2017; Vu et al. 2016). Moreover, there is new surprising evidence for the existence of some Ce^{3+}-dependent methanol dehydrogenases also in protozoans and invertebrates (De Simone et al. 2018).

Lanthanide compounds frequently have magnetic, catalytic and optic properties and therefore they are currently widely used in industry and medicine. Since both metallic lanthanides and their numerous compounds show an accumulating number of applications, there is an increased possibility of contamination into tissues and organs, potentially affecting metabolic processes. Of particular note, gadolinium-based contrast agents are currently widely used in the MRI diagnostics of both the

CNS and peripheral organs due to their high magnetic moment (Kanda et al. 2014; Adding et al. 2006). These standard paramagnetic contrast agents are considered safe and non-genotoxic, however some patients with preexisting renal disease have reported symptoms of nephrogenic systemic fibrosis or gadolinium deposition disease (Lyapustina et al. 2018; Goischke 2017; Perazella and Rodby 2007). Although brain depositions of mainly linear gadolinium contrasts may also occur, any adverse health effects or structural abnormalities associated with these compounds in the human CNS have so far not been reported (Chehabeddine et al. 2019; Choi and Moon 2019; El-Khatib et al. 2018). Interestingly, a high resolution small animal MRI study revealed that a thulium-based macrocyclic complex may be an accurate sensor of temperature and pH in the rat brain (Coman et al. 2009). The luminescent marker, europium-albumin can be applied to examine blood-brain barrier permeability in experimental lipopolysaccharide induced meningitis (Ivey et al. 2005). Europium- superparamagnetic iron oxide particles may be alsoseful for recent studies on the role of the brain choroid plexus in the mechanism of monocyte movement during neuroinflammatory processes (Milward et al. 2017). Europium probes can bind selectively to some drug sites on human serum proteins that suggests their potential usefulness in current diagnostics and basic pharmacological studies (Shuvaev et al. 2016).

The potential therapeutic applications of the lanthanides, primarily based on their similarity to calcium, have been the basis for research since the early part of the twentieth century (Zhang et al. 2011;Fricker et al. 2006). Currently, cerium nitrate is used as a cream with silver sulfadiazene for the treatment of burns (Vitse et al. 2018;Oen et al. 2012). Lanthanum carbonate (Fosrenol), acts as a phosphate binding agent and has been approved for the treatment of hyperphosphatemia in renal dialysis patients and in calciphylaxis (Aaseth and Bjørke-Monsen 2018; Chan et al. 2014). A lanthanide texaphyrin complex (motexafin gadolinium) has been evaluated in Phase III clinical trials for the treatment of brain metastases in non-small cell lung cancer (Mehta et al. 2009). It is also worth noting, that lanthanide radionuclides;^{166}Ho (usually in a chitosan biodegradable complex form), ^{169}Yb, ^{170}Tm and ^{177}Lu are often applied in oncological brachytherapy in various organs (Ha et al. 2013; Krishnamurthy et al. 2011; Escala-Cornejo et al. 2018).

Accumulating reports show that lanthanides may affect several aspects of neuronal physiology and brain function through regulating the opening of ion channels, modulating synaptic transmission or potentially modifying cellular oxidative equilibrium. As lanthanide ions are able to cross the blood-brain barrier, the toxicological properties of these elements also merit attention. However, despite these potential drawbacks there are a number of recent suggestions that lanthanide oxides, in the form of nanoparticles, may have unique and clinically promising neuroprotective properties under conditions such as ischemic brain injury. We have therefore comprehensively reviewed the growing literature on lanthanides focusing on their role in neuronal physiology.

2. Lanthanides as modulators of neuronal ion channel physiology

Due to the aforementioned molecular analogy with calcium, lanthanide ions have been shown to affect the activity of some neuronal membrane channels, including ionotropic receptors in both the central and peripheral nervous system (Fig.2.). Indeed, numerous metal ions, including lanthanides may modify channel gating or block ion currens (Elinder and Arhem 2003). Because of its uniquely strong gating activity, La^{3+} is sometimes called a “supercalcium” (Brown et al. 1990) and the effects of lanthanides on voltage-gated ion channels including potassium and calcium have been previously reported in diverse cell types (Pałasz and Czekaj 2000). Trivalent lanthanide cations directly block ion flow through neuronal voltage-gated K^+ channels (VGKC) with a potency that varies inversely with the ionic radius (Alshuaib et al. 2005, Enyeart 1998). However, the suppression of K^+ flow by lanthanides seems to be regulated by an alternative mechanism to traditional channel pore occlusion. Lanthanides reduce K^+ currents by altering voltage-dependent gating and modifying ion interactions with Ca^{2+} unspecific binding sites (Watkins and Mathie 1994). A number of non-voltage-gated K^+ channels are also blocked by La^{3+} and Gd^{3+} (Lesage and Lasdunski 2000; Patel and Honore 2001) and an inward rectifier K^+ channel in rat corticotropes is in turn insensitive to La^{3+}

(Kuryshev 1997). Lanthanides can interact with the Ca^{2+}-binding sites of both T and L channels, while calcium-specific or nonspecific lanthanide-binding sites have been identified in the structure of some receptors e.g. glutamate mGluR, acetylcholine and insulin (Pałasz and Czekaj 2000). The blockade of low-voltage-activated T-type Ca^{2+} channels by lanthanides is caused by pore occlusion with a potency that varies inversely with ionic radius (Mlinar and Enyeart 1993); while L-type Ca^{2+} channel inhibition directly correlates with the radius (Lansman 1990). La^{3+} may also enhance Na^{+} current (I_{Na}) of the voltage-gated sodium channel (VGSC) in isolated rat hippocampal CA1 neurons, thus shifting the activation curve to positive potential and decrease neuronal excitability (Du and Yang 2009). This effect was concentration and voltage-dependent and abolished by both La^{3+} elimination and wash out. One can therefore hypothesize, that the La^{3+} binding site is located extracellularly to the sodium channel. Of note, lanthanum may increase the I_{Na} activation even at very low micromolar concentrations span style="font-family:Arial; -aw-import:spaces"> (Du and Yang 2009).

