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Meeting Report

Highlights of the 37th Annual Meeting of the Society for Neuroscience

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Abstract

Over 30,000 neuroscientists from all over the world attended the 37th Annual Meeting of the Society for Neuroscience (November 3-7, 2007, San Diego), which each year covers a wide range of research interests within the neurosciences, from basic neurophysiology to the most recent therapeutic advances. This article will highlight selected presentations from this year's meeting, with special emphasis on drugs and therapeutic targets for pain and neurodegenerative diseases. Therapies of natural origin will also be discussed.

Highlights of special lectures

Mechanisms underlying prevention of cognitive decline and restoration of memory in age-dependent neurodegenerative disorders

Age-related cognitive disorders and neurodegeneration affect large numbers of people. As Dr. Li-Huei Tsai from the Picower Institute for Learning and Memory at the Massachusetts Institute of Technology pointed out, the incidence of Alzheimer's disease (AD) doubles every 5 years and the number of people with AD is expected to reach 15 million by the year 2050 (1). AD is an age-dependent neurodegenerative disease that progressively attenuates cognitive ability and culminates in dementia. While different factors, including the elevated production of β-amyloid (Aβ) peptides, as well as mutations in the genes encoding amyloid precursor protein (APP), presenilin 1 (PS1) and presenilin 2 (PS2), are linked to the etiology of familial AD, the cause for the sporadic form of AD is still under investigation. Many risk factors that have been proposed to upregulate Aβ production are implicated in this process. The pathological features of AD are varied and include decreased brain volume (as much as 30%) due to neuron and synapse loss. Amyloid plaque formation due to Aβ accumulation and neurofibrillary tangles (NFTs) formed by hyperphosphorylated tau protein aggregates are the hallmarks of the disease. Aβ has a direct impact on synaptic function, as shown by inhibition of long-term potentiation (LTP) –a cellular memory correlate– in rats (2), decrease in AMPA and NMDA receptor-dependent currents (3) and increased GABA function (4). At least for familial AD, the amyloid hypothesis suggests that Aβ deposition is the earliest factor affecting synaptic function in AD. As for risk factors for sporadic AD, the ApoE4 genotype, aging and neurotoxicity are thought to cause a gradual increase in Aβ. In addition, mutations of tau protein, which are the cause of frontal temporal dementia, have also been associated with cognitive impairment in AD, although they are not a primary cause for the disease. In recent years, cyclin-dependent kinase 5 (CDK5), an atypical cyclin-dependent kinase with a predominant brain localization, has been recognized to play a role in mediating learning deficits and neuronal loss in AD. The physiological functions of CDK5 are important to shape brain architecture, as it regulates neuronal migration and positioning, cytoskeleton function and also plays a role in synaptic function via regulation of the synaptic vesicle cycle, synaptogenesis, dendritic spine formation and synaptic plasticity. The activity of CDK5 is dependent upon binding to p35, a regulatory subunit required for activation, but cleavage of p35 by calpain, leading to p25, has been associated with hyperactivation of CDK5 and subsequent neuronal death. Using a transgenic mouse model to inducibly overexpress human p25, researchers at Dr. Tsai's laboratory observed upregulation of CDK5 activity and profound neurodegeneration following induction of p25. At 4 weeks after induction, mice exhibited intense neuronal loss, brain atrophy, a marked decrease in brain volume, astrogliosis and tau pathology, as well as augmented production and accumulation of $A\beta_{42}$, which correlated with impaired synaptic plasticity and memory deficits. Surprisingly, early after induction (2 weeks) and before neurodegenerative changes took place, facilitated learning and LTP, together with increased NMDA receptor-mediated currents, were noted. These findings led to the hypothesis that a compensatory response against impaired plasticity may be a mechanism behind neurodegeneration.

These observations may have consequences for designing new treatments for AD. In general, major approaches for the treatment of AD include promoting neuronal survival (memantine) or enhancing neuronal function via acetylcholinesterase (AChE) inhibitors, which have shown modest efficacy in the clinical setting. Experimentally, other strategies are being pursued, such as targeting Aβ via vaccination and reduction of its production/aggregation, or targeting tau. However, alternative strategies have shown promise in experimental studies. For instance, caloric restriction appears to reduce the risk of AD and attenuate Aβ deposition, and has also been shown to increase lifespan in many model organisms via activation of the *SIRT2* gene, an NAD+-dependent histone deacetylase (HDAC), which in mammals possesses seven homologues (*SIRT1-7*). In particular, *Sirt1* activation with the red wine polyphenol resveratrol protects against neurodegeneration and ameliorates cognitive impairment in p25 transgenic mice (5) and improves survival of mice on a high-fat diet (6). The *SIRT1* gene is thought to provide cell protection against stress (caloric restriction, oxidative stress) by enhancing the gene expression of antioxidant molecules and upregulating DNA repair. The *SIRT1* gene is found in a locus on chromosome 10 associated with familial AD, and it may therefore be interesting to investigate whether mutations or polymorphisms in *SIRT1* lead to increased susceptibility to AD.

Environmental enrichment is another alternative strategy that has shown beneficial effects in experimental models of AD. In p25 transgenic mice previously trained in the fear-conditioning paradigm, exposure to an environment rich in sensory stimuli restored impaired freezing behavior (loss of consolidated long-term memory) to control levels, indicating improved access to long-term memories that, surprisingly, had not been erased, but remained inaccessible due to neurodegeneration. These findings correlated with increased dendrite sprouting and synapse number, but not with new neuronal growth, a finding which suggested re-establishment of the synaptic network. Moreover, exposure to an enriched environment was found to induce hippocampal and cortical acetylation and methylation of histones, and treatment with the HDAC inhibitor sodium butyrate facilitated learning in wild-type mice. Also, HDAC inhibition with sodium butyrate improved learning and the recovery of long-term memories in p25 transgenic mice due to increased dendrite sprouting and synapse number, thus mimicking enriched environment conditions. Together, these results indicate the potential utility of HDAC inhibitors in AD and other neurodegenerative disorders where memory is impaired (7).

Linking sleep loss and circadian dysfunction to obesity and the metabolic syndrome

Dr. Fred W. Turek from Northwestern University provided new insights into the influence that sleep exerts on human metabolic function (8). The average daily amount of sleep time has progressively decreased since the beginning of the 20th century — a trend that is inverse to that of obesity and metabolic syndrome, which have steadily increased. Moreover, a correlation between lack of sleep and the presence of obesity and secondary complications such as insulin resistance, hyperglycemia or dyslipidemia, which may lead to diabetes and cardiovascular disease, has been established. Short sleepers were seen to present with insulin resistance, reduced leptin and increased ghrelin levels, which may lead to obesity (9). Moreover, sleep restriction has also been associated with an increase in food drive. These observations are supported by studies in an experimental genetic model of mice bearing a mutant version of the circadian gene *Clock*. Mutant animals, which exhibit profound alterations in circadian rhythmicity, experienced a significant increase in body weight when fed either a regular or a high-fat diet, which correlated with adipocyte hypertrophy and elevated cholesterol, triglyceride and glucose levels, but reduced serum insulin (10). Another study described altered sleep patterns in leptin-deficient mice featuring an increase in sleep time, as well as in sleep fragmentation, which prevents sleep consolidation (11).

