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Meeting Report

Neuroscience research highlights: towards new therapeutic avenues

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Abstract

The 36th Annual Meeting of the Society for Neuroscience took place in Atlanta, Georgia on October 14-18, 2006. This meeting brought together international members from different disciplines within the neurosciences, all interested in building on new research developments in neurotherapeutics. This article highlights selected work emerging from this meeting.

Introduction

Around 30,000 scientists from around the world participated in the 36th Annual Meeting of the Society for Neuroscience to discuss a wide variety of topics in the neurosciences, ranging from discoveries in basic neurophysiology to the underlying causes of neurological and psychiatric disorders. This report focuses on newly discovered pharmacological targets and the most innovative advances in drug therapy for chronic pain, Alzheimer's disease (AD) and other diseases of the nervous system.

New drug targets

Soluble epoxide hydrolase (sEH)

Tissue injury results in the release of a diverse group of inflammatory mediators that sensitize nociceptors, leading to heightened pain transmission. Long-chain fatty acids, particularly arachidonic acid (AA), are molecules that play a pivotal role in associated inflammatory cascades. Another branch of the arachidonate cascade is the cytochrome P-450-catalyzed conversion of AA and linoleic acid (LA) to a group of metabolites, including epoxyeicosatrienoic acid (EEH), a putative endothelium-derived hyperpolarizing factor, which is further metabolized by the enzyme soluble epoxide hydrolase (sEH) to proinflammatory dihydroxyeicosatrienoic acids. Researchers from the University of California, Davis, have reported on the antinociceptive effects of two sEH inhibitors in a model of inflammatory pain. AUDA-BE and AUDA-950 potently inhibit human sHE with IC_{50} values of 0.8 and 14.1 nM, respectively. These sEH inhibitors, when administered systemically or topically, reverse behavioral hyperalgesia in lipopolysaccharide (LPS)- and carrageenan-induced models of inflammatory pain, without affecting baseline pain responses (1).

Pick1 (protein interacting with C kinase-1)

Pick1 (protein interacting with C kinase-1), a PDZ domain-containing protein, has been shown to bind to protein kinase C (PKC) α and the AMPA receptor subunit GluR2 in neurons of the CNS. It functions as a targeting and transport protein to present the activated form of PKCα to GluR2, leading to GluR2 Ser880 phosphorylation and playing a role in synaptic AMPA receptor trafficking. Previous evidence has suggested that synaptic AMPA receptor trafficking underlies the molecular mechanisms of many forms of neuronal plasticity in the CNS. Spinal central sensitization, a specific form of neuronal plasticity, is thought to be an essential mechanism underlying the development and maintenance of chronic pain. Research emerging from Johns Hopkins University and Hong Kong University of Science and Technology has shown that Pick1 may be critical for the development and maintenance of pain hypersensitivity in various persistent/chronic pain models. The development of Pick1 knockout mice was associated with impaired thermal and mechanical hyperalgesia under chronic inflammatory (induced by Freund's complete adjuvant [FCA]) and neuropathic pain (spinal nerve ligation) conditions; however, these animals exhibited intact responses to acute noxious stimuli. Furthermore, Pick1 deletion blocked FCA-

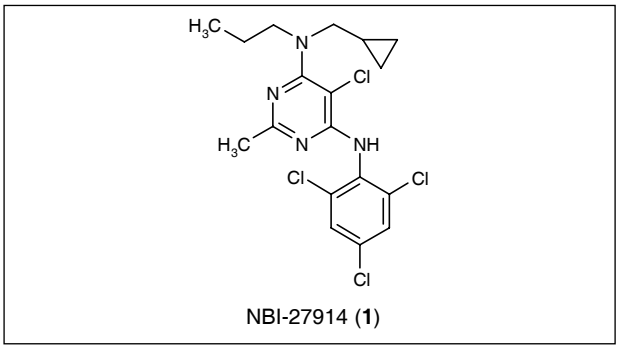
induced increases in PKCα phosphorylation at GluR2 Ser880 and GluR2 internalization in the spinal cord (2).

The leukocyte integrin $\alpha_4\beta_1$

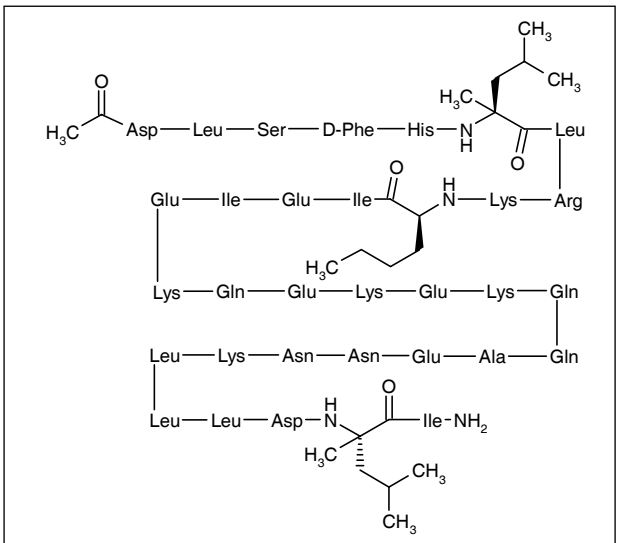
Spinal cord injury (SCI) involves the primary injury and a subsequent progression of secondary events that cause significant further damage. Leukocytes, in particular neutrophils, undergo oxidative burst, generating a series of reactive oxygen metabolites. Moreover, indiscriminate phagocytosis causes further spinal cord injury. Leukocyte emigration from the bloodstream to inflammatory sites entails a sequence of leukocyte adhesion molecule interactions with the endothelial cell and extracellular matrix ligands. Different families of integrins mediate cellular adhesion. The leukocyte integrin $\alpha_4\beta_1$ (CD49d/CD29 or very late antigen-4 [VLA-4]) is expressed by neutrophils, macrophages and lymphocytes and plays an important role in their activation, migration into tissue, adhesion and activation of cell signaling pathways. Ligation of $\alpha_4\beta_1$ also induces free radical production by neutrophils. Biogen Idec, in collaboration with Canadian research groups, has presented new clinically relevant data indicating the neuroprotective potential of targeting the $\alpha_4\beta_1$ integrin. Intravenous application of a monoclonal antibody to the α_4 subunit of the $\alpha_4\beta_1$ integrin in a rat model of compression SCI during the acute period following injury decreased inflammatory cell accumulation in the injured cord, reduced the expression of oxidative enzymes, decreased intraspinal levels of free radicals and limited cord damage by lipid peroxidation (3).