γ-aminobutyric acid (GABA) receptor-dependent pathways are believed to establish the main inhibitory system of the brain. La^{3+} affects $GABA_A$ and increases receptor affinity to the agonist through special domain binding at the chloride channel, distinct from that of picrotoxin, barbiturates, benzodiazepines, Cu^{2+} and Zn^{2+}. This mode of action was described in the pyramidal neurons of hippocampal CA1 area where La^{3+} increases $GABA_A$ affinity to the ligand and potentiates GABA-activated currents (Boldyreva 2005). Lanthanides with higher atomic numbers also have stimulatory effects, the potency of which increases with atomic number. For instance, a study on cultured rat dorsal root ganglion neurons has shown that Tb^{3+} prolongs the opening time of the $GABA_A$ chloride channel (Narahashi et al.1994, Ma and Narahashi 1993). An increased $GABA_A$ sensitivity and enhanced chloride current after La^{3+} administration is also reported for isolated cerebellar Purkyne cells (Kolbaev et al. 2002). It is therefore likely that Tb^{3+} binds to the allosteric active site of the $GABA_A$ receptor-ion channel complex, extending its mean opening time by increasing the affinity of GABA (Ma *et al*., 1994). Lanthanides potentiate the $GABA_A$ response and this effect may vary inversely to the radii of their hydrated ion hence the opening time of the channel and the amplitude of the lanthanide-induced voltage decreases with the atomic number as follows: Lu^{3+}>Er^{3+}>Tb^{3+}>Eu^{3+}>Nd^{3+}>Ce^{3+}> La^{3+}

(Ma *et al*., 1993). Conversely, a voltage clamp study has shown no correlation between the size of the lanthanide ion and the magnitude of the $GABA_A$ current evoked by La^{3+}, Ce^{3+}, Nd^{3+}, Gd^{3+}, Tb^{3+}, Er^{3+} and Yb^{3+} acting on the $GABA_A$ receptor of cholinergic neurons in rats (Kumamoto and Murata, 1996). Another study shows that $GABA_A$-dependent chloride influx to cultured rat cerebellum granule cells was inhibited by La^{3+} (Barila et al. 2001). Lanthanum ions exhibited a potentiating influence on recombinant $\alpha_1\beta_2\gamma_2$ and $\alpha_1\beta_3\gamma_2$ but conversely inhibitory modulation of $\alpha_6\beta_3\gamma_2$ and $\alpha_6\beta_3\delta$ $GABA_A$ receptors (Im et al. 1992; Saxena et al. 1997). The antagonistic La^{3+} effect on native $GABA_A$-Rs in mouse granule neurons is probably caused by its selective binding to $\alpha 6$ subunit (Mäkelä et al. 1999). There are also reports that Gd^{3+} may inhibit the K^+-Cl^- co-transporter (KCC) function and increase intracellular chloride concentration in cultured rat spinal cord neurons. This Gd^{3+} action was abolished by furosemide, a blocker of both KCC and the Na^+-K^+-Cl- co-transporter (NKCC), but not bumetanide, a specific NKCC inhibitor. It is noteworthy that Gd^{3+} did not block the muscimol-induced outward currents recorded by conventional whole-neuron patch-clamp technique. Hence, Gd^{3+} may affect the inhibitory action of brain GABA that is a consequence of relatively hyperpolarized, KCC-dependent chloride-equilibrium (ECl) potential (Ishibashi et al. 2009). Gd^{3+} may decrease the amplitude of proton activated currents in isolated Purkinje cells in a dose-dependent manner, with the intensity of blockade seeming to be independent from membrane potential. Interstingly, Gd^{3+}-related inhibition of the activated receptor was faster and stronger in comparison to the inactivated one. Lanthanide ions may therefore modulate the inhibitory output from cerebellar cortex via regulation of GABA-ergic ganglion cell physiology (Sharonova et al. 2008).

Beyond the modulation of GABA, both La^{3+} and Gd^{3+} act as potent blockers of the vanilloid-type heat-activated ion channels TRPV2 in cultured rat dorsal root ganglion neurons. This finding may help to introduce a new pharmacological tool to distinguish between heat signaling of TRPV2 and the similar capsaicin-receptor, TRPV1, which is strongly sensitized by lanthanides (Leffler et al. 2007). Of interest, Gd^{3+} strongly blocks stretch-sensitive ion channels (SACs) in the sarcolemma of skeletal muscle fibers (Coirault et al. 1999). Both Gd^{3+} and La^{3+} were also potent inhibitors of the lysoplasmenylcholine-induced current and equally delayed the onset of myocyte contractions in the rabbit heart, but surprisingly Gd^{3+} sensitive SACs were

not blocked by this ion (Caldwell and Baumgarten 1998). A recent study reports that both Eu^{3+} and Sm^{3+} exhibit an agonistic affinity to both Ca^{2+}-binding sites of the ryanodine receptor (RyR). Interestingly, the voltage-dependent properties of the aforementioned ion action suggests that the activating Ca^{2+} binding domain is located in the pore entrance of the RyR channel (Sárközi et al. 2017). Several key aspects of synaptic activity and plasticity are strictly controlled by cellular calcium homeostasis (Catterall et al., 2013; Maggio and Vlachos, 2014), therefore some neuronal mechanosensitive, Ca^{2+}-related SACs e.g. Piezo-1 may also play, a so far understudied, role in brain function (Velasco-Estevez et al. 2018). Potentially, both SACs and transient receptor potential (TRP) channels in various types of central and peripheral sensory neurons may be blocked by Gd^{3+} (Mueller-Tribbensee et al. 2015). Among the mammalian transient receptor potential channels (TRPCs) with a Ca^{2+}-permeable pore, only two isoforms TRPC4 and TRPC5 are potentiated by La^{3+} (Jun et al. 2003; Schaeffer 2002), others (TRPC 1-3, and 6-7) are in turn blocked by both La^{3+} and Gd^{3+} (Riccio et al. 2002; Inoue et al. 2001). Interestingly it has also been demonstrated that pretreatment with Gd^{3+} attenuated ischemia/reperfusion-induced infarct size in rats by the blockage of stretch-activated calcium channels (Gulati et al., 2013).