Recent investigations have shown that not only does genetic modification of circadian rhythm regulators affect metabolism, but alterations in energy balance also have an impact on circadian rhythmicity. Kohsaka *et al.* demonstrated that a high-fat diet increased the free-running period of mice, hence lengthening the circadian period, after only 1 week. Moreover, a high-fat diet also affected the diurnal pattern of food intake and locomotor activity, when mice usually eat very little and are supposed to be resting. These behavioral changes were associated with attenuated amplitude of *Clock* gene expression and impaired circadian regulation of nuclear hormone receptor networks (12).

Together, these findings directly implicate sleep debt as a risk or causative factor for imbalances in energy metabolism and pathological conditions such as obesity and diabetes. It is important to note that circadian *Clock* genes can be found in many tissues throughout the body and that approximately 10% of the genes in any given tissue follow circadian rhythmicity in their expression. Therefore, dysregulation of internal synchronization caused by sleep deprivation, travel across time zones, etc., may have an impact on normal biological processes and lead to disease states (9).

Protein folding and misfolding in neurobiology

Susan Lindquist from the Whitehead Institute of Biomedical Research in Cambridge, Massachusetts described how alterations in protein folding can lead to neurodegenerative diseases such as Parkinson's disease (PD) and Huntington's disease (HD) (13). Protein misfolding is regulated by cellular quality control mechanisms, which initiate degradation of misfolded proteins. However, some proteins misfold into toxic species that are able to escape these intracellular surveillance mech-

anisms and form massive aggregates, such as those found in PD and HD. Thus, accumulation of misfolded α-synuclein (α-Syn) leads to the formation of cellular inclusions known as Lewy bodies –a hallmark pathological finding in PD. Although α-Syn has been localized at presynaptic terminals, its exact function remains unknown. In humans, mutations in α-Syn and duplication or triplication of the α-Syn locus have been associated with PD, and in experimental models of PD overexpression of α-Syn leads to neurodegeneration. Studies in yeast provided new clues about the mechanisms of α-Syn-mediated neurotoxicity, as well as about its normal cellular function. Expression of α-Syn induced cell death and endoplasmic reticulum (ER) stress by impairing ER-associated protein degradation. Moreover, α-Syn accumulation suppressed early trafficking of protein vesicles from the ER to the Golgi apparatus, suggesting that protein accumulation may account for ER stress. Overexpression of genes involved in vesicle trafficking, and in particular the small Rab GTPase Ypt1p (involved in the tethering and docking of the transport vesicle to Golgi target membranes), rescued neuron loss in fly, worm and mammalian models of α-Syn-induced neurodegeneration (14).

Another important example of protein misfolding-induced neurodegeneration is HD, which is caused by a polyglutamine (polyQ) expansion within exon 1 of the *huntingtin* gene that induces huntingtin misfolding and its posterior deposition, forming insoluble protein aggregates. Recent findings in yeast have shown that sequences flanking the polyQ region specifically modulate polyQ toxicity (15). These sequences were able to transform a protein bearing the polyQ expansion from benign to toxic, and *vice versa* (16).

Researchers at FoldRx Pharmaceuticals, including Dr. Lindquist, one of the company's scientific founders, have described in recent patents compounds and methods for the treatment of misfolding diseases (WO 2005107792) and for the inhibition of α-Syn toxicity in particular (WO 2006073734, WO 2006034003 and WO 2007126841).

New drug targets

A number of presentations discussed the potential of known or recently discovered proteins as targets for therapeutic intervention. Here we present selected relevant findings on targets for cognition disorders and pain, as well as for depression. We also highlight the role of acid-sensing ion channels in different diseases of the CNS.

Cognition enhancement

1. Potassium channel-interacting proteins (KChIPs)

KChIPs associate with and regulate the activity of voltage-gated potassium (Kv4) channels, which contribute to somatic and dendritic transient outward potassium (A-type) currents that play a key role in regulating neuronal excitability. Both KChIPs and Kv4 channels are highly expressed in the hippocampus and their role in learning and memory has been suggested. Researchers at Wyeth and Baylor College of Medicine in Houston have investigated the properties of the KChIP3 subtype in the contextual fear-conditioning paradigm, a hippocampus-dependent learning task. KChIP3 knockout mice exhibited enhanced learning 24 h after training, evidenced by increased freezing, an effect that persisted 1 month after training. Interestingly, membrane KChIP3 expression in wild-type animals decreased 6 h after fear conditioning compared to untrained controls, whereas at the same time point nuclear KChIP3 expression increased and KChIP3 mRNA levels were not affected, suggesting no genomic regulation of KChIP3. These findings indicate that downregulation of the KChIP3 protein is required during the acquisition phase of hippocampus-dependent learning (17).

2. Rac

The small GTP-binding protein Rac has been implicated in hippocampus-dependent learning and memory, as membrane translocation and activation occur in the hippocampus following associative contextual fear learning (18). Scientists at Baylor College of Medicine in Houston have now investigated whether Rac is required for the development of LTP, the cellular correlate for learning and memory. LTP was induced in hippocampal slices via high-frequency stimulating trains, which was associated with Rac activation and was dependent on NMDA receptor activation, as NMDA blockade suppressed both LTP and Rac activation. Rac activation appeared to be critical for the development of LTP, as the Rac-GTP inhibitor NSC-23766 completely suppressed LTP induction, although it did not block basal synaptic transmission (19). Future experiments with Rac-deficient mouse models are planned.

Pain

1. Rac

LTP is also known to occur in the spinal cord after injury and contributes to the development and persistence of neuropathic pain. In particular, sustained LTP requires protein synthesis and *de novo* formation of postsynaptic dendritic spines. Yale University scientists have investigated whether these structural changes occurring after spinal cord injury (SCI) modulate neuronal hyperexcitability and therefore neuropathic pain. They discovered that injured rats displayed a higher density of mature spines 1 month after SCI than noninjured controls, and that selective inhibition of Rac1, which modulates spine morphology, with NSC-23766 markedly reduced spine density after injury. Moreover, electrophysiological recordings demonstrated hyperexcitability of multireceptive neurons to a range of noxious and non-noxious stimuli, which could be blocked by NSC-23766 treatment. Rac1 inhibition rescued decreased pain thresholds commonly exhibited by SCI animals (20).

2. Methyl-CpG-binding protein 2 (MeCP2)

Researchers at University College in London have identified a role for the transcriptional repressor MeCP2 in the induction of inflammatory pain. MeCP2 has been attributed a role in controlling the expression of genes involved in neuronal maturation and mutations in the *MeCP2* gene are a known cause of Rett's syndrome. After induction of peripheral inflammation in the rat ankle joint, scientists found increased MeCP2 phosphorylation in lamina I projection neurons (key in pain development) and upregulation of several MeCP2 target genes, including serum- and glucocorticoid-inducible kinase (*Sgk1*) and FK506-binding protein 5 (*Fkbp5*), genes known to be important in experience-dependent plasticity. Furthermore, antisense knockdown of *Sgk1* delayed the onset of inflammatory hyperalgesia by at least 1 day (21).