CRF_1

The amygdala is involved in emotional responses to sensory stimuli and emotional learning and memory. Pain has a strong emotional-affective component and the amygdala plays an important role in the central processing and modulation of pain. Previous studies have shown synaptic plasticity and neuronal sensitization in the laterocapsular division of the central nucleus of the amygdala (CeLC) in a model of arthritic pain. Corticotropin-releasing factor (CRF) can act as a neuromodulator of synaptic transmission via CRF_1 and CRF_2 receptors, which are present in the amygdala. Researchers from the University of Texas have discovered that CRF_1 receptors specifically contribute to the output function of the CeLC with regard to modulation of spinal and supraspinal pain behaviors in a model of arthritic pain. In arthritic rats, the CRF_1 antagonist NBI-27914 (**1**), but not the CRF_2 antagonist astressin2-B (**2**), administered into the CeLC, reduced the duration of audible and ultrasonic vocalizations and increased spinal reflex thresholds. Therefore, targeting the endogenous activation of CRF_1 receptors in the amygdala could be beneficial for arthritic pain (4). Further electrophysiological studies confirmed that the CRF_1 antagonist NBI-27914 also significantly inhibits elevated responses of CeLC neurons in arthritic rats, while astressin2-B has no effect (5).



NBI-27914 (**1**)



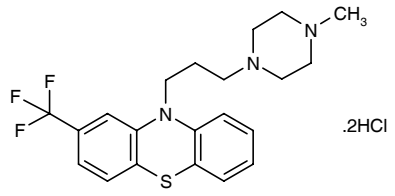
Astressin2-B (**2**)

Calcium/calmodulin-dependent kinases (CaMKs)

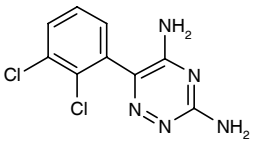
The calcium/calmodulin-dependent kinases (CaMKs) are involved in a large number of cellular responses induced by hormones, neurotransmitters and other signaling. The current family of multifunctional CaMKs consists of CaMKI, CaMKII and CaMKIV. These kinases translate and coordinate calcium fluxes into appropriate cellular responses via phosphorylation. Researchers from the University of Illinois have presented new data suggesting that CaMKII contributes to the pathogenesis of persistent inflammatory and neuropathic pain. *In vivo* application of trifluoperazine (**3**), a clinically used antipsychotic and a potent CaMKII inhibitor, was shown to reverse allodynia and hyperalgesia as a result of FCA-induced inflammation of the rat hind paw. Furthermore, CaMKII T286A mutant mice exhibited a significantly reduced phase II response to formalin and mice with spinal nerve ligation did not develop allodynia or hyperalgesia (6).

Aquaporin-4

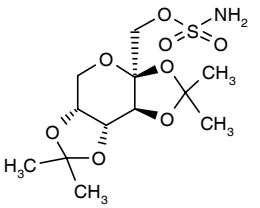
Aquaporin-4 (AQP4) is a transmembrane water channel. Recent studies have highlighted the link between



Trifluoperazine (**3**)



Lamotrigine (**4**)

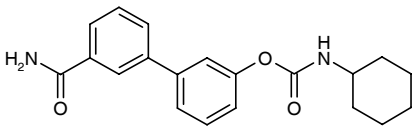


Topiramate (**5**)

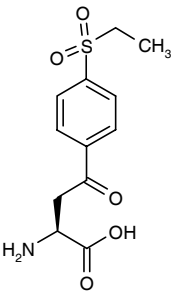
AQP4 and epilepsy. For example, AQP4 knockouts are highly resistant to pentylenetetrazol (PTZ)-induced seizures (7). A research collaboration among U.S. and Japanese groups has shown, via computational screening and *in vitro* studies, that antiepileptic drugs currently marketed in the U.S. all display some affinity for the AQP4 pore site, with significant inhibitory effects seen for lamotrigine (**4**) and topiramate (**5**). These observations provide further evidence for the antiepileptic effects of targeting AQP4, which could result in the development of novel antiepileptics (8).

Fatty acid amide hydrolase (FAAH)

The enzyme fatty acid amide hydrolase (FAAH) catalyzes the intracellular hydrolysis of the endogenous cannabinoid anandamide. Therefore, inhibition of FAAH has been proposed as an approach that may have utility in the treatment of anxiety and depression via enhancement of the endogenous cannabinoid system. URB-597 (**6**) is a novel FAAH inhibitor that has demonstrated antidepressant and anxiolytic potential. Researchers at the University of California, Irvine, discovered that stress-induced decrease in food intake in a rat model of chronic mild stress could be reversed by chronic URB-597 treatment, together with a dose-dependent elevation of anandamide in midbrain (9). URB-597 produced additional antiinflammatory effects in a model of LPS-induced paw inflammation in mice, which were mediated by cannabinoid CB_2 receptor stimulation (10).



URB-597 (**6**)



UPF-874 (**7**)

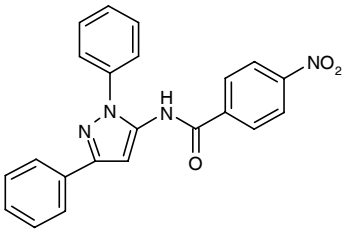
Kynurenine aminotransferase II (KAT II)

Selective inhibition of kynurenine aminotransferase II (KAT II), a major biosynthetic enzyme of kynurenic acid (KYNA), may have a fundamental role in the understanding of CNS processes related to cognitive function. Previous studies have shown that reducing KYNA formation can improve cognitive performance due to enhanced NMDA and α7 nicotinic acetylcholine receptor function. Researchers from Italy and the U.S. have described the first selective synthetic KAT II inhibitor, UPF-874 (**7**), which showed potent KAT II inhibition (IC_{50} = 6.1 μM) *in vitro* and no significant inhibition of KAT I or other prominent enzymes in the kynurenine pathway (up to 1 mM). *In vivo* infusion of UPF-874 into the hippocampus of conscious rats (5 mM) rapidly and reversibly reduced extracellular levels of KYNA (11, 12). UPF-874 has been claimed in patent literature (13).

