Preface

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Nervous systems disorders represent one of the leading and ever-increasing adverse health outcomes worldwide. Protecting the nervous system remains a high priority, even though progress to develop neuroprotective agents remains disappointingly slow. In an ongoing attempt to enhance treatment approaches for nervous system disorders, clinical and basic researchers and drug developers and regulators meet every two years to present new perspectives and evaluate progress of neuroprotective strategies.

The purpose of the International Conference on Neuroprotective Agents (ICNA) is to bring together clinical and basic science researchers from many countries and disciplines in a common forum to address various approaches to neuroprotection in extremely pleasant surroundings. It is within such a small and congenial structure that ideas and concepts can be most freely exchanged in a stimulating and relaxed venue. A relatively large number of speakers are afforded the opportunity to present their most recent data and views on neuroprotection.

The 11th ICNA was held at the rustic and beautiful L'Hôtel-Musée Premières Nations, Wendake, near Quebec City, Canada, on September 30–October 3, 2012. The usual format of oral presentations Monday morning and afternoon and Tuesday and Wednesday mornings, with an evening poster session and

social gathering Monday, was followed. The 14 papers that comprise this special issue of *Molecular Neurobiology* were part of the 11th ICNA. As in the nine prior ICNA meetings, the articles in this special issue span the gamut of pathways to neurotoxicity and neuroprotection, neuroprotection approaches and agent evaluation, and the impact of nanomaterials on neurotoxicity and neuroprotection.

In the first grouping of pathways to neurotoxicity and neuroprotection, Jeonghan Lee and coauthors from Slobodan Todorovic's laboratory investigated the role of T-type calcium channels in the dorsal root ganglia as having a central function in tuning neuronal excitability and altering sensory processing including pain. Previous studies have implicated redox agents in control of T-channel activity; however, the mechanisms involved are not fully understood. They observed that extracellular application of nitrosoglutathione (GSNO) and *S*-nitroso-*N*-acetyl-penicillamine rapidly reduced T-type current amplitudes. GSNO did not affect voltage dependence of steady-state inactivation and macroscopic current kinetics of T-type channels. Expression of wild-type $\text{Ca}_v3.2$ channels or a quadruple Cys-Ala mutant in human embryonic kidney cells revealed that Cys residues in repeats I and II on the extracellular face of the channel were required for channel inhibition by GSNO. The authors propose that SNO-related molecules *in vivo* may lead to alterations of T-type channel-dependent neuronal excitability in sensory neurons and in the central nervous system (CNS) in both physiological and pathological conditions such as neuronal ischemia/hypoxia.

In the second report in this grouping, Teng and co-workers functioning in Anya Lin's laboratory describe the role of heme oxygenase (HO)-1 in arsenite-induced neurotoxicity investigated using primary cultured cortical neurons. Incubation with sodium arsenite (arsenite) was found to cause cell death of primary cultured cortical neurons in concentration- and time-dependent manners. Furthermore, arsenite induced caspase 3 activation and decreased procaspase 12 levels, indicating that

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apoptosis is involved in the arsenite-induced neurotoxicity. The oxidative mechanism underlying arsenite-induced neurotoxicity was investigated. Western blot assay showed that arsenite significantly increased heme oxygenase (HO)-1 levels, a redox-regulated protein, and co-incubation with glutathione-attenuated arsenite-induced HO-1 elevation and caspase 3 activation, suggesting that oxidative stress is involved in the arsenite-induced neurotoxicity. The authors conclude that HO-1 appears to be neuroprotective in the arsenite-induced neurotoxicity in primary cultured cortical neurons. In addition to antioxidants, HO-1 elevation may be a neuroprotective strategy for arsenite-induced neurotoxicity.

Furthering the focus on pathways to neurotoxicity and neuroprotection, Vesna Jevtovic-Todorovic reviewed the literature indicating that exposure of developing animals to a variety of anesthetic agents resulted in both histopathological and behavioral alterations in a developmental stage-dependent manner. A causal relationship between a specific anesthesia protocol and specific cognitive disturbances has not been reported for children, suggesting that the majority of commonly used general anesthetics could be detrimental. The authors conclude that in view of this rapidly emerging information, it is of paramount importance to better understand the etiology of poor neurocognitive outcomes that may be anesthesia induced so that prevention strategies can be developed.