3. Lanthanide action in neurotransmitter release machinery and synaptic function

Lanthanide ions have long been reported to influence synaptic physiology as well as mechanisms of neurotransmitter exocytosis in various types of neurons (Fig.2.). Almost 50 years ago Ricardo Miledi from University College London perceived that La^{3+} are able to block calcium-related neurotransmission (Miledi 1971). Cytophysiological effects of lanthanides result largely from the fact that the sizes of their ionic radii are comparable to that of Ca^{2+} enabling them to compete with calcium at various steps of the synaptic transmission process. It was initially reported that La^{3+}, Gd^{3+} and Lu^{3+} at a concentration of 100 nM–100μM can directly trigger the release of neurotransmitters (Vaccari et al., 1999) but La^{3+} blocks the Ca^{2+}-dependent pathway of exocytosis (Przywara et al., 1992; Vaccari et al., 1999). Possibly, La^{3+}

inhibits the binding of Ca^{2+} to the synaptosome membrane, decreases the neural Ca^{2+} and Mg^{2+} ATPase activity (Basu et al. 1982). However, lanthanide ions cannot replace Na^{+} in its neuronal channels. Later studies indicated that fast triggering of SNARE-related neurotransmitter release by lanthanum is not dependent of La^{3+} influx into neurons (Chung et al. 2008). Potentially, La^{3+} activates an extracellular domain by binding to a presumable presynaptic receptor e.g. glutamate mGluR or nonselective calcium channels (Chung et al. 2008, Smith et al. 2004). Metabotropic GluRs possess binding sites for lanthanides (Abe et al. 2003), thus, the rapid effect of La^{3+} can be also mediated by intracellular Ca^{2+} release from endoplasmic stores. The most noteworthy feature of rapid La^{3+}-triggered neurotransmitter exocytosis is a very strict dependence on synaptobrevin-2 (VAMP-2) presynaptic protein. In murine hippocampal cultured neurons, lack of synaptobrevin-2, but not synaptotagmin-1, silenced the rapid action of La^{3+} in the presynaptic terminal, however the delayed neurotransmitter release was still visible (Chung et al. 2008). This seems rather unexpected given other calcium-related neurotransmitter release cannot be fully blocked in synaptobrevin-2–deficient neurons. Probably, La^{3+} may act at an extracellular site to initiate rapid SNARE-dependent neurotransmission, whereas delayed exocytosis may be caused by slow La^{3+} influx into the neuron (Chung et al. 2008). The multi-faceted activity of La^{3+} at the level of the presynaptic neurochemical machinery might be connected with neurotoxic effects occurring after long-term exposure to soluble lanthanum salts (Feng et al. 2006). On the other hand Gd^{3+} ions trigger calcium-independent neurotransmitter release in a dose-dependent manner and facilitate spontaneous release of the glutamate analogue [3H]D-aspartate. It may suggest that lanthanides induce a vesicular neurotransmitter exocytosis by the mechanisms common for all transitional metals (Lopatina et al. 2005), e.g. Gd^{3+} and La^{3+} trigger neurotransmitter release in rat brain synaptosomes. Interestingly the application of RGDS peptide, an inhibitor of integrins, significantly decreased Gd^{3+}-induced aspartate release with no effect upon hypertonicity-evoked fusion. Genistein, a selective blocker of tyrosine kinases; and citrate, an inhibitor of lanthanides-dependent aggregation, did not abolish the neurotransmitter exocytosis. It suggests that integrins contribute to the Gd^{3+}-evoked aspartate release (Waseem et al. 2008). Interestingly, Eu^{3+} may inhibithe cellular uptake of norepinephrine acting as NERT blocker (Bryan-Lluka and Bonish, 1997).

Glutamate signaling plays a fundamental role in the neurochemistry of memory, cognitive tasks, attention, affective control and developmental synaptogenesis (Robbins and Murphy 2006; Deng et al. 2007). Recent findings prove that lanthanides may affect the NMDA receptor-related long-term potentiation (LTP) in the rat hippocampal CA1 neurons and damage spatial learning and memory. For instance, La^{3+} increased NMDA receptor NR1, NR2A and NR2B subunit expression that may impair cognitive and memory processes (Hu et al. 2018; Du et al. 2015). The expressions of glutamate/aspartate transporters (GLAST and GLT-1), glutamine syntethase (GS) and phosphate-activated glutaminase (PAG) were decreased. This NMDA receptor overactivation causes glutamate-induced excitotoxic neuronal injury and is usually connected with Ca^{2+} excess and apoptosis (Sun et al. 2018a).