$mGluR_5$

Targeting metabotropic glutamate receptors (mGluR) has emerged as a novel approach in the treatment of neurological disorders such as anxiety, where blockade of the $mGluR_5$ subtype has demonstrated therapeutic benefit. Recent investigations at Schering-Plough have found that mice lacking $mGluR_5$ display anxiolytic-like behavior such as that induced by $mGluR_5$ antagonists (MPEP and MTEP), including increased time in the open arms of the elevated plus maze and reduced marble-burying behavior. Both $mGluR_5$ antagonists induced sedative-like effects in wild-type and knockout mice, thus ruling out $mGluR_5$ mediation of these side effects and encouraging the development of new anxiolytic drugs targeting $mGluR_5$ (14).

Another study highlighted the therapeutic potential of VU-29 (**8**), a novel small nonpeptide allosteric potentiator



VU-29 (**8**)

of $mGluR_5$, as a cognition-enhancing drug. In CA1 hippocampal slices, VU-29 facilitated the induction of long-term potentiation (LTP), a cellular correlate of learning and memory processes, when paired to subthreshold electrical stimulation. Additionally, it was found to increase NMDA receptor-mediated excitatory postsynaptic potentials (EPSPs) in CA1 pyramidal neurons. In turn, VU-29's effects on LTP were suppressed in the presence of an NMDA receptor blocker. Furthermore, pretreatment of hippocampal slices with an Src kinase inhibitor blocked the development of VU-29-induced LTP, indicating that phosphorylation of the NMDA receptor subunits by the Src kinase family may mediate this effect (15).

Receptor trafficking and new therapeutic agents for mood disorders

A session chaired by Dr. Rasenick from the College of Medicine, University of Illinois, Chicago, revolved around the mechanisms of protein trafficking at synapses involved in synaptic plasticity, the pathophysiology of psychiatric diseases and therapeutic drug action.

Antidepressant-sensitive norepinephrine transporter

Dr. Uhna Sung from the Center for Molecular Neuroscience, Vanderbilt University, Nashville, Tennessee, discussed recent findings on norepinephrine transporter (NET) physiology and its modulation by antidepressant therapy. Noradrenergic signaling is, in part, regulated by the action of NET, which mediates norepinephrine (NE) reuptake from the synapse back to presynaptic vesicles. Pharmacological blockade of NET by antidepressants increases synaptic NE concentrations and potentiates noradrenergic transmission. However, NET also regulates noradrenergic transmission by modifying its expression under certain conditions, such as depolarization and chronic stress. Chronic cold stress was found to increase NET trafficking from the cytoplasm to the plasma membrane in NE axons in rat prefrontal cortex and also to induce tyrosine hydroxylase (TH) expression, as a response to increased activity triggered by stress situations (16). Thus, NET trafficking could be involved in the pathophysiology of affective disorders such as depression which can be precipitated by chronic exposure to stress. Moreover, NET surface trafficking is regulated by calcium and CaMKI and II. Ongoing research is focusing on protein complexes that support trafficking of antidepressant-sensitive NET, in addition to the already identified protein phosphatase 2A anchoring subunit and 14-3-3 proteins. Ubiquitin and ubiquitin system enzymes have also been found in NET complexes in CAD cells, a CNS-derived catecholaminergic neuronal cell line, and preliminary observations reported that antidepressants may increase ubiquitination and NET protein levels.

AMPA receptor trafficking by antidepressants or mood stabilizers

Dr. Jing Du from the National Institute of Mental Health (NIMH) presented an overview of modulation of AMPA receptor trafficking by mood stabilizers. AMPA receptors belong to the category of ionotropic glutamate receptors (GluR) and are formed by four subunits: GluR1, GluR2, GluR3 and GluR4. AMPA receptors are responsible for the majority of excitatory synaptic transmission in the CNS and have been involved in forms of synaptic plasticity underlying learning and memory processes. Recent data from Dr. Du's lab revealed that AMPA GluR1 receptor trafficking may be involved in the adaptive synaptic plasticity underlying the treatment of bipolar disorder. Chronic lithium and valproate treatment decreased AMPA receptor subunit GluR1 expression in synaptosomal preparations from the hippocampus of treated animals. Surface GluR1 expression was also attenuated by lithium and valproate in cultured hippocampal neurons, which correlated with a reduction in GluR1 phosphorylation at a specific protein kinase A (PKA) site (GluR1p845) needed for transporting the receptor to the surface (17). Moreover, Dr. Du commented on recent findings on a TAT fusion protein that inhibits phosphorylation at the PKA site (TAT-p845) and which mimicked lithium and valproate effects on GluR1. AMPA also appears to be essential for manic-like behaviors since amphetamine-induced hyperactivity (mania model) can be decreased by GYKI-52466, an AMPA receptor antagonist. TAT-p845 markedly reduced amphetamine-induced hyperactivity when injected into the rat hippocampus, and it decreased conditioned place preference in rats. TAT-TGL, a GluR1 sequence-based peptide interfering with the GluR1 PDZ-ligand domain, also blocked mania-like effects. Research on small molecules for human therapy should be pursued as the use of TAT protein can have widespread undesired activity in the CNS.