In the final report in this grouping, Gregory Oxenkrug reviewed the literature suggesting that insulin resistance (IR) underlines aging and aging-associated medical (diabetes, obesity, dyslipidemia, hypertension) and psychiatric (depression, cognitive decline) disorders. He hypothesizes that dysregulation of tryptophan (TRP)–kynurenine (KYN) and KYN–nicotinamide adenine dinucleotide (NAD) metabolic pathways is one of the mechanisms of IR. One suggested mechanism of IR is inflammation- and/or stress-induced upregulation of TRP–KYN metabolism in combination with P5P deficiency-induced diversion of KYN–NAD metabolism towards formation of xanthurenic acid and other KYN derivatives affecting insulin activity. Monitoring of KYN/P5P status and formation of xanthurenic acid might help to identify subjects at risk for IR. Pharmacological regulation of the TRP–KYN and KYN–NAD pathways and maintaining of adequate vitamin B₆ status may contribute to the prevention and treatment of IR in conditions associated with inflammation/stress-induced excessive production of KYN.

The second grouping of reports focuses on neuroprotection approaches and agent evaluation and includes a review by Cheng Wang and co-workers describing the use of neuronal stem cells to assess anesthetics used in children. The existing data from research using in vivo animal models have implicated some general anesthetics as being toxic to the developing brain and causing cognitive deficits later in life. Because of obvious limitations, it is not possible to thoroughly explore the effects of early life stress—e.g., prolonged exposure to

anesthetic agents—on neurons in vivo in human infants or children. However, the availability of stem cell-derived models, especially human embryonic neural stem cells, along with their capacity for proliferation and ability to differentiate, has provided a potentially invaluable tool for examining the developmental effects of anesthetic agents in vitro. This review presents key concepts in stem cell biology with respect to the nervous system, presents an overview of neural development, and summarizes the involvement of neural cell types in developmental neurotoxicity associated with anesthetic exposure.

In a second report in this grouping, W. Gibson Wood and co-workers provide a review reporting on statin effects on Bcl-2 family members, apoptosis, and cell death and cell protection. Much, but not all of the evidences supporting proapoptotic effects of statins, is based on data in cancer cell lines and the use of relatively high drug concentrations. Studies indicating an antiapoptotic effect of statins are fewer in number and generally used much lower drug concentrations and normal cells. Those conclusions are not definitive, and certainly, there is a need for additional research to determine if statin repositioning is justified for non-cardiovascular diseases.

A third report by Damien Kuffler reviews the literature concerning prevention of neuropathic pain. One potentially important treatment is the application of platelet-rich plasma (PRP) to painful sites (prolotherapy), for which there is no published explanation of the potential mechanism/s by which it acts. It is concluded that PRP eliminates neuropathic pain primarily by stem cell- and platelet-released factors initiating the complex cascade of wound healing events, starting with the induction of enhanced inflammation and its resolution, followed by tissue remodeling, wound repair, and finally, the induction of axon regeneration. However, some of these PRP-released factors probably also act directly to promote axon regeneration, thereby eliminating neuropathic pain.

A fourth review in this grouping of neuroprotection approaches and agent evaluation focuses on the Peruvian plant *Lepidium meyenii* (maca) that has been shown to possess neuroprotective activity in vitro and in vivo. One of the most active macamides, *N*-3-methoxybenzyl-linoleamide, was studied for its mechanism of interaction with fatty acid amide hydrolase (FAAH) and possible inhibitory activity on mono-acyl glycerol lipase, the second enzyme responsible for endocannabinoid degradation. The *N*-3-methoxybenzyl-linoleamide displayed significant time- and dose-dependent FAAH inhibitory activity. These results suggest the potential application of isolated macamides from maca as FAAH inhibitors, which may act in the CNS to provide analgesic, anti-inflammatory, or neuroprotective effects by modulating the release of neurotransmitters.

Stephen Skaper and co-workers reviewed the literature concerning the neuroprotective effects of *N*-palmitoylethanolamine (PEA). PEA is produced and hydrolyzed by microglia; it down-modulates mast cell

activation and increases in glutamate-treated neocortical neurons ex vivo and in injured cortex; PEA levels increase in the spinal cord of mice with chronic relapsing experimental allergic encephalomyelitis. The neuroprotective actions of PEA may be mediated through “receptor pleiotropism,” i.e., both direct and indirect interactions of PEA with different receptor targets, e.g., cannabinoid CB2 and peroxisome proliferator-activated receptor alpha.