Furthermore, disturbed intracellular calcium balance may disintegrate mitochondrial physiology and eventually trigger apoptosis. Lanthanum-related neurotoxicity may also be due to modulation of NO-cGMP signaling mechanisms; La3+ ions increase both calcium and glutamate levels in the rat hippocampus. A dose-dependent increase of inducible nitric oxide synthase (iNOS) expression as well as elevated NO and cGMP levels were also observed (Du et al. 2015). La^{3+} and Gd^{3+} are also antagonists of AMPA and kainate glutamatergic receptors (KARs) in cultured rat hippocampal, cortical and dorsal root ganglion neurons, possibly due to their direct interaction with the ligand molecule rather than competitive antagonism or channel pore blockade (Hong et al. 2004, Huettner et al., 1998). Interestingly, AMPA receptors require around 20-times higher concentrations of lanthanide ions (100 micromoles) for their half-maximal blockade than KARs. Gd^{3+} potently reduces AMPA receptor desensitization and exposes some properties of the positive modulators of AMPA-R activity (Lei and MacDonald 2001). La^{3+} may also distinctly reduce p-IKKα/β and p-IkBα in the rat hippocampus that inhibit the NF-κB signaling pathway. Because NF-κB signaling appears to be involved in the process of memory consolidation (O'Sullivan et al. 2010), it should not be excluded that learning impairment observed in rats exposed to La^{3+} is due to inhibition of this regulatory system. Indeed, the highly decreased expression of c-Fos, c-jun and BDNF seems to support this hypothesis (Zheng et al. 2013). A La^{3+}-dependent impairment of hippocampal memory processing may be also associated with a suppression of the

ERK/MSK1 signaling system and presence of significant abnormalities in the synaptic ultrastructure e.g. non-uniform membrane curvature and flattened postsynaptic density (Liu et al. 2014).

On the other hand, a recent report suggests that these cognitive disturbances may be additionally enhanced by neuronal autophagy process in hippocampal neurons. Possibly, La^{3+} generates oxidative stress that activates JNK/c-Jun and JNK/FoxOs but supresses AKT/mTOR signaling pathways and eventually promotes the origin of autophagosomes (Gao et al. 2019). It should also be taken into account that La-dependent memory and learning deficits can be related to the inhibition of astrocyte-neuron lactate shuttling in the hippocampal neurons, caused mainly by the downregulation of astrocyte monocarboxylate transporter 1, 2 and 4 (MCT 1 2 and 4) expression and a decrease in lactate dehydrogenase (LDH) content and activity (Jin et al. 2017). A suppression of lactate turnover in astrocytes may therefore be considered as an alternative mechanism of the potentially neurotoxic action of La^{3+} in the brain (Sun et al. 2018b).

4. Lanthanides and neuronal oxidative stress

Oxidative stress is a complex and dynamic process of cellular deterioration, caused by an imbalance between the generation of reactive oxygen species (ROS) and the availability and action of superoxide scavengers or other antioxidant factors (Du et al., 2009). It is well known that aerobic cells are susceptible to the effects of oxidative stress. However, the central nervous system is especially vulnerable to the action of ROS due to different causes and mechanisms, including: high consumption of oxygen to carry out physiological processes (about 20% of the bloodstream oxygen), high composition of polyunsaturated fatty acid and the selectivity of the blood-brain barrier which reduces the diffusion of some antioxidants such as vitamin E tocopherols (Schula et al., 2011). ROS levels in oxidative stress trigger processes of neurodegeneration and cell death, mainly affecting mechanisms of lipid peroxidation and structural damage to proteins and DNA (Markesbery et al., 2007). In the last decade, oxidative stress has been associated with

neurodegenerative diseases such as Azheimer's disease (Lovell and Markesbery, 2007), Parkinson's disease (Nikam et al., 2009; Zhou et al., 2008) and amyotrophic lateral sclerosis (Chi et al., 2007); disorders of the autistic spectrum (Gónzalez-Fraguela et al., 2013) and neuronal hyperexcitation (Cardenas-Rodriguez et al., 2013).

As mentioned above, lanthanides present different applications in agriculture, technological industry, pharmacology and biomedicine, due to the diversity of their physical, chemical and biological effects. However, the effects of their accumulation on the human body are still controversial, especially at the level of the central nervous system. In this regard, Zhao et al (2011) demonstrated that three lanthanides produced direct or indirect injury to the mouse brain. In this study, mice were injected with $LaCl_3$, $CeCl_3$ and $NdCl_3$ in the abdominal cavity and monitored for migration, with the compounds detected in the forebrain, causing nervous tissue damage, oxidative stress and subsequently altering the normal metabolism of neurochemicals. La^{3+}, Ce^{3+} and Nd^{3+} increased both ROS production and lipid peroxidation. Brain activities of the main endogenous antioxidant enzymes: superoxide dismutase (SOD), catalase, ascorbic acid and glutathione peroxidases (APx, GSH-Px) were in turn strongly reduced (Zhao et al. 2011, Fig.3.).

Posterior studies (Yang et al. 2013) also found that in the hippocampus of rats exposed to $LaCl_3$ a neuronal deterioration and increased level of apoptosis occurred. This was mainly due to an elevation in the glutamate and intracellular Ca^{2+} concentrations and in the ratio between proapoptotic Bax and antiapoptotic Bcl-2 protein (Wu et al. 2013). La^{3+} may therefore affect the neuronal excitability, neurotransmitter turnover and metabolic pathways via oxidative stress and cholinergic signaling impairment. Of note, La^{3+} may increase ROS concentration and trigger apoptosis in neuroglia. It was found that La^{3+} downregulated Nrf2 gene expression and reduced the activity of SOD, dehydrogenase quinone 1 (NQO1), heme oxygenase-1 (HO-1), glutathione peroxidase 1 ($GSH\text{-}Px_1$) and glutathione-s-transferase (GST) in cultured rat astrocytes (Zhang et al. 2017). On the other hand, L-cysteine may be cautiously considered as a neuroprotective agent against chronic, potentially toxic exposure to soluble lanthanide compounds (Liapi et al. 2009).