Presynaptic protein interactions regulating glutamate release in the action of stress and antidepressants

Dr. Maurizio Popoli from the University of Milan proposed new targets for the development of antidepressants according to recent findings on the role of glutamate transmission in psychiatric pathophysiology. Research from Dr. Popoli's lab has led to the discovery that antidepressants modulate glutamate neurotransmission in the hippocampus by influencing protein inter-

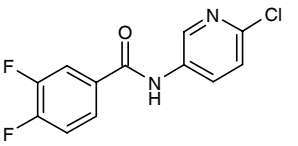
actions critical for the formation of the SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor) complex (18). Chronic treatment with mechanistically different antidepressants (fluoxetine, reboxetine and desipramine) significantly reduced depolarization-evoked glutamate release in hippocampal nerve terminals. This dampening effect on glutamatergic transmission may be due to a redistribution of protein interactions between the components that regulate neurotransmitter vesicle release, such as those forming the SNARE complex. Antidepressants caused a dramatic reduction in αCaMKII autophosphorylation, which is known to favor SNARE complex assembly and exocytosis by interacting with syntaxin-1. Chronic antidepressant treatment decreased the expression in synaptic membranes of phosphorylated αCaMKII, as well as that of the three proteins forming the core SNARE complex (syntaxin-1, synaptobrevin and SNAP-25). Interestingly, a significant reduction in syntaxin-1/αCaMKII interaction contrasted with the increased binding between syntaxin-1 and Munc-18, an association known to dampen neurotransmitter release. These results, in addition to explaining how antidepressants stabilize glutamatergic neurotransmission in the hippocampus, provide new targets for therapeutic intervention based on the redistribution of protein-protein interactions in the presynaptic machinery.

G-protein signaling in microdomains of the plasma membrane is altered in depression or by antidepressant treatment

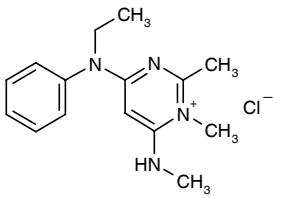
Other mechanisms of action of antidepressants were explored by Dr. Robert J. Donati from the Illinois College of Optometry. Recent findings revealed that chronic treatment with structurally and functionally different antidepressants such as desipramine and fluoxetine interfere with G-protein α subunit (Gs-α) localization in cholesterol-rich plasma membrane domains or lipid rafts (19). Lipid rafts influence molecular signaling by favoring specific protein-protein interactions and compartmentalizing cellular membrane processes. Antidepressant drugs caused Gs-α to exit from membrane lipid rafts in C6 glioma cells, which could translate into an increased functional interaction with adenylyl cyclase and enhancement of CREB signaling. Microtubule-disrupting drugs such as colchicine affected Gs-α raft localization in a similar way as antidepressant drug treatment, thus suggesting that these drugs alter the interaction between Gs-α and the microtubule cytoskeleton, in particular β-tubulin (20).

Functionally diverse ion channels play pivotal roles in the pathobiology of chronic pain

The role of ion channels and associated subunits in the initiation and maintenance of chronic pain was examined in this minisymposium, which also evaluated channel-targeting agents and new targets for the management of this condition.



ICA-27243 (**9**)



ZD-7288 (**10**)

KCNQ channels as targets for antinociceptive therapies

Dr. Aaron C. Gerlach from Icagen presented data on selective openers of KCNQ or Kv7 channels. KCNQ channels are low-threshold voltage-gated potassium channels that comprise five known KCNQ proteins (KCNQ1-5). KCNQ2 and KCNQ3 are mostly expressed in the CNS, where they form a heteromultimeric channel that regulates the M-current, a subthreshold potassium current that stabilizes the membrane potential and controls neuronal excitability. Mutations in KCNQ2 and 3 have been associated with benign familial neonatal convulsions, an inherited form of epilepsy. Icagen's ICA-27243 (**9**), a novel KCNQ channel activator, has demonstrated high selectivity for KCNQ2/3 channels (EC_{50} = 0.5 μM) and efficacy in animal models of pain by reversing capsaicin- and spinal nerve ligation-induced hyperalgesia. In rat dorsal root ganglion neurons (DRG), ICA-27243 hyperpolarized resting membrane potential, augmented the threshold for DRG depolarization and inhibited spontaneous firing.

HCN pacemaker channels and pain

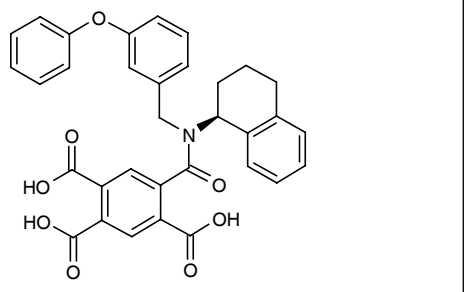
Dr. Alan D. Wickenden from Johnson & Johnson presented current developments on the molecular mechanisms underlying neuropathic pain. Results presented by Dr. Wickenden suggested that hyperpolarization-activated, cation-nonselective, cyclic nucleotide-modulated (HCN) channels, responsible for the I_h or pacemaker current that controls rhythmic generation of action potentials, could play a role in the initiation and maintenance of persistent pain. Axotomized sensory neurons are known to produce abnormal spontaneous firing or ectopic discharges that may contribute to neuropathic pain. In a recent study, intravenous infusion of the specific I_h antagonist ZD-7288 (**10**) inhibited spontaneous firing in injured DRGs *in vivo*. In further *in vitro* studies, ZD-7288 induced an almost total blockade of ectopic discharges from large myelinated fibers (Aβ) while partially suppressing ectopic discharge from thinly myelinated fibers (Aδ) In addition,

ZD-7288 was able to reverse mechanical allodynia in spinal nerve-ligated rats (21).

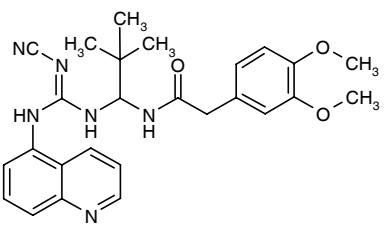
Neural and glial purinergic receptors in nociceptive and neuropathic pain states

The role of purinergic P2X receptors in nociception was reviewed by Dr. Michael F. Jarvis from Abbott Laboratories. The $P2X_3$ receptor subtype is abundantly expressed in nociceptive primary sensory neurons, where it forms a heteromeric channel comprising $P2X_2$ and $P2X_3$ subunits. Increasing evidence supports the role of $P2X_3$ receptors in chronic pain, as genetic deletion of $P2X_3$ receptors or decreased $P2X_3$ expression using antisense oligonucleotides reduces mechanical allodynia in animal models of chronic inflammatory pain (22). Also, pharmacological antagonism of $P2X_3$ receptors with Abbott's highly selective non-nucleotide $P2X_3/P2X_2$ receptor antagonist A-317491 (**11**) has been shown to reduce chronic hyperalgesia and allodynia in several animal models of neuropathic and inflammatory pain, via both peripheral and spinal $P2X_3/P2X_2$ receptors (23).