3. Transforming growth factor-activated kinase 1 (TAK1)

TAK1 is a member of the mitogen-activated protein (MAP) kinase kinase kinase (MAPKKK) family and is involved in tumor necrosis factor (TNF), interleukin-1 (IL-1) and Toll-like receptor (TLR) signaling pathways. Japanese researchers have identified a potential role for TAK1 in neuropathic pain. Peripheral nerve injury increased TAK1 expression in the ipsilateral rat spinal dorsal horn that was restricted to astrocytes and not present in neurons or microglia. Downregulation of TAK1 via intrathecal infusion of an antisense oligonucleotide prevented nerve injury-induced tactile allodynia, but not heat hyperalgesia, and also reversed c-Jun *N*-terminal kinase 1 (JNK1) activation in spinal astrocytes. JNK1 colocalizes with TAK1 in spinal astrocytes after lumbar spinal nerve ligation. Targeting the TAK1/JNK1 pathway may provide benefit in treating pain caused by nerve injury (22).

4. Inflammatory nociceptors

Nociceptors are primary sensory neurons specialized in detecting and responding to noxious stimuli that damage or may damage tissue. A research team at Harvard Medical School has discovered that nociceptors are not only able to detect noxious stimuli, but also tissue inflammation via IL-1β sensing. IL-1β is a major proinflammatory cytokine and a potent endogenous pyrogen. In this study, IL-1β increased the excitability of sensory dorsal root ganglion (DRG) neurons in culture, which was associated with a 2-fold increase in tetrodotoxin (TTX)-resistant sodium currents, particularly that mediated by Nav1.9 channels, without modifying voltage dependence, but decreasing slow inactivation kinetics of TTX-resistant sodium channels. Moreover, IL-1β caused MAPK phosphorylation in cultured DRG neurons, which was associated with neuronal hyperexcitability. *In vivo*, intraplantar injection of IL-1β induced mechanical and thermal hypersensitivity, which was not suppressed by cyclooxygenase type 2 (COX-2) inhibition (23). These findings demonstrate how sensory nociceptors can also directly signal the presence of ongoing tissue inflammation.

Depression

Two-pore domain potassium channels are critical regulators of neuronal excitability, as they contribute to background or leak currents, which set the resting membrane potential and oppose depolarizing inputs. TREK-1 belongs to this family of ion channels and is abundantly expressed in prefrontal cortex and hippocampus, and also in areas involved in emotional memory, such as the striatum, the amygdala and the hypothalamus. In the search for novel therapeutic targets, French researchers investigated whether TREK-1 could be involved in depression in TREK-1 knockout mice. Interestingly, TREK-1-deficient mice exhibited increased resistance to depression when tested in different models (forced swim test, conditioned suspension of motility, tail suspension test and learned helplessness test). Moreover, TREK-1 knockout mice showed similar behavior to wild-type animals treated with antidepressant drugs such as paroxetine, fluoxetine or amitriptyline. In addition, TREK-1 deletion potentiated neurogenesis promoted by chronic fluoxetine treatment and reduced the stress-induced increase in cortisol levels. In correlation with these results, TREK-1-deficient mice showed increased serotonergic neurotransmission (24).

Spotlight on acid-sensing ion channels

Acid-sensing ion channels, or ASICs, are proton-gated cation channels widely expressed in peripheral sensory neurons (SNs) and CNS neurons. Although their exact function is still unknown, ASICs in peripheral SNs have been implicated in mechanosensation, nociception and taste transduction, whereas in central neurons ASICs appear to have a role in synaptic transmission and learning and memory processes. They have also been implicated in diverse CNS disorders, from pain to neurodegeneration or anxiety. Six different ASIC subunits (ASIC1a, ASIC1b, ASIC2a, ASIC2b, ASIC3 and ASIC4), generated by alternative splicing of four ASIC genes (*Accn2*, *Accn1, Accn3* and *Accn4*), have been identified and assembled into homomeric or heteromultimeric complexes to form functional channels in neurons. Additionally, two genes encoding ASIC4 and a rodent channel, BLINaC, relatively close to ASICs, have also been identified, but it has not been shown whether they mediate proton-evoked currents. Neurons in the CNS preferentially express the ASIC1a subunit. A drop in extracellular pH below 7 will trigger ASIC channel activation, resulting in the entry of sodium and/or calcium ions (25). Experimental animal studies have implicated ASICs in different disease conditions, including pain, stroke and neurodegenerative and psychiatric diseases.

1. Stroke

Dr. Zhi-Gang Xiong at Portland Dow Neurobiology Laboratories proposed ASICs as potential therapeutic targets in stroke (26). During brain ischemia, a reduced oxygen supply leads to anaerobic glycolysis with subsequent

lactate accumulation, which together with increased proton release from ATP hydrolysis causes the pH to fall to 6.5 or below if ischemia is severe. Calcium toxicity plays a key role in ischemic brain injury, and NMDA glutamate receptors have been considered the main players in mediating intracellular calcium overload in the ischemic brain. Recent findings showed that acidosis-induced calcium entry/toxicity appears to be mediated, at least in part, by ASIC1a channels via a glutamate-independent mechanism and suggested that ASIC1a blockade may be a neuroprotective strategy to prevent neuronal death (27). Both pharmacological ASIC1a blockade (by the tarantula-derived peptide psalmotoxin) and *ASIC1a* gene deletion significantly reduced infarct volume in the mouse middle cerebral artery occlusion (MCAO) model of focal ischemia, an effect that was potentiated by NMDA channel blockade with memantine, which may indicate calcium entry via alternative routes. The time window for neuroprotection by ASIC1a blockade in brain ischemia has recently been shown to last up to 5 h after the initiation of focal ischemia in the mouse MCAO model, with persistent effects for up to 1 week (28). These findings point to the promise of ASIC1a channel blockade for the treatment of stroke. However, ASICs display fast inactivation kinetics with quick desensitization when exposed to persistent ischemia, suggesting that they might be initiators of ischemic toxicity and glutamate-induced toxicity. Therefore, it has been the object of debate whether they are important or not during brain ischemia. The possibility has been suggested that they may initiate the process and that glutamate might play a more delayed role.

2. Multiple sclerosis

Axonal degeneration is the parameter that best correlates with clinical symptoms in multiple sclerosis (MS) patients. Multiple molecular mechanisms contribute to axonal injury in MS, including sodium ion channels and exchangers like the sodium/potassium ATPase, among others (29). Dr. Manuel A. Friese at the University of Oxford recently unveiled a role for ASIC1a in axonal degeneration associated with autoimmune inflammation of the CNS (30, 31). Deletion of the ASIC1 subunit improved disease severity in mice with experimental autoimmune encephalomyelitis (EAE), a T-cell-dependent model resembling human MS. Inflammatory CNS tissue of EAE mice displayed lower pH values than healthy controls, which correlated with upregulation of ASIC1 mRNA, compatible with ASIC1a activation in EAE, although this has not been directly demonstrated. Moreover, pharmacological ASIC1a blockade with amiloride or *Asic1* gene disruption significantly attenuated axonal loss and improved EAE clinical scores.