It was also found that intragastric administration of $CeCl_3$ to mice significantly affected learning ability, due to an alteration in homeostasis of trace elements, enzymes and neurotransmitters in the brain (Zha et al. 2011). Cerium compounds

are increasingly used in industry, including fertilizers and have been shown to enter the ecological environment and human body via food chains (Ni, 2002; Hu; et al.; 2004; Kostova, 2005), It is therefore paramount to understand potential long-term neurotoxic effects. Another study by Zhe et al. (2013) reports that the exposure of $CeCl_3$ in mice increases oxidative stress in the hippocampus, besides altering 154 genes involved in multiple processes such as learning and memory, programmed neuron death, response to stress, immunity and inflammation. A study by Cheng et al. (2013) reports that long-term exposure to $CeCl_3$ supports ROS production and triggers apoptosis in the mouse hippocampus. Ce^{3+} significantly increased the expression of apoptosis-related genes e.g. antagonizing transcription factor (TRB), ubiquitin-conjugating enzyme e2 (UBE2V1), cysteine-serine-rich nuclear protein1 (AXUD1) and cell division 37 homolog (CDC37). The expression of several genes involved in the neurochemistry of memory and learning such as Fos, Adcy8 and Slc5a7 were in turn down-regulated. Indeed, a significant impairment of spatial recognition memory also occurred (Cheng et al. 2013). All mentioned genes are therefore considered as potential biomarkers of lanthanides neurotoxicity.

Gadolinium, a lanthanide whose derivatives have been widely used as a contrast medium in magnetic resonance (Adding et al., 2006), has been shown to induce the generation of ROS in human liver cells (Liu et al., 2003). A study by Xia et al (2011) confirmed that the oxidative stress caused by this element triggers the stress of the endoplasmic reticulum in rat cortical neurons, causing neuronal death, mainly due to a significant increase in Ca^{2+} concentration. Gd^{3+} supports the ROS origin in neurons but the mechanism of their action is different from that of La^{3+} (Dong et al. 2009) and the greater studied more toxic ions e.g. Al^{3+} and Cd^{2+} (Toimela and Tähti 2004; Niu et al. 2005). Furthermore, Gd^{3+} does not bind to thiol groups and has no significant redox activity. It is likely, that Gd^{3+} may affect the endoplasmic reticulum IRE1-XBP1, PERK and ATF6 pathways, increase GRP78 expression that finally induces an unfolded protein response (UPR) signaling route. These molecular events activate CCAAT/enhancer binding protein homologous protein (CHOP or Gadd153) and trigger apoptosis (Xia et al.2011). Interestingly, the N-acetylcysteine application may eliminate oxidative neurotoxic effects of Gd^{3+}.

On the other hand, new drugs containing lanthanide ions have appeared in the pharmaceutical industry in recent years, based on the similarity of their biological properties with calcium. It has been observed that lanthanides can act as

antioxidants or pro-oxidants, depending on the environment, nature of binding and tissue concentration. Their strong affinity to reactive oxygen species intervenes in the elimination of free radicals, producing non-toxic compounds and exerting antioxidants *in vivo*. However, this property is in turn responsible for the competitive binding of lanthanides to proteins, altering several biologically relevant electron transfer pathways and finally resulting in toxicity (Valcheva-Traykova et al., 2014). More research is therefore needed for their application in the field of medicine, since its use requires a positive balance between antioxidant activity and toxic effects.

5. Neuroprotective properties of lanthanide oxides nanoparticles

One of the most intriguing properties of lanthanides is their neuroprotective effect – ability to protect different cells from various forms of dangerous oxidative and nitrosative stress present in pathological conditions by its modulation (Fig.4.). Conventional antioxidants that are currently available scavenge a single free radical before they are destroyed in the process, so there is a pressing need to find novel targets with therapeutic potential. Most researchers have focused on neuroprotective and pharmaceutical properties of cerium oxide (CeO_2) nanoparticles (CeNPs), also known as nanoceria, which are widely used as inorganic catalysts in industrial material applications, because of their potent free radical-scavenging properties via dual oxidation state (Rzigalinski et al., 2017). Nanoceria are able to either donate or receive electrons as they alternate between the +3 and +4 valence states and their catalytic activities mimic those of the neuroprotective enzymes superoxide dismutase and catalase.

A breakthrough study was published by Schubert et al. (2006), where nanoparticles composed of cerium oxide or yttrium oxide were seen to protect nerve cells from oxidative stress, with neuroprotection independent of particle size. The

researchers established that both types of lanthanide nanoparticles act as direct inorganic antioxidants to limit the amount of reactive oxygen species required to kill cells. Two years later it was experimentally proven that the application of a single dose of nanoceria at a nanomolar concentration is biocompatible, regenerative and provides a significant neuroprotective effect on adult rat spinal cord neurons (Das et al., 2008). The possibility of nanoceria application to prevent ischemic insult was also suggested from an oxidative injury assay. Estevez et al. (2011) took up this research problem and have explored the use of nanoceria as a potential therapeutic agent for stroke using animal model of cerebral ischemia. They found that ceria nanoparticles reduce ischemic cell death by approximately 50%. This effect was caused by reduction of superoxide (O(2)(•-)) and nitric oxide concentrations, decrease of the ischemia-induced 3-nitrotyrosine levels and a modification of tyrosine residues in proteins affected by the peroxynitrite radicals, which are crucial in the dissemination of oxidative injury in biological tissues.

Nanoceria's efficacy in neutralizing biologically generated free radicals has been tested also by the Heckman et al. (2013). They report the *in vivo* characteristics of CeNPs, with ~4.0 h half-life, in an animal model of immunological and free-radical mediated oxidative injury leading to neurodegenerative disease (mice with a murine model of multiple sclerosis). The administered intravenously CeNPs were well tolerated, able to penetrate the brain, reduce reactive oxygen species levels, and alleviate clinical symptoms and motor deficits. Ciofani *et al.* (2013, 2014) have published two articles based on their studies on the PC12 cell line that represents a valuable model for many features of central dopaminergic neurons. As it was expected nanoceria confirmed a potent anti-reactive oxygen species action but, interestingly, also showed beneficial effects on both neuron-like cell differentiation and dopamine production. Experimental evidences at a gene level reveal that CeNPs modulate transcription of genes involved in natural cell defenses, down-regulate genes involved in inflammatory processes, and up-regulate some genes involved in neuroprotection. Nanoceria may also be potentially helpful in the treatment of Alzheimer's disease, because its well known that nitrosative stress caused by peroxynitrite and mitochondrial dysfunction participate in the pathogenesis of this disorder. Application of CeNPs reduces levels of reactive nitrogen species, protein tyrosine nitration Aβ-induced mitochondrial fragmentation and neuronal cell death after exposure to peroxynitrite (Dowding et al., 2014).