$P2X_7$ receptors represent additional pharmacological targets for pain. $P2X_7$ receptors are relatively insensitive to ATP (EC_{50} > 100 μM) and are located in glial cells and peripheral macrophages. Activation of $P2X_7$ receptors modulates the release of interleukin-1 (IL-1), suggesting a role in inflammatory pain. $P2X_7$ receptor deletion has been associated with decreased inflammation in experimental collagen induced-arthritis and attenuated inflammatory thermal hyperalgesia and nerve injury-induced mechanical allodynia. A-740003 (**12**) is a competitive ATP-sensitive $P2X_7$ receptor antagonist that blocks $P2X_7$ agonist-evoked IL-1β release in human macrophage/monocyte THP-1 cells *in vitro*. In an *in vivo* rat model of spinal nerve injury, A-740003 dose-dependently reduced nociception. In addition, it attenuated mechanical allodynia in two models of neuropathic pain (chronic constriction injury of the sciatic nerve and vincristine-induced neuropathy) and decreased thermal hyperalgesia in chronic inflammatory conditions (24).



A-317491 (**11**)



A-740003 (**12**)

Microglia-neuron signaling in neuropathic pain

Dr. Michael W. Salter from the Hospital for Sick Children in Toronto presented an overview on microglia-neuron signaling and its role in neuropathic pain, and suggested new targets for therapeutic intervention. Microglial cells are distributed throughout the CNS and can respond to noxious stimuli. In the spinal dorsal horn, microglial activation occurs following peripheral nerve injury, which features hypertrophy, proliferation and expression of cell-surface molecules, including $P2X_4$ receptors, together with activation of p38 mitogen-activated protein kinase (MAPK) (25). Recent findings revealed that stimulation of $P2X_4$ receptors in microglia caused a shift in transmembrane anion gradient (E_{anion}) to more depolarized potentials in spinal lamina I (LI) neurons in the dorsal horn of the spinal cord, together with a reduction in GABAergic inhibition, which translated into increased pain sensitivity. Previous studies have shown that peripheral nerve injury induces comparable LI neuron hyperexcitability, hence reducing the nociceptive threshold (26). $P2X_4$ receptor-evoked release of brain-derived neurotrophic factor (BDNF) from activated microglia to LI neurons was considered the mechanism of microglia-LI neuron communication, as functional blockade of BDNF-TrkB signaling prevented the shift in E_{anion} and reversed peripheral nerve injury-induced allodynia in rats (27).

Sodium channel β2-subunits regulate the excitability of DRG neurons and modulate the response to pain

Dr. Lori L. Isom's work on sodium channel β2-subunits has provided evidence for new mechanisms underlying neuropathic pain and proposed novel drug targets. Neuropathic pain is characterized by hyperexcitability of primary sensory neurons, which has been related to altered expression of voltage-gated sodium channels (VGSCs). Auxiliary β-subunits are essential modulators of VGSC function. Moreover, upregulation of β2-subunit expression occurs in sensory neurons after nerve injury, and more recently, β2-subunits have been found to modulate electrical excitability in DRG neurons *in vivo* by regulating the tetrodotoxin-sensitive (TTXs) sodium current. β2 Knockout mice displayed reduced TTXs sodium currents in small-fast DRG neurons, while they remained unaffected in small-slow neurons. Gene deletion of the β2-subunit also resulted in decreased the TTXs VGSC subtype $Na_v1.7$ mRNA and protein expression (28).

The emerging importance of the neurovascular link in health and disease

Dr. Peter Carmeliet from the University of Leuven and the Flanders Interuniversity Institute of Biotechnology in Belgium discussed the link between blood vessels and neurons and recent findings that could lead to novel therapies for neurodegenerative disorders. Blood vessels and nerves course alongside one another and the development of their networks is regulated by common cues. Vascular endothelial growth factor (VEGF) promotes angiogenesis, which is important in development but remains inactive in normal adults, except in the cycling ovary and in the placenta during pregnancy. Abnormal angiogenesis is associated with pathological processes, such as cancer and ocular and inflammatory disorders, where excessive angiogenesis occurs. In contrast, insufficient angiogenesis can lead to ischemic tissue disease (29). Mutations in the VEGF gene promoter (-2578A/A) have been linked to symptoms resembling amyotrophic lateral sclerosis (ALS) in mice, including progressively weaker muscles and spinal cord injury. Low levels of VEGF protein appear to be correlated with a higher risk for developing ALS in mice and humans (30). Intracerebroventricular delivery of recombinant VEGF protein in a rat model of ALS has been shown to delay the onset of paralysis, improve motor performance and prolong survival, without signs of associated toxicity (31). Similar results were previously obtained using a lentiviral vector expressing the VEGF gene in a mouse ALS model (32). Other neurodegenerative disorders presenting similarities to ALS may benefit from VEGF therapy. For instance, the -2578A/A VEGF genotype has also been associated with an increased risk for developing AD, indicating a potential new treatment option in a subset of AD patients (33).

New forms of brain drug delivery

Transvascular delivery of therapeutics to the brain with molecular Trojan horses

Large molecules have limited access to the brain due to the existence of the blood-brain barrier (BBB). Dr. William M. Pardridge from the University of California at Los Angeles, proposed novel brain drug delivery strategies using Trojan horses, which help transport larger compounds to the CNS (34). These agents are of varied nature and include endogenous peptides, modified proteins or peptidomimetic monoclonal antibodies (MAbs). Endogenous molecules, such as small nutrients or vitamins, access the brain using endogenous BBB transporters, while larger substances use receptor-mediated transporters (RMTs). Molecular Trojan horses bind to these specific receptors on the BBB to deliver drugs into the brain following systemic administration. A recent example is BDNF, which, when attached to a peptidomimetic MAb targeting the transferrin receptor (TfR), was able to reach its brain target, significantly reduce stroke volume and improve motor function in rats with middle cerebral artery occlusion (MCAO) (35). Similar neuroprotective effects were obtained with fibroblast growth factor-2 (FGF-2) and vasoactive intestinal polypeptide (VIP) conjugated to a TfR MAb (34). Nonviral gene transfer to the brain has also been achieved with Trojan horse technology by incorporating nonviral plasmid DNA into liposomes coated with polyethylene glycol (PEG) strands, with only a small fraction conjugated to a Trojan horse. In a mouse model of human brain cancer, suppression of human epidermal growth factor receptor (EGFR) expression and increased survival were achieved by intravenous injection of an expression plasmid encoding an interference RNA against the human EGFR mRNA. The plasmid was encapsulated in pegylated immunoliposomes doubly targeted to both the mouse TfR and the human insulin receptor (HIR), to enable transport across the mouse BBB and the human brain cancer cell membrane, respectively (36). This new therapeutic approach has shown promise in experimental models of different neurological disorders, including stroke, brain cancer and AD.