Ashraf Virmani and coauthors review the literature concerning the use of nutritional supplements to protect against free radicals and neuroinflammation processes that may underlie many neurodegenerative conditions. Curcumin, carotenoids, acetyl-L-carnitine, coenzyme Q10, vitamin D, and polyphenols, and other nutraceuticals have the potential to target multiple pathways in these conditions. The authors conclude that augmenting neuroprotective pathways using diet and finding new natural substances that can be more efficacious, i.e., induction of health-promoting genes and reduction of the expression of disease-promoting genes, could be incorporated into future neuroprotective strategies.

The final report in the grouping of neuroprotection approaches and agent evaluation, coauthored by S.D. Woods, Robert Skinner, and others, focuses on the oxygen-carrying capacity of dodecafluoropentane emulsion (DDFPe) in 250-nm nanodroplets and its ability to provide neuroprotection in the New Zealand White rabbit using the middle and/or anterior cerebral arteries occlusion model. Although the biological half-life in the blood was brief (<2 min), DDFPe decreased ischemic stroke infarct volumes, and the authors suggest that further development is warranted.

In the final grouping of reports which focuses on nanomaterials and their impact on neurotoxicity and neuroprotection, Hari Sharma and coauthors reviewed the literature describing the possible role of exposure to nanoparticles of silica (SiO₂) in combination with hypertension, high environmental temperature, and restraint stress to enhance brain pathology and sensory motor dysfunction in a rodent model at three different ages. Hypertensive rats subjected to 4-h restraint at room temperature did not exhibit blood–brain barrier (BBB) dysfunction, brain edema, neural injury, or alterations in Rota rod or inclined plane angle performances. However, when these hypertensive rats were subjected to restraint at 33 °C, breakdown of the cortical BBB, increased brain water content, neuronal damage, and behavioral

impairment were observed. SiO₂ exposure to these rats further exacerbated BBB breakdown, brain edema, and neural injury after identical restraint, hypertension, and elevated ambient temperature (33 °C). The authors conclude that hypertension significantly enhances restraint-induced brain pathology and behavioral anomalies at high ambient temperature, and SiO₂ exposure further exacerbated brain pathology and cognitive dysfunction.

In the second report in this grouping, David Zhang and co-workers describe the ability to rapidly detect neurotransmitter release using electrochemical detection methods using carbon nanofiber nanoelectrodes integrated into the Wireless Instantaneous Neurotransmitter Concentration Sensing System. This approach is able to resolve a ternary mixture of dopamine (DA), serotonin (5-HT), and ascorbic acid, as well as to detect individual neurotransmitters in concentrations as low as 50 nM for DA and 100 nM for 5-HT using differential pulse voltammetry.

In the final review in this grouping, Aruna Sharma and coauthors reviewed the impact of repeated administration of engineered nanoparticles (NPs) from metals, e.g., Cu, Ag, or Al (50 mg/kg, i.p. daily for 1 week) on altering BBB disruption and inducing brain pathology in adult rats. The authors concluded that smaller sized particles produced more blood barrier and neural insults and that older and younger animals were more sensitive than adult animals. The Ag and Cu NPs exhibited greater brain damage compared to Al NPs in all age groups regardless of their size. The NPs-induced brain damage correlated well with the upregulation of neuronal nitric oxide synthase activity in the brain, indicating that NPs-induced neurotoxicity may be mediated via increased production of nitric oxide.

The co-founders of the International Conference on Neuroprotective Agents, Dr. Bruce Tremblay and Dr. William Slikker, Jr., wish to thank the many scientists and clinicians for their participation over the years since the initial ICNA meeting was held in Rockland, Maine, in 1991, with meetings held every other year since 1994 at various venues worldwide. The articles in this special issue of *Molecular Neurobiology* reflect the range of neuroprotective strategies that has become a hallmark of the ICNA, and the meeting held in Wendake, Québec, Canada, was consistent with the ICNA goals of combining intellectual diversity with social collegiality in the pursuit of progress in neuroprotection.