Additionally it was presented that nanoceria are internalized by perikarya and accumulate at the mitochondrial outer membrane and plasma membrane. Assessment of the CeNPs axonal translocation conducted on the frog sciatic nerve fibers in an *ex vivo* preparation have demonstrated, that CeO_2 nanoparticles translocate within the nerve (Kastrinaki et al., 2015). This movement depends on both axonal integrity and electrical activity and its speed is similar to the slow axonal transport rate.

Recently more attention has been focused on the role of microglia in neuropathological processes. The ability of CeNPs to mitigate neurodegeneration by microglial activation and related inflammatory processes has been studied via exposure of rats to high intensity light (Fiorani et al.2015). Nanoceria maintained retinal visual response after light-induced damage and reduced neuronal death and "hot spot" extension preserving outer nuclear layer morphology. There was also recently reported that a single administration of nanoceria into the vitreous body exerted long-term neuroprotective effects on rat retina (Tisi et al. 2019). These findings support the hypothesisthat CeNPs may be potent therapeutic agents in retinal neurodegenerative events and correlate with a previously published study (Kong *et al*.2011) reporting that in the mutant mouse, which exhibits progressive cochlear and retinal degeneration, nanoceria protect the retina by decreasing reactive oxygen species, up-regulating of the neuroprotection-associated gene expression, down-regulating apoptotic signaling and/or enhancing survival pathways. Another example of usefulness and potential of CeNPs for mitigating neuropathological effects and modifying the course of recovery after injury is a study by Bailey et al. (2016). It was shown that nanoceria reduce neuronal death and calcium dysregulation after *in vitro* trauma, preserve endogenous antioxidant systems and decrease macromolecular free radical damage. Furthermore, it improves cognitive function in the rat model of mild lateral fluid percussion brain injury which generally is associated with oxidative stress, mitochondrial dysfunction and poor functional outcome. A neuroprotective and antioxidant role for CeNPs was well documented by Ranjbar *et al*. (2018) using the paraquat-induced model of oxidative stress in male rats. CeNPs in groups co-administered with paraquat significantly ameliorated lipid peroxidation, DNA damage, and caspase-3 levels while increasing antioxidant capacity and total thiol molecule contents as well as enhancing nestin and Neurod1 mRNA levels in the brain. According to the current

state of neurobiological knowledge, one of the possible directions of lanthanide therapeutic action is the modulation of neurogenesis. Using polyethylene glycol-coated CeNPs, Arya et al. (2016) have evaluated the neuroprotective, as well as the cognition-enhancing activities, of nanoceria during hypobaric hypoxia via relation with generation of reactive nitrogen and oxygen species. A presence of CeNPs in the rodent brain resulted in significant reduction of oxidative stress and associated hypoxia-related injury. Moreover, nanoceria ameliorated hypoxia-induced memory impairment and stimulated neuronal survival and neurogenesis in the hippocampus.

The most recently published research concerned the anti-inflammatory properties of nanoceria (Hekmatimoghaddam et al., 2019). This study, based on the brain neuroinflammation model induced by both proteolipid protein and parathion, showed that the expression of interleukins (IL-6, 10 and 17) genes and their serum levels were significantly decreased after administration of gelatin hydrogel containing cerium oxide nanoparticles coated with interleukin-17. Collectively, the above studies suggest that nanoceria should be considered as very promising therapeutic agent, especially in the treatment of ischemic brain injuries and neurodegenerative diseases. However, there are still many concerns related to the pharmacological effects of CeNPs and further studies are needed to confirm their potential clinical usefulness.

6. Concluding remarks

The era when a few specialized scientists were exposed with lanthanide compounds are definitely over. Nowadays, due to the dynamic development of electronic technologies and modern medical diagnostics, almost everyone may be exposed to lanthanide-containing substances. Screen luminophors, strong magnets, computer memories, MRI contrast agents and even flints for lighters are everyday sources of these elements. The risk of potential penetration of lanthanides into the human body including the central nervous system is therefore significantly increased. It is likely that lanthanide ions uniquely modulate several important neurochemical processes, thus altering functions in both neurons and glial cells. The majority of cytophysiological and potentially toxic effects of lanthanides observed at the level of neuronal ion channels, receptor molecules and synaptic machinery result largely

from the fact that the sizes of their ionic radii are similar to that of calcium. Some lanthanide ions are frequently applied in basic pharmacological studies as selective blockers of ionotropic receptors. Lanthanides are also considered to impair mitochondrial functions and SER functions and initiate the oxidative injuries of the nervous tissue. On the other hand, cerium and yttrium oxides in the form of nanoparticles seems to be very promising neuroprotective agents after ischemic brain injury in preclinical studies. Given, that all the aforementioned intriguing mechanisms of lanthanide effects on neuronal and glial biochemistry are still poorly understood, this field requires urgent further focus.

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Figure captions

Fig.1. An outline of chemical characteristics of the lanthanides, scandium and yttrium.