New peptide vectors for brain drug delivery

Researchers at AngioChem have developed aprotinin peptide vectors called Angiopeps to transport drugs across the BBB and into the brain following intravenous administration and through a receptor-mediated process. Paclitaxel, which does not access the brain due to the action of the P-glycoprotein (P-gp) efflux pump at the BBB, was conjugated to Angiopep, thus bypassing P-gp and concentrating in brain parenchyma. In brain tumor animal models, therapeutic levels of paclitaxel were achieved, resulting in inhibition of tumor growth and increased survival (37).

New therapeutic strategies in AD

Nontoxic cocaine derivatives

Researchers from Cornell University have described the potential benefits of nontoxic cocaine derivatives for AD. Their work stems from previous studies (39) which identified a sequence of 7 nucleotides, common to agents that bind to a cocaine-specific inhibitory site (CIS) of the nicotinic acetylcholine receptor (nAChR), in high-affinity RNA aptamers against β-amyloid protein(1-40) (Aβ[1-40]) (40). Current research efforts have focused on the investigation of agents that bind to the cocaine binding site on the nAChR and displace cocaine without inhibiting the receptor, thus mimicking the effect of cocaine but without the toxic effects. Interestingly, micromolar concentrations of a cocaine derivative fitting this profile, ecgonine (41), were found to dose-dependently inhibit Aβ(1-40) aggregation, whereas 3-acetoxyecgonine methyl ester (a closely related derivative that does not alleviate cocaine inhibition of the nAChR) did not inhibit Aβ(1-40) aggregation. Therefore, cocaine deriva-

tives that bind to the CIS on the nAChR and displace cocaine could be a useful strategy to prevent Aβ-induced neurotoxicity (42).

An orally active antiamyloidogenic agent

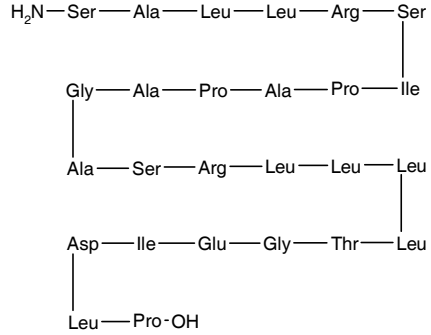
Researchers from ProteoTech described the development of exebryl-1, a disease-modifying small-molecule therapeutic that causes marked clearance of brain amyloid load and improves memory in transgenic mouse models of AD. The active components of the rain forest woody vine *Uncaria tomentosa* have been shown to have Aβ-inhibitory activity. Research has led to the development of exebryl-1, a derivative of PTI-0038, one of the major synthetic compounds derived from this natural product. Exebryl-1 is a small-molecule analogue that demonstrated reductions in fibrillar and soluble Aβ of 40-60% in aged amyloid precursor protein (APP) transgenic animals, a model for AD. This compound also improved spatial memory by approximately 70%, to levels comparable to those in nontransgenic animals. After a single oral dose, exebryl-1 rapidly reached brain tissue and reached peak concentrations at 4 h. No signs of toxicity were observed in preliminary studies (43).

Inhibitors of RAGE/Aβ interaction

The receptor for advanced glycation end products (RAGE) is thought to be a primary transporter of Aβ across the BBB into the brain from the systemic circulation, while the low-density lipoprotein receptor-related protein LRP-1 mediates the transport of Aβ out of the brain (44). Overexpression of RAGE at the BBB increases brain influx of circulating Aβ, which is associated with neurovascular stress. Researchers from the University of Rochester have been screening new compounds as inhibitors of RAGE/Aβ interaction. They recently highlighted FPS-2 from a group of tertiary amides as their lead compound. Preliminary *in vivo* data from APPsw$^{+/-}$ mice treated intraperitoneally once daily over a period of 8-10 months have shown reduced levels of Aβ40 and Aβ42 in the hippocampus, increased cerebral blood flow and a significant improvement in learning and memory (45).

sLRP

Soluble clusters II and IV of LRP-1 (sLRP), which mediate the transport of Aβ out of the brain, can bind directly and with high affinity to Aβ peptides. Further research from the University of Rochester has investigated the potential for sLRP to prevent the transport of circulating Aβ40 into the brain through its peripheral binding and sequestration. Intravenous administration of sLRP in mice facilitated a significant reduction in brain endogenous Aβ40 and 42 levels (52% and 17%, respectively) and markedly improved learning and memory and cerebral blood flow responses in APPsw$^{+/-}$ mice (46).



Colivelin (**13**)

Colivelin

Previous studies have identified a gene, designated humanin, which encodes a short polypeptide and abolishes neuronal cell death caused by multiple different types of familial AD genes and Aβ (47). Researchers from Tokyo have reported on the therapeutic potential of a humanin derivative, colivelin (**13**). Recent investigations have confirmed the neuroprotective effect of colivelin following intracerebroventricular administration (10 pmol once every 6 days) in multiple murine AD models, such as cholinotoxin Aβ injection paradigms (48). In recognition of the invasiveness of intracerebroventricular injection, and as the occipital lobes are spared in AD, the effectiveness of intranasal delivery to the CNS (via the olfactory bulb) has been investigated. Colivelin given intranasally provided a dose-dependent reduction in cholinotoxin- and scopolamine-induced amnesia. Further studies provided evidence that colivelin suppresses dysfunction in the central cholinergic system by activating the JAK2 (Janus kinase 2)/STAT3 (signal transducer and activator of transcription) axis (49).