3. Psychiatric disorders

A role for ASICs in mediating fear and anxiety has also been suggested. Dr. John A. Wemmie at the Veterans Affairs Medical Center in Iowa discovered a few years ago that levels of ASIC1a channel protein, as well as ASIC1a-mediated currents, were particularly high in the mouse amygdala and that ASIC1a deletion led to impaired fear conditioning (32). Moreover, overexpression of ASIC1a in transgenic mice enhanced context fear conditioning, a model of acquired anxiety (33). In a recent study by the same research team, ASIC1a has also been found to participate in the expression of innate (or unconditioned) fear responses (34). The fox odor component trimethylthiazoline (TMT) was used to evoke innate fear to a natural predator in mice. In this context, both loss of ASIC1a and acute pharmacological blockade with psalmotoxin suppressed TMT-induced unconditioned fear behavior. Immunohistochemistry revealed abundant ASIC1a expression in the bed nucleus of the stria terminalis, periaqueductal grey and amygdala –all structures that form part of the anxiety and fear circuitry. Although data associating ASIC1a with human fear and anxiety disorders are not yet available, it seems plausible that modifying ASIC1a channel function could be of therapeutic relevance in managing these conditions. Interestingly, ASIC subunit composition has been suggested to be critical in mediating fear conditioning. Experimental overexpression of ASIC3 channels, which are not usually expressed in the CNS, impaired ASIC1a-dependent fear conditioning in mice, potentially by modifying subunit composition of ASIC1a channels (35).

In animal models of anxiety (stress-induced hyperthermia, four-plate test), the nonspecific ASIC blocker A-317567 demonstrated anxiolytic-like activity and caused an increase in extracellular levels of GABA in the rat amygdala, suggesting a potential role for GABAergic neurotransmission in mediating the anxiolytic-like effects (36).

Novel therapies

Spotlight on ampakines

Glutamate receptors of the AMPA type are major mediators of fast excitatory synaptic transmission in the CNS. In the last few years, AMPA receptors have been increasingly implicated in synaptic plasticity underlying learning and memory processes and have therefore emerged as a potential therapeutic target for the development of cognition-enhancing drugs. The development of positive AMPA receptor modulators, or ampakines, originally discovered by Dr. Gary Lynch at the University of California, Irvine, opened a new avenue for the treatment of cognition deficits associated with different neurological and psychiatric disorders. Ampakines are small synthetic molecules that have good to excellent bioavailability and rapidly cross the blood-brain barrier. They slow deactivation and attenuate desensitization of AMPA receptor currents, increase synaptic responses and enhance LTP. At this year's meeting, ampakines were the subject of different presentations that not only highlighted their potential to treat cognition deficits, but also disclosed new actions of these compounds that may provide benefit in other CNS conditions.

French and U.S. researchers have reported inhibition of cognitive decline in middle-aged rats with daily admin-

istration of **S-18986** (**1**) (Servier) for 4 months. S-18986 treatment reversed age-related deficits in a reinforcer devaluation task in a dose-dependent manner, which was associated with increased prefrontal cortex activity in compensation for a decline in hippocampal function. Moreover, S-18986 treatment re-established the oxidative status that was shifted to pro-oxidant cascades in middle-aged rats (37). Another study showed spatial memory improvements and increased locomotor activity in rats chronically treated with S-18986. At the cellular level, S-18986 appeared to reduce molecular markers of aging (33).

The ampakine **CX-546** (**2**) (Cortex) was evaluated in mice lacking Neto1, an NMDA receptor-interacting protein, which display impaired spatial learning and memory due to diminished NMDA receptor density and NMDA receptor-mediated excitatory postsynaptic currents. Ampakine treatment rescued spatial memory deficits and impaired LTP in Neto1-deficient mice to wild-type levels (39).

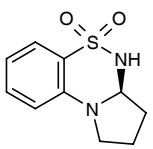
Dr. Lynch's research group demonstrated that ampakine treatment with **CX-929** was able to rescue synaptic plasticity (LTP) in a mouse model of HD via an increase in endogenous brain-derived neurotrophic factor (BDNF) levels. Twice-daily injections of CX-929 for 4 days to CAG140 knock-in mice, which have a CAG expansion within one of the endogenous full-length *huntingtin* alleles, increased hippocampal BDNF to wild-type levels. Spine density in CX-929-treated mice was higher than in vehicle-treated HD knock-in controls and similar to in wild-type animals. LTP deficits of CAG140 were completely restored by CX-929. Ampakines may therefore be a potential chronic therapy for treating early cognitive dysfunction in HD (40).

A novel ampakine compound, **RU-32**, has been developed by Russian scientists with the aim of improving or restoring old weakened memories formed hours or days before its intake. When administered 5 min before passive avoidance training in 1-day-old chicks to induce short-term memory, RU-32 (0.005-0.1 mg/kg i.p.) dose-dependently enhanced memory. If training was coupled with a reminder, thus inducing long-term memory, administration of RU-32 also significantly potentiated memory retention, suggesting therapeutic potential in improving memory loss due to neurodegenerative diseases (41).

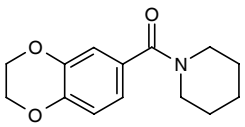
Ampakine treatment with CX-546 was also shown to markedly improve BDNF expression and functional recovery in a mouse model of Rett's syndrome, a neurodevelopmental disorder associated with profound motor and cognitive deficits. CX-546 treatment (40 mg/kg i.p. twice daily) increased BDNF mRNA levels by 42% in cranial sensory ganglia of mice lacking MeCP2, which is usually mutated in Rett's syndrome. CX-546 also improved respiratory dysfunction exhibited by *Mecp2*-null mice by restoring mean respiratory frequency and minute volume values to levels in wild-type animals. These results suggest that enhanced BDNF expression in neural structures important for cardiorespiratory control contributes to normal respiratory behavior (42).

Anesthetic-induced respiratory depression is a major clinical problem. Ampakines have shown potential to ameliorate respiratory suppression without affecting sedation or analgesia. Researchers at the University of Alberta, Canada, observed that CX-546 stimulated baseline respiratory frequency increased in perinatal rat brainstem-spinal cord preparations and neonatal medullary slices *in vitro*. Furthermore, opioid-induced breathing depression *in vivo* was restored by CX-546, without affecting analgesia in response to thermal stimuli (43). CX-546 appeared to increase respiratory frequency by enhancing the drive potential and inward respiratory synaptic current of inspiratory neurons in the pre-Bötzinger complex, the putative site of inspiratory rhythmogenesis (44).

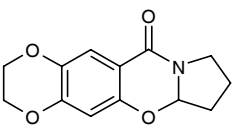
The pharmacology of ampakine compounds is susceptible to modulation by transmembrane AMPA receptor regulator proteins (TARPs), which physiologically regulate AMPA receptor trafficking and the electrophysiological properties of AMPA receptors. Thus, TARPs were shown to augment AMPA receptor expression in a heterologous system and affected the association/dissociation rates of **CX-614** (**3**), either increasing or reducing it, depending on the TARP and AMPA receptor subtypes (45).