Fig.2.A collective scheme of the main effects of lanthanides on synaptic transmission and neuronal physiology. An expression of several neuronal receptors, membrane transporters, regulatory proteins and their genes as well as activity of some enzymes can be modulated by lanthanide ions. Lanthanum, the best surveyed member of the rare-earths family may facilitate the neurotransmitter release via activation of synaptobrevin-2 molecule Lanthanum may also stimulate the GABAA receptor to open chloride channel and cause postsynaptic hyperpolarization. Additionally it is able to affect the voltage-gated potassium and sodium channels (VGSC, VGKC), AChE activity and to trigger the neural apoptosis through the stimulation of Bax and inhibition of Bcl-2 expressions. Cerium increases the expression of apoptosis-related genes e.g. antagonizing transcription factor (TRB), ubiquitin-conjugating enzyme e2 (UBE2V1), cysteine-serine-rich nuclear protein1 (AXUD1) and cell division 37 homolog (CDC37); while suppressing several genes involved in the neurochemistry of memory and learning e.g. Fos, Adcy8 and Slc5a7.Abbreviations: AChE;acetylocholinoesterase, AMPA; α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptor, Axud1; cysteine-serine-rich nuclear protein1, Adcy8;calcium-stimulated adenylyl cyclase, Cdd37; cell division 37 homologue, Fos; proto-oncogene AP-1 transcription factor subunit, G; protein G, GLAST;glutamateaspartate transporter GS; glutamine syntethase, KAR; kainate glutamatergic receptor, mGluR; metabotropic glutamate receptor, NERT; norepinephrine transporter, NMDA; N-methyl-D-aspartate glutamatergic receptor, PAG; phosphate activated glutaminase, Slc5a7; solute carrier family 5 member 7 gene, SNARE; soluble NSF attachment protein, TRPVs; vanilloid-type heat-activated ion channels,Ube2v1; ubiquitin-conjugating enzyme e2, VGKC; voltage gated potassium channel, VGSC; voltage gated sodium channels.

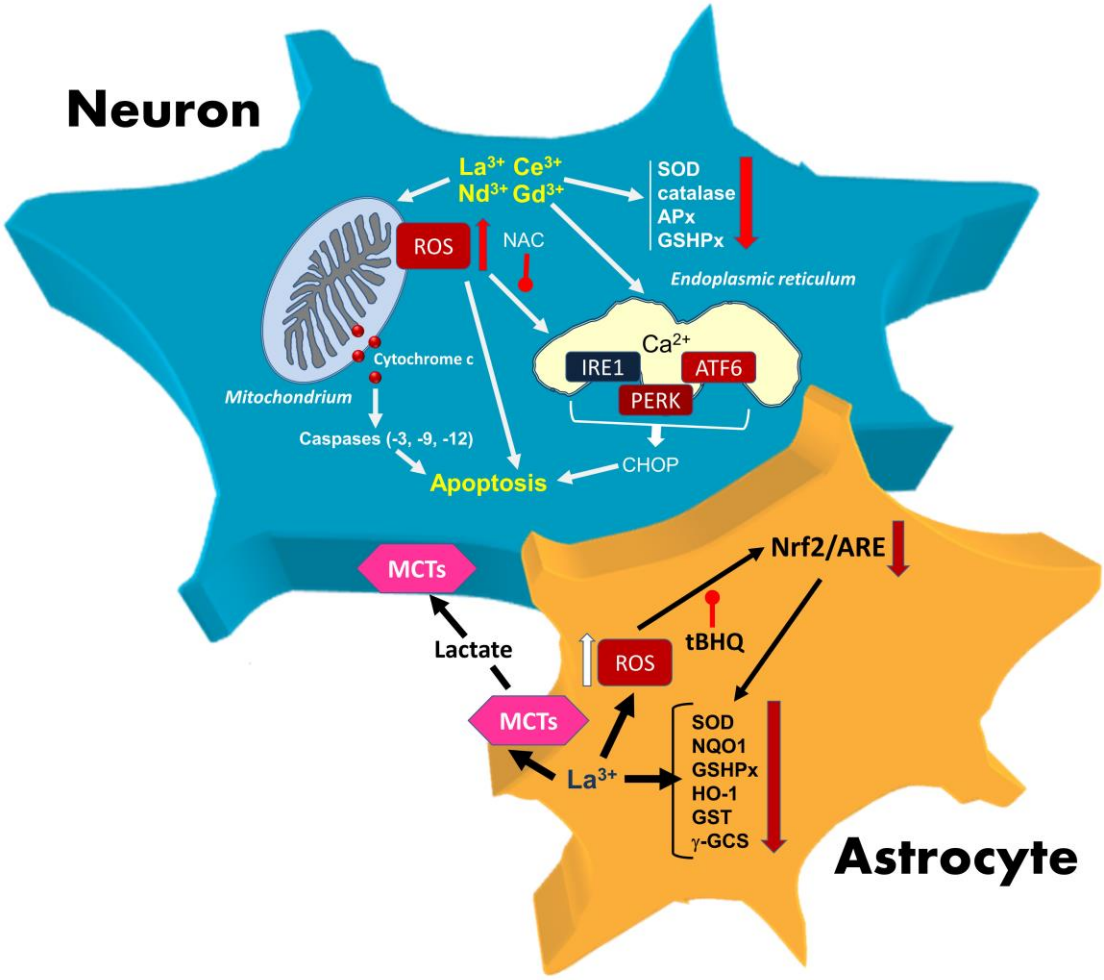
Fig.3. Mechanism of lanthanides-induced oxidative injury in neurons and astrocytes. Lanthanum promotes both ROS production and lipid peroxidation in neurons and astrocytes and decreases activities of key endogenous antioxidant enzymes: superoxide dismutase (SOD), catalase, ascorbic acid and glutathione peroxidases (APx, GSH-Px). Gadolinium with a minimal redox activity does not bind to thiol groups but affects the endoplasmic reticulum IRE1-XBP1, PERK and ATF6 pathways, increasing GRP78 expression that finally trigger unfolded protein response (UPR) signaling pathways via the CCAAT/enhancer binding protein homologous protein (CHOP or Gadd153) activation apoptosis is triggered. Abbreviations: CHOP; CCAAT/enhancer binding protein homologous protein, GST;

glutathione-S-transferase, γ-GCS; γ-glutamine cysteine synthase, HO-1; hemeoxygenase1, NAC; N-acetylcysteine, NQO1; dehydrogenase quinone 1, Nrf2/ARE;nuclear factor erythroid-derived 2-like 2 antioxidant response, TBHQ;tertbuthyl-hydroquinone, UPR; unfolded protein responses.