Neuroprotection

Histone deacetylase (HDAC)

In the last several years, histone deacetylase (HDAC) inhibitors have enjoyed a great deal of attention as oncolytic drugs, due to their ability to reactivate tumor suppressor genes and possibly normalize malignant phenotype (50). New studies are focusing on their potential use as neuroprotectants. The HDAC inhibitors valproate (valproic acid), sodium butyrate and trichostatin A have been evaluated by scientists at the National Institutes of Health (NIH) for their antiinflammatory and neuroprotective properties in a preclinical stroke model. Subcutaneous administration of these compounds (300, 300 and 0.5 mg/kg, respectively) to rats following permanent MCAO produced a reduction in infarct volume and an improvement in motor, sensory and reflex performance. Sodium butyrate was also found to induce heat shock protein, block ischemia-induced downregulation of

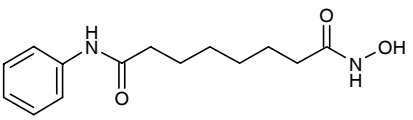
phosphorylated Akt and suppress upregulation of p53, inducible nitric oxide synthase (iNOS) and cyclooxygenase type 2 (COX-2), and both valproic acid and sodium butyrate suppressed microglial activation and reduced the number of microglia in the ischemic area. These findings support clinical evaluation of the three compounds for the treatment of stroke (51).

A study from the University of Massachusetts and the CNRS demonstrated that acute or chronic 28-day pretreatment of mice with the combination of sodium butyrate and fluoxetine, a selective serotonin reuptake inhibitor (SSRI), improved behavioral despair according to immobility scores in the tail suspension test. As sodium butyrate exerts antidepressant-like effects in mice, the potential therapeutic benefit of combined regimens with other antidepressants deserves further exploration (52).

Data reported by researchers from U.S. and U.K. universities also suggested that HDAC inhibitors could be helpful in preventing neurodegeneration in Huntington's disease (HD). Genetic studies with yeast cells expressing a mutated huntingtin (mhtt) fragment demonstrated that transcriptional dysregulation of the kynurenine pathway may be a critical event in mhtt-mediated toxicity. Moreover, elevated levels of 3-hydroxykynurenine and quinolinic acid, both of which are neuroactive metabolites of the kynurenine pathway able to induce excitotoxic neuronal death, have been found in the brains of HD patients, as well as in animal and yeast models of HD. Interestingly, vorinostat (SAHA, **14**), an HDAC inhibitor just recently approved for the treatment of cutaneous T-cell lymphoma (CTCL), can block the kynurenine pathway in microglial cells and decrease the levels of 3-hydroxykynurenine in microglia isolated from HD mice (53).

Nicotinamide adenine dinucleotide (NAD)

Axonal degeneration is present at different stages of multiple sclerosis (MS), with subsequent axonal loss occurring as the disease progresses. The extent of axonal damage is thought to correlate with the permanent neurological dysfunction seen in MS. Researchers at the Children's Hospital and the Brigham & Women's Hospital in Boston have found that experimental autoimmune encephalomyelitis (EAE), an animal model for MS, may share similarities to Wallerian degeneration, a self-destructive process observed at the distal portion of a transected axon after injury. Induction of EAE in slow Wallerian degeneration (WldS) mutant mice overexpressing a chimeric nuclear protein that protects sick or injured axons from degeneration decreased axon loss compared to EAE control mice, indicating that the WldS phenotype moderately protects from axonal damage. The WldS protein is composed of the ubiquitin assembly protein Ufd2a and the nicotinamide adenine dinucleotide (NAD) biosynthetic enzyme Nmnat1. This research team previously demonstrated that degenerating axons show reduced NAD levels. In more recent studies, reduced NAD concentrations were found in the spinal cord of wild-type EAE animals compared to WldS EAE mice. Additionally, daily nicotinamide administration (125 or 500 mg/kg s.c.) markedly increased NAD levels in both wild-type and WldS mice. Nicotinamide also reduced the areas of immune cell infiltration and demyelination in both EAE models, and improved behavioral deficits. Together, these results suggest a potential therapeutic application for nicotinamide in MS (54).



Vorinostat (SAHA, **14**)

Natural products in neurological disorders

Gingko biloba

The standardized *Ginkgo biloba* leaf extract Egb-761 inhibits Aβ oligomerization in a transgenic cell line expressing Aβ (55). Additional studies have confirmed that Egb-761 markedly suppresses small heat shock protein 16.2 (sHSP16.2), a chaperone protein associated with intracellular Aβ expression (56). Further investigations at Columbia University demonstrated that ginkgolide A, ginkgolide B, ginkgolide J (constituents of Egb-761) and *Gingko biloba* extracts enriched in terpene trilactones (TTL) rescue long-term potentiation (LTP) deficits in the hippocampal CA1 region caused by Aβ, whereas ginkgolide C and bilobalide had no effect. Both ginkgolide J and TTL were able to prevent Aβ-induced cell death (57). *In vitro* studies in rat brain slices demonstrated that ginkgolide A, ginkgolide B and ginkgolide C protect neurons against damage caused by neurotoxic insult by verapamil, a calcium channel blocker, with superior efficacy compared to flavonoid glycoside constituents (58). TTL components of *Gingko biloba*, Yuyu's YY-1224 and YY-1824, also provided protection against dopaminergic neurotoxicity induced by MPTP or methamphetamine and appeared to be more effective than Egb-761, suggesting potential for parkinsonian syndromes (59). It has also been postulated that bilobalide is a potent neuroprotective agent that reduces brain edema formation under ischemic conditions by more than 50% in the MCAO stroke model (60).

Spirulina

The potential benefits of the blue-green algae spirulina in the aging brain were explored at the University of South Florida. *In vitro*, spirulina partially reduced LPS-induced tumor necrosis factor-α (TNF-α) release in microglia. *In vivo*, aged rats fed a diet containing 0.1% spirulina for 1 month experienced a significant increase in hippocampal neurogenesis (61).