S-18986 (**1**)



CX-546 (**2**)

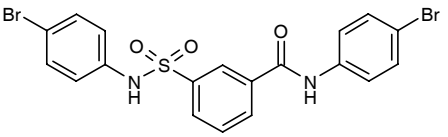


CX-614 (**3**)

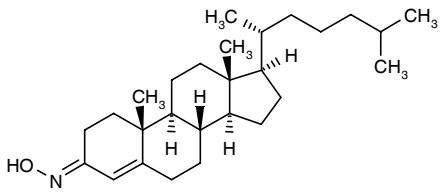
Huntington's disease

As described above, HD is an autosomal dominant neurodegenerative disease caused by a glutamine expansion within exon 1 of the *huntingtin* gene, which causes huntingtin misfolding and its posterior deposition, forming insoluble protein aggregates. The small molecule

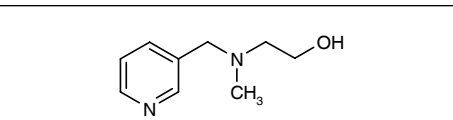
C2-8 (**4**) has been shown to inhibit polyglutamine-mediated aggregation *in vitro* and to rescue neuronal degeneration in a *Drosophila* model of HD. A recent study by researchers at Massachusetts General Hospital in collaboration with the Novartis Institute for Biomedical Research demonstrated that C2-8 (50 mg/kg for 5 days) penetrates the blood-brain barrier, with a mean concentration in the mouse cerebral cortex of 25 μM, which greatly exceeds the *in vitro* IC_{50} value (0.05 μM). Acute and chronic tolerability studies in mice showed no effects of C2-8 on body weight. Moreover, C2-8 administered at 100 or 200 mg/kg twice daily resulted in improved motor performance in a transgenic mouse model of HD (the R6/2 mouse), and was associated with decreased atrophy of striatal neurons and reduced volume of intranuclear huntingtin aggregates in the striatum, indicating an inhibitory effect on aggregate growth (46, 47). These results establish C2-8 as a promising drug lead to develop effective therapies for HD.



C2-8 (**4**)



TRO-19622 (**5**)



JAY-2-22-33 (**6**)

Amyotrophic lateral sclerosis

TRO-19622 (**5**) is a small-molecule cholesterol-like drug candidate from Trophos that enhances motor neuron survival and nerve regeneration in various preclinical models. Following a phase I study in healthy volunteers that demonstrated good safety and dose-proportional pharmacokinetics, a double-blind, randomized, placebo-controlled phase Ib trial was performed in patients with amyotrophic lateral sclerosis (ALS) to assess safety and trough plasma concentrations. TRO-19622 was administered (with a meal, as food increases exposure) as add-on therapy to riluzole (50 mg b.i.d.) at doses of 125, 250 or 500 mg once daily orally for 1 month to 9 patients at each dose. The treatment was well tolerated, with most adverse events being mild to moderate and not dose-related, with a similar incidence in all groups. One patient on the highest dose withdrew due to a severe adverse event of pneumonia, which appeared not to be drug-related. No changes in weight, laboratory values, vital signs or ECG parameters were observed. Mean trough plasma concentrations in the ALS patients were higher than those previously reported in healthy volunteers, with no gender differences. Plasma levels showed interindividual but not intraindividual variability. All patients reached target concentrations at doses of 250 mg/day and above (48). The company recently commenced a phase Ib study in patients with spinal muscular atrophy (SMA), for which it holds orphan drug status in the E.U., and TRO-19622 is also being evaluated in a phase IIa trial in patients with painful diabetic neuropathy. Phase II/III trials for ALS are anticipated to begin in 2008.

About 20% of cases of familial ALS harbor mutations in the gene encoding superoxide dismutase 1 (SOD1), and the ability of kSOD1 to induce motor neuron degeneration appears to be related to the protein's propensity to misfold. Therefore, immunotherapeutic approaches targeting misfolded SOD1 may offer a promising therapeutic strategy in the treatment of fALS1. A group at the University of Toronto has designed a dendrimeric multiple antigenic peptide specific for misfolded SOD1 to generate the SOD1-exposed dimer interface antibody, or **SEDI antibody**. They detected misfolded SOD1 in motor neurons of mutant SOD1 transgenic mice and fALS cases harboring SOD1 mutations using the antibody. Subsequently, transgenic SOD1(G37R) mice were immunized i.p. with the SEDI peptide and showed improved motor performance, delayed disease onset, extended survival and delayed disease progression. The immunotherapy also preserved motor axons and reduced astrogliosis and microgliosis (49).

Cognition-enhancing drugs

Lay Line Genomics is developing variants of human nerve growth factor (NGF) for noninvasive delivery in the treatment of AD. At the Society for Neuroscience meeting, data were presented for **hNGF-61**, which shows minimum differences in amino acid sequence and composition compared to wild-type hNGF, similar affinity for TrkA and p75 receptors and the same biological activity as wild-type hNGF, as measured by TrkA phosphorylation, differentiation of PC12 cells and the proliferative response of TF1 cells. In the AD11 anti-NGF mouse model, intranasally administered hNGF-61 (480 ng/kg) reversed both the behavioral deficit in the object recognition test and neurodegeneration, effects which persisted after 1-month washout, indicating a disease-modifying effect. On the other hand, it was not associated with body weight loss or spinal cord hyperinnervation (50).

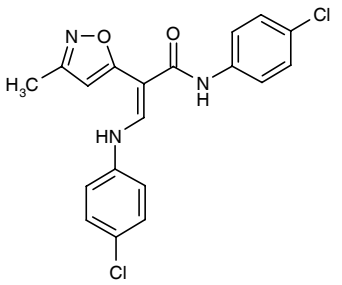
JAY-2-22-33 (**6**), a choline derivative, is a neuroprotective and cognition-enhancing drug identified at the

University of Georgia. In initial experiments it demonstrated cytoprotective activity in PC12 cells, with an EC_{50} of 39 nM, and it transiently increased intracellular calcium levels in primary rat cortical neurons at 100 μM. Further studies in rhesus monkeys trained on a delayed matching-to-sample task showed that treatment with JAY-2-22-33 (5-150 mg/kg i.m.) significantly improved task accuracy at all but the lowest dose, with the greatest improvement seen on 100 mg/kg; the effect was still significant on the day after administration. Thus, JAY-2-22-33 may be useful for the treatment of both neurodegenerative and cognition disorders (51).

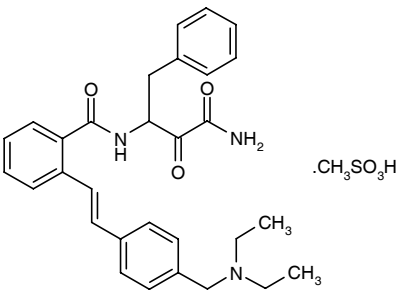
Preclinical and clinical data provide support for the development of selective nicotinic acetylcholine receptor (nAChR) positive allosteric modulators for use in the treatment of cognitive disorders, including AD. A highly selective lead α7 nAChR positive allosteric modulator, compound **7**, was discovered at the University of California, Irvine. In addition to favorable pharmacokinetics, this compound exhibited efficacy in rodent models of schizophrenia. The compound also significantly improved cognitive performance in the 8-arm radial maze and in a memory acquisition paradigm in rats, while being nontoxic in α7 nAChR-expressing cells and not potentiating nicotine-induced seizures (52).