Fig.4. Neuroprotective effects of lanthanide compounds.

Element	Ion forms	Ionic radii (pm)	Electronegativity (Pauling scale)	Electron configuration	Discovery
Lanthanum	La^{3+}	122	1.10	$[Xe]5d^16s^2$	C. G. Mosander, 1839, Stockholm
Cerium	Ce^{3+} Ce^{4+}	107, 94	1.12	$[Xe]4f^26s^2$	J. J. Berzelius, W. Hisinger, 1803, Sweden
Praseodymium	Pr^{3+}	106	1.13	$[Xe]4f^36s^2$	K. Auer von Welsbach, 1885, Vienna
Neodymium	Nd^{3+}	104	1.14	$[Xe]4f^46s^2$	K. Auer von Welsbach, 1885, Vienna
Promethium*	Pm^{3+}	106	1.13	$[Xe]4f^56s^2$	J. A. Marinsky, L.E. Glendenin, C.D Coryell, 1945, USA
Samarium	Sm^{2+} Sm^{3+}	111, 100	1.17	$[Xe]4f^66s^2$	P. E. Lecoq de Boisbaudran, 1879, Paris
Europium	Eu^{2+} Eu^{3+}	112, 98	1.20	$[Xe]4f^76s^2$	E. A. Demarçay, 1901, Paris
Gadolinium	Gd^{3+}	97	1.20	$[Xe]4f^75d^16s^2$	J. C. Galissard de Marignac, 1880, Geneva
Terbium	Tb^{3+} Tb^{4+}	93 , 81	1.22	$[Xe]4f^96s^2$	C. G. Mosander, 1843, Stockholm
Dysprosium	Dy^{3+}	91	1.22	$[Xe]4f^{10}6s^2$	P. E. Lecoq de Boisbaudran, 1886, Paris
Holmium	Ho^{3+}	89	1.23	$[Xe]4f^{11}6s^2$	P. T. Cleve, 1878, Uppsala (Sweden)
Erbium	Er^{3+}	89	1.24	$[Xe]4f^{12}6s^2$	C.G. Mosander, 1842, Stockholm
Thulium	Tm^{3+} Tm^{4+}	104, 94	1.25	$[Xe]4f^{13}6s^2$	P. E. Lecoq de Boisbaudran, 1886, Paris
Ytterbium	Yb^{2+} Yb^{3+}	113, 86	1.22	$[Xe]4f^{14}6s^2$	J. C. Galissard de Marignac, 1878, Geneva
Lutetium	Lu^{3+}	85	1.27	$[Xe]4f^{14}5d^16s^2$	G. Urbain, 1907, Paris
Scandium	Sc^{3+}	83	1.36	$[Ar]3d^14s^2$	L. F. Nilson, 1879, Uppsala (Sweden)
Yttrium	Y^{3+}	106	1.22	$[Kr]4d^15s^2$	J. Gadolin, 1794, Ábo (Finland)

*radioactive, artificially obtained element, not found in nature on Earth


Neuron
La3+ Ce3+
Nd3+ Gd3+
SOD
catalase
APx
GSHPx
ROS
NAC
Endoplasmic reticulum
Ca2+
IRE1
ATF6
PERK
CHOP
Cytochrome c
Mitochondrium
Caspases (-3, -9, -12)
Apoptosis
MCTs
Lactate
Nrf2/ARE
tBHQ
ROS
MCTs
La3+
SOD
NQO1
GSHPx
HO-1
GST
γ-GCS
Astrocyte

Lanthanide compound	Neuroprotective effects	References
Nanoceria Cerium oxide (CeO_2)	decrease of interleukin IL-17, IL-10, and IL-6 gene expressions and their serum levels in the brain inflammation model	Hekmatimoghaddam et al. 2019
	amelioration of the oxidative DNA damage and caspase-3 level , increasing total antioxidant capacity and total thiol molecules, enhancing nestin and Neurod1 mRNA expression levels in the rat brain	Rajnbar et al. 2018
	reduction of reactive oxygen species levels, alleviation of clinical symptoms and motor impairment in mice with an animal model of MS	Heckman et al. 2013
	decrease of macromolecular free radical neuronal injury, improvement of cognitive function after *in vivo* mild traumatic brain damage	Bailey et al. 2016
	reduction in reactive oxygen species, decrease of the ischemia-induced 3-nitrotyrosine levels, a modification to tyrosine residues in proteins affected by the peroxynitrite radical in the mouse hippocampal slices in animal model of cerebral ischemia	Estevez et al. 2011
	decrease of reactive nitrogen species levels and protein tyrosine nitration in neurons exposed to peroxynitrite, reduction of peroxynitrite and Aβ-induced mitochondrial fragmentation	Dowding et al. 2014
	reduction of microglial activation and their migration toward outer nuclear layer in the rat light-damaged retina photoreceptor cells	Fiorani et al. 2015
	a potent anti-reactive oxygen species activity, improvement of both cell differentiation and dopamine production in cultured neuron-like PC12 cells	Ciofani et al. 2013
Yttrium oxide (Y_2O_3)	limitation of the amount of reactive oxygen species required to kill the cells	Schubert et al. 2006
Gadolinium chloride ($GdCl_3$)	significant attenuation of ischemic reperfusion-induced infarct size, behavioral and biochemical changes in mice brain	Gulati et al. 2013