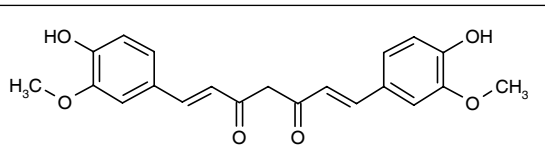
Blueberry

Studies highlighted that the beneficial effects of blueberry may be due to direct reductions in oxidative stress and/or inflammatory signaling. MAPK and NF-κB signaling pathways have been shown to be involved in blueberry-induced downregulation of iNOS and COX-2. In the BV2 murine microglial cell line, blueberry C-18 fraction suppressed MAPK phosphorylation and blocked LPS-stimulated NF-κB activity (62). Deficits in calcium buffering induced by dopamine or Aβ42 in primary hippocampal neuronal cells can also be antagonized by blueberry extract. Hippocampal neurons treated with blueberry exhibited suppressed Aβ-induced elevations in MAPK phosphorylation and also blocked dopamine- and Aβ-induced increases in PKCγ and CREB. Thus, it appears that the beneficial effects of blueberry polyphenols may involve reductions in stress signaling (63).

It has been shown that muscarinic receptor subtype determines vulnerability to oxidative stress. The effects of blueberry were tested in COS-7 cells transfected with the M_1 and M_3 muscarinic receptor subtypes and exposed to dopamine or Aβ42 in the presence or absence of C2 ceramide (C2C). Pretreatment with blueberry extract prevented Aβ42-induced increases in MAPK phosphorylation in M_1-containing cells. Additionally, blueberry extract was able to reduce dopamine-induced increases in CREB and PKCγ phosphorylation in both M_1- and M_3-transfected cells (64).

Curcumin

Curcumin (**15**), a natural component of the spice turmeric possessing antiinflammatory and antioxidant properties, has shown potential for the treatment of AD. Chronic treatment with curcumin over 6 months in APPsw transgenic mice (Tg2576) overproducing mutant APP reduces β-secretase (BACE1) expression levels by 78%. Concomitant reduction of Aβ levels together with iNOS, COX-2 and IL-1β was also found. *In vitro*, curcumin was able to prevent elevated BACE1 and Aβ levels in neuron cultures exposed to oxidant agents. Curcumin can also suppress Aβ oligomer-induced translocation of p21-activated kinases (PAKs), which have been implicated in synaptic and cognitive deficits in AD. In Tg2576 mice exposed to safflower oil, curcumin was able to prevent PAK reduction and synaptic deficits associated with this diet (65). Curcumin's reversal of neurotoxic effects was further postulated to result from its suppression of proinflammatory mediators. Microglial production of inflammatory factors, such as TNF-α, NO, prostaglandin E_2 (PGE_2), IL-1β, intracellular reactive oxygen species (ROS) and extracellular superoxide can be reduced by curcumin treatment. The protective effects of curcumin against MPP-induced toxicity in dopaminergic neurons were found to be mediated by microglia, as these effects were not found in microglia-depleted or neuron-enriched cultures (66).



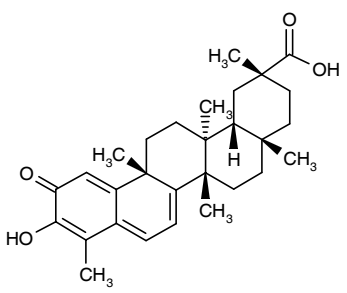
Curcumin (**15**)

Plant extracts

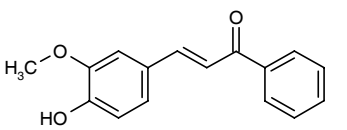
Celastrol (tripterin, **16**), is a potent antiinflammatory and antioxidant compound extracted from a perennial creeping plant belonging to the Celastraceae family. Studies in a model of MPTP-induced neurotoxicity demonstrated that celastrol injections can attenuate associated dopaminergic neuronal loss in the substantia nigra compacta and significantly reduce the production of inflammatory mediators in activated microglia (67).

Other studies investigated the plant *Delphinium denudatum*, or more specifically its FS-1 fraction. FS-1 concentration-dependently reduced the duration, frequency and amplitude of seizure-like events induced by combined application of bicuculline and 4-aminopyridine in rat hippocampal entorhinal cortex slices, an *in vitro* model of resistant epilepsy, resulting in eventual complete blockade (68).

Collaborative research between the Ewha Woman's University in Seoul and the University of Mississippi has led to the synthesis of analogues of yakuchinone B, a diarylheptanoid compound found in the medicinal plant *Alpinia oxyphylla*. The antiinflammatory properties of these compounds were evaluated in cultured cortical neurons and microglia. Within this series, compound **17** significantly reduced glutamate-induced excitotoxicity in cortical neurons. It also attenuated neurotoxicity induced by oxidative stress (hydrogen peroxide and oxygen-glucose



Celastrol (tripterin, **16**)



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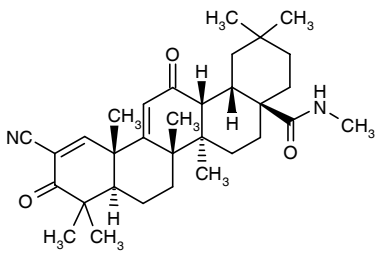
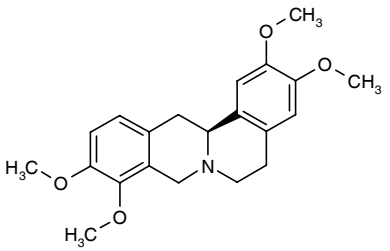


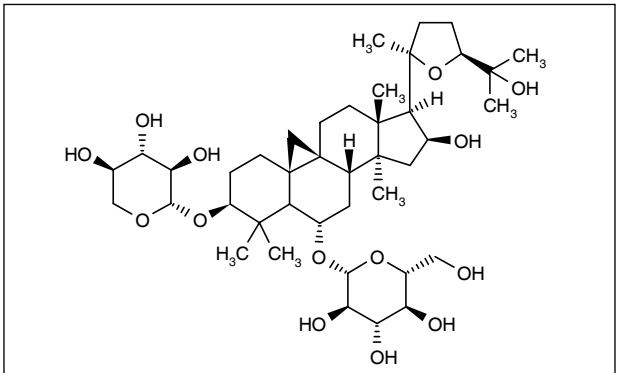
TP-224 (**18**)



levo-Tetrahydropalmatine (l