Based on experimental evidence indicating that calpain activation is involved in NMDA receptor-related excitotoxicity, a group of Abbott scientists and their collaborators examined the *in vitro* and *in vivo* effects of **A-705253** (**8**), a nonpeptide, water-soluble calpain inhibitor (K_i = 27 nM), on excitotoxic cell death and neurodegeneration. Using a model of glutamate-induced cell death in rat hippocampal slices, A-705253, like MK-801, significantly prevented cell death at concentrations of 10 nM to 10 μM, showing comparable activity at 10 nM to MK-801 at 10 μM. Cytotoxicity was only observed at very high concentrations (100 μM). The compound also potently inhibited caspase-3 activity at concentrations of 10 nM and above (53). *In vivo* studies were also performed in rats with NMDA-induced lesions of the nucleus basalis magnocellularis (NBM), which is analogous to the nucleus basalis of Meynert in humans involved in cognitive processes. A-705253 dose-dependently and significantly prevented deficits in a novel object recognition task in these animals starting at 3 mg/kg, with complete prevention at 10 mg; no effect was seen on exploration. A-705253 was also shown to dose-dependently prevent cholinergic neurodegeneration at these doses and the highest dose significantly prevented gliosis. The results suggest that calpain inhibition may represent a novel approach to the treatment of neurodegenerative disorders (54).

Currently available therapies for AD and schizophrenia have limited efficacy and are associated with side effects, and alternatives are being actively pursued. Selective targeting of the nAChR α7 subtype has been proposed as a promising approach. Wyeth and Siena Biotech have identified a novel, potent and selective, small-molecule nAChR α7 full agonist, **SEN-12333/WAY-317538**, and discussed preclinical findings for the compound at the meeting. *In vitro*, the compound gave K_i and EC_{50} values for the α7 receptor of 260 and 2270 nM, respectively, showing good to excellent selectivity relative to α1, α3 and α4 nAChRs, the $5\text{-}HT_3$ receptor and hERG; in electrophysiological experiments it gave an EC_{50} of 1.2 μM. It prevented NMDA-induced toxicity in rat cortical neurons *in vitro* and partially protected against quisqualic acid-induced cell death in the NBM when administered at a dose of 3 mg/kg/day i.p for 7 days. SEN-12333/WAY-317538 enhanced memory retention in a rat novel object recognition test, with a significant effect at 3 mg/kg i.p., and it also reversed scopolamine-induced deficits at this dose. Further testing in rats revealed reversal of scopolamine-induced deficits in passive avoidance and of apomorphine-induced deficits in prepulse inhibition at the dose of 3 mg/kg i.p. The results suggest both neuroprotective and cognition-enhancing effects and potential utility in the treatment of cognitive dysfunction associated with AD and schizophrenia (55).



Compound **7**



A-705253 (**8**)

Memory Pharmaceuticals and Roche have also examined the cognition-enhancing effects of nAChR α7 agonists, including the partial agonist **MEM-64638**, and the cholinesterase inhibitor donepezil (Aricept) in several monkey models. In contrast to donepezil which exhibited activity indicative of an attention-enhancing effect, MEM-64638 (0.3-3 mg/kg p.o.) improved performance in tasks of executive function and working memory in a manner consistent with a memory-enhancing effect (56). However, unlike the partial agonist GTS-21 and the full partial agonist AR-R17779, MEM-64638 did not improve visuospatial working memory in monkeys (57).

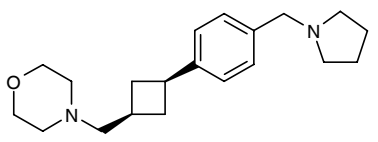
Pfizer's new selective histamine H_3 receptor antagonist, **PF-00389027** (**9**), has demonstrated that this type of drug may hold potential for treating neurological disorders involving impaired attention, learning, memory and vigilance. *In vitro*, PF-00389027 potently inhibited histamine H_3 agonist binding to H_3 receptors (K_i < 10 nM) and showed > 100-fold selectivity over other histamine receptors, G-protein-coupled receptors (GPCRs), ion channels and enzymes. *In vivo*, PF-00389027 blocked H_3 receptor agonist-induced dipsogenia in a dose-dependent manner, with an ED_{50} value of 0.9 mg/kg, s.c. PF-00389027 also caused an increase in extracellular histamine and acetylcholine levels, indicating H_3-antagonist activity. Electrophysiological recordings in anesthetized rats showed increased cognition-associated theta activity in the hippocampus after i.v. PF-00389027 administration. Moreover, PF-00389027 improved performance in the novel object recognition task in mice at 1 and 3.2 mg/kg, s.c. (58). PF-00389027 has also been cited in the patent literature (US2005171181).

Pain management

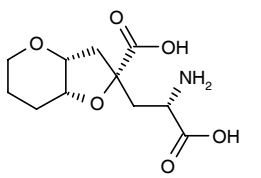
PLX-5568 is a novel small-molecule kinase inhibitor and the lead compound in Plexxikon's pain program. PLX-5568 inhibits multiple kinase pathways that mediate nociceptive signals and presents an excellent pharmaceutical profile with high oral bioavailability. At oral doses of 5 mg/kg, PLX-5568 induced maximal antinociception in the mouse hot plate assay. Moreover, PLX-5568 caused dose- and time-dependent inhibition of the mouse tail flick response elicited by thermal stimuli. Thermal hyperalgesia induced by carrageenan injection in rats was equally suppressed by oral PLX-5568 (15 mg/kg) and i.p. morphine (3 mg/kg). Similar results were obtained in the complete Freund's adjuvant-induced inflammation model. Locomotor activity in the rotarod model was not affected by PLX-5568 treatment, indicating a good safety profile. Plexxikon has advanced PLX-5568 to development and is planning an IND filing for the first quarter of 2008 (59).

TY-005 (**10**) is a novel bifunctional peptide with opioid-agonist and NK_1 receptor-antagonist pharmacophores, prepared at the University of Arizona. The peptide exhibited high affinity for human mu and delta opioid receptors (K_i = 36.3 and 2.8 nM, respectively) and the human NK_1 receptor (K_i = 0.082 nM), as well as potent functional agonist activity at mu and delta opioid receptors and antagonist activity at substance P receptors. Intrathecally administered TY-005 produced an antinociceptive effect in normal rats, without inducing motor impairment, and it dose-dependently attenuated nerve injury-induced tactile and thermal hypersensitivity in rats following both intrathecal and i.v. administration. Chronic administration was not associated with the development of tolerance to the antinociceptive effect (60).

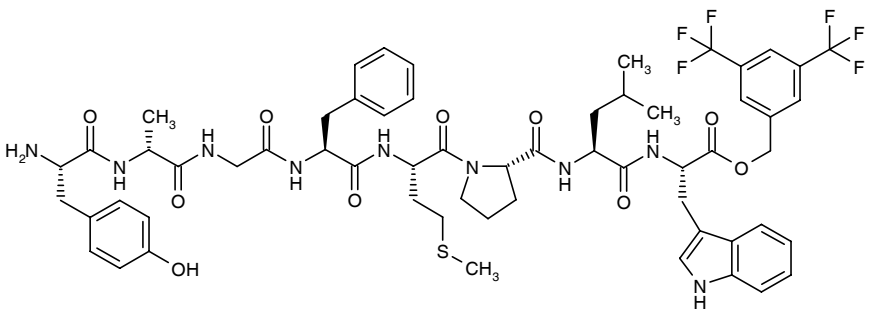
MSVIII-19 (**11**) is a novel, selective GluR5 receptor antagonist derived from the marine sponge toxin dysiherbaine by a team at Washington University and Northwestern University. It potently inhibited glutamate-evoked currents from GluR5 and GluR/KA2 kainate receptors (IC_{50} = 23 nM and 1.9 μM, respectively), while having significantly less effect on GluR6-containing kainate receptors. Whereas it had no significant effect on motor function (rotarod test), acute thermal pain sensitivity (tail flick test) or mechanical sensitivity in models of inflammatory pain (complete Freund's adjuvant and formalin tests) in mice, it significantly reduced thermal sensitivity in the above models of inflammatory pain following intrathecal injection of 0.5 nmol and attenuated mechanical hypersensitivity in the chronic constriction injury model of neuropathic pain (61).



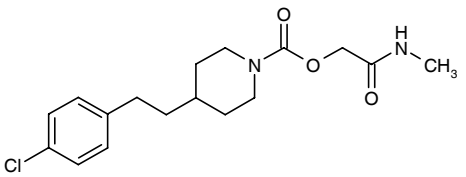
PF-00389027 (**9**)



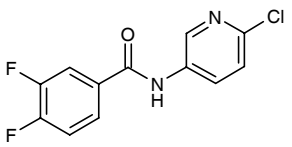
MSVIII-19 (**11**)



TY-005 (**10**)



VER-154403 (**12**)



ICA-27243 (**13**)

The enzyme fatty acid amide hydrolase (FAAH), which catalyzes the intracellular hydrolysis of the endogenous cannabinoid anandamide, has emerged as a target for analgesic drugs. Researchers at Vernalis have found that the orally active FAAH antagonist **VER-154403** (**12**) caused a dose-dependent inhibition of FAAH (IC_{50} = 13 nM). VER-154403 restored normal thermal sensitivity to intraplantar carrageenan-treated rats without affecting thermal sensitivity in the contralateral paw. At oral doses of 1, 3 and 10 mg/kg, VER-154403 significantly attenuated paw licking duration following formalin injection into the rat paw, without affecting locomotor activity. Anandamide levels were modestly increased in the right thalamus and reticular formation of VER-154403-treated animals, whereas the levels of 2-arachidonylglycerol (2-AG), another FAAH substrate, were significantly elevated in the left and right thalamus, periaqueductal grey tissue, reticular formation and spinal cord, and also the ipsilateral but not the contralateral paw. Increased 2-AG in both peripheral and central tissues associated with pain processing appears to underlie VER-154403's analgesic activity (62).

ICA-27243 (**13**) has been developed at Icagen as an opener of KCNQ2/3 channels and was tested in models of neuropathic and inflammatory pain. KCNQ2/3 channels are voltage-gated potassium channels that regulate neuronal excitability, and their activation is associated with membrane hyperpolarization and hence reduced neuronal excitability, which may be beneficial in hyperexcitable conditions such as pain. In DRG neurons, ICA-27243 activated KCNQ2/3-mediated currents and caused a dose-dependent hyperpolarization of the resting membrane potential, together with a 3-fold increase in the current required for action potential generation (63). In the rat spinal nerve ligation model, ICA-27243 (3-30 mg/kg) both orally (p.o.) and intrathecally (i.t.) reversed mechanical hyperalgesia in a dose-dependent manner, and this effect was blocked by pretreatment with the KCNQ antagonist XE-991, indicating that the central activity of KCNQ2/3 channels contributes to ICA-27243's efficacy in neuropathic pain (64). Moreover, ICA-27243 (3-30 mg/kg p.o. and i.t.) significantly suppressed thermal and mechanical hyperalgesia in the carrageenan-induced acute and the Freund's complete adjuvant chronic inflammatory pain models, respectively, effects which were markedly attenuated by XE-991 pretreatment (65).

The protein kinase C γ (PKCγ) isozyme, located in excitatory interneurons in lamina II of the spinal cord, has been shown to be important in the regulation of nociception, particularly inflammatory and neuropathic pain. **KA-1613** is a novel small-peptide inhibitor of PKCγ developed by KAI Pharmaceuticals in collaboration with the University of South Carolina that dose-dependently attenuated mechanical allodynia and thermal hyperalgesia in the rat lumbar spinal transection model when administered as a continuous infusion via osmotic minipump for 1 week before transection at doses ranging from 10 to 1000 pmol/day. The analgesic effects were accompanied by a reduction in membrane-bound, but not cytosolic, PKCγ in the lumbar spinal cord. KA-1613 demonstrated comparable antinociceptive activity when implanted at the day of transection or 7 days after transection. These findings suggest that intracellular PKCγ translocation is involved in the generation and maintenance of neuropathic pain (66).

CNS therapies of natural origin

1. Cognition-enhancing drugs

Yukmijihwang-tang is an herbal extract composed of six herbal medicines that has been widely used for centuries as an antiaging medicine in Asian countries. Korean scientists have investigated the effects of Yukmijihwang-tang derivatives (YMJd) on learning and memory in rats receiving ibotenic acid injections to severely impair cholinergic neurons in the medial septum. Daily administration of YMJd (100 mg/kg i.p.) for 3 weeks significantly reversed ibotenic acid-induced impaired performance in the Morris water maze test and reduced the loss of choline acetyltransferase immunoreactivity in the medial septum. These finding suggest that YMJd improves learning and memory via a neuroprotective action on the central ACh system (67).

The *Gingko biloba* terpene-strengthened extract YY-1224 has shown cognition-enhancing effects in mice exposed to $A\beta_{1\text{-}40}$ via inactivation of the *Cox2* and platelet-activating factor receptor (*Ptafr*) genes and by preventing the Aβ-induced reduction in muscarinic M_1 receptor expression (68). In addition, improved locomotor activity, associated with dopaminergic neuron protection and reduced *Ptafr* gene expression in the nigrostriatum, was observed upon prophylactic YY-1224 treatment to rats treated with MPTP. In both studies, YY-1224 was superior to the standard *Gingko biloba* extract Egb-761.

Reversible inhibition of AChE activity by a novel extract of *Tabernaemontana divaricata* (TDE), a plant commonly found in tropical gardens, has been reported by Thai researchers, who suggested potential benefit in AD. At a concentration of 0.1 mg/ml, TDE inhibited AChE

by more than 90%. When tested on hippocampal slice preparations *in vitro*, TDE transiently suppressed glutamatergic synaptic transmission via activation of cholinergic muscarinic receptors due to ACh accumulation at presynaptic sites (69).

J6 is a newly isolated polysaccharide from the flowers of *Nerium indicum* that may protect against neuronal death in AD, according to researchers at the University of Hong Kong and the Chinese Academy of Science. Pretreatment with J6 decreased caspase-3 activity and Aβ-induced cytotoxicity in cultured cortical neurons exposed to Aβ peptides, which was associated with inhibition of JNK1 signaling, unlike previously reported *N. indicum*-derived polysaccharides (J2, J3 and J4) known to activate the Akt survival pathway (70).

Grape seed-derived polyphenols contained in the commercially available Meganatural AZ grape seed extract may be useful for preventing further cognitive deterioration in cases of mild cognitive impairment (MCI), as reported by Dr. Pasinetti's laboratory at the Mount Sinai School of Medicine, New York. Daily treatment with Meganatural AZ extract (20 mg/kg) in transgenic Tg2576 mice was well tolerated and resulted in improved performance in the Morris water maze test, indicating reduced cognitive impairment. These results were correlated with inhibition of Aβ oligomerization in the hippocampus and cortex and neuritic plaque reduction (71). As moderate Cabernet Sauvignon wine consumption has been associated with reduced Aβ neuropathology and delayed cognitive deterioration in transgenic AD mice (72), Dr. Pasinetti's lab investigated whether Muscadine, a red wine with a polyphenolic profile different from Cabernet Sauvignon, elicited similar effects. Indeed, chronic moderate Muscadine wine consumption by Tg2576 mice equivalent to one 5-oz drink per day in women and two drinks per day in men attenuated the development of AD-type cognitive decline in both the Barnes maze and the water maze tests, and decreased hippocampal Aβ oligomerization. Current work is focusing on an isolated resveratrol-free polyphenol extract from Cabernet Sauvignon, which has shown *in vivo* efficacy, as well as on isolating other individual bioactive compounds. In addition, a water-soluble polyphenol extract from a Concord purple grape juice also reduced plasma levels of $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ by about 2-fold, which may represent an alcohol-free alternative to moderate wine consumption to prevent AD (73).

The natural γ-secretase inhibitor and antidiabetic compound NIC5-15 (pinitol) is currently being examined in Dr. Pasinetti's lab as a potential anti-AD treatment. Previous studies found that diet-induced insulin resistance promoted amyloidosis in Tg2576 mice, which may be due to a functional decrease in insulin receptor (IR)-mediated signaling in the brain (74). Ongoing studies using NCI5-15 (80 mg/kg/day) given to insulin-resistant Tg2576 mice showed increased glucose utilization and improved spatial memory. NIC5-15 was found to increase IR phosphorylation, indicating enhanced activity, which was associated with a dose-dependent reduction in insulin resistance-induced Aβ peptide formation in Tg2576 mouse brain (75).

Japanese researchers have shown that daily treatment with rosmarinic acid, a natural peroxynitrite scavenger, improved $A\beta_{25\text{-}35}$-induced memory impairment in mice and reduced Aβ-induced protein nitration in the hippocampus at doses of 0.25 mg/kg. These findings suggest that daily consumption of rosmarinic acid may protect against AD neurodegeneration (76).

Walnuts are rich in α-linolenic acid, an essential omega-3 fatty acid, as well as in lipids and other antioxidant compounds. Researchers at the Human Nutrition Research Center on Aging in Boston have demonstrated the benefit of a walnut-supplemented diet in cognition. Old rats fed with a 2% or 6% walnut diet showed cognitive and motor improvement. A 6% walnut diet represents the equivalent to 1 oz of walnuts per person per day, and is the recommended amount to reduce LDL cholesterol (77). This research team further explored the effects of chronic daily intake of a blueberry-enriched diet on brain morphology. Aged rats fed a 2% blueberry extract-enriched diet for 8 weeks exhibited neuroplastic changes evidenced by increased dendritic branching and spine density in the frontal cortex (78).

2. Ischemic injury/stroke

Cinnamon is a source of polyphenols, which have recently demonstrated neuroprotective actions in animal models of ischemic injury. Water-soluble polyphenols from cinnamon extracts protected PC12 cells from death triggered by oxygen/glucose deprivation (OGD) and attenuated OGD-induced depolarization of the mitochondrial membrane potential. Cinnamon-derived polyphenols, but not green tea polyphenols or resveratrol, blocked glial cell swelling in response to ischemic conditions (79).

The roots of *Pueraria thunbergii* have been used for centuries in traditional Korean medicine to treat stroke. A recent study evaluated the neuroprotective effects of *P. thunbergii* (70% ethanol extract) and its main components, namely daidzin, daidzein, genistein and puerarin, in two rat models of brain ischemia. Oral administration of *P. thunbergii* extract (PTE) at 300 mg/kg 90 min after focal cerebral ischemia or immediately after global cerebral ischemia (4-vessel occlusion) significantly attenuated neuronal death by 1 week after ischemia. Similar protection was observed with daidzin and genistein when given at 10 mg/kg. Comparable results were obtained in the MCAO model of focal ischemia, where PTE, daidzin and genistein treatment resulted in marked reductions in infarct volume (80).

Japanese scientists have reported the beneficial effects of a mango (*Mangifera indica* L.) extract against neurodegeneration caused by excessive zinc release after ischemia. Pretreatment with hydrosoluble mango fruit extract of immortalized hypothalamic neurons immediately prior to zinc exposure reduced cell apoptosis. Further purification experiments revealed citrate as the active ingredient in mango extract, which did not prevent zinc entry into cells, suggesting a neuroprotective mech-

anism other than zinc chelation (81). Mango extract and mangiferin, a major active component, protected primary rat cortical cells against death induced by glutamate excitotoxicity in a study conducted by Cuban and Spanish researchers. Both preparations significantly reduced the glutamate-induced elevation of intracellular reactive oxygen species (ROS) and promoted the recovery of baseline mitochondrial membrane potential values (82).

Aequorin is a small calcium-binding protein isolated from the crystal jelly fish *Aequorea victoria*, which has been shown to protect neurons from ischemic cell death by researchers at the University of Wisconsin. An intrahippocampal infusion of 4% aequorin to adult, early and late middle-aged and aged rats resulted in a significant increase in viable neurons compared to vehicle-treated controls, regardless of age group (83).

The neuroprotective effects of the carotenoid pigment astaxanthin, an antioxidant compound commonly found in crustaceans, against ischemic brain injury were examined in the rat MCA ligation model. Intracerebroventricular administration of astaxanthin before MCAO decreased ischemia-induced glutamate release in cerebral cortex, loss of aconitase activity (marker of ROS production) and translocation of cytochrome *c* from mitochondria. Two days after MCAO, animals treated with astaxanthin exhibited improved locomotor activity and reduced cerebral infarction compared to vehicle-treated controls (84).

3. Spinal cord injury

Omega-3 fatty acids, in particular docosahexaenoic acid (DHA), have demonstrated neuroprotection after SCI in animal models. Researchers at the University of Texas-Health Science Center in Houston have continued to explore the potential benefit of a phospholipid derivative of DHA, namely didocosahexaenoyl-*sn*-glycero-3-phosphocholine (DDPC), on the recovery of motor function and the development of neuropathic pain after SCI in rats. Treatment with both DHA and DDPC resulted in significantly improved scores on the Basso, Beattie, Bresnahan (BBB) Locomotor Rating Scale for 1 week after SCI and up to 2 weeks after SCI in the DDPC group only. One month after SCI, 80% of vehicle-treated rats showed signs of neuropathic pain compared to only 20% of animals receiving DDPC (85).

4. Parkinson's disease

Baicalein is a major flavonoid contained in the traditional Chinese herb *Scutellaria baicalensis* Georgi, which is known to possess antiinflammatory and antioxidant activity. Johns Hopkins researchers in collaboration with Boehringer Ingelheim have investigated whether baicalein has neuroprotective effects in PC12 cells expressing an inducible α-Syn E46K mutation causative of familial parkinsonism with Lewy body dementia. α-Syn neurotoxicity was concentration-dependently inhibited by baicalein treatment (3 nM-10 μM) and this effect was associated with preservation of proteasome activity and mitochondrial membrane potential in baicalein-treated cells. Moreover, baicalein prevented α-Syn-induced neuronal aggregation and reduced apoptosis in transiently transfected N2A cells (86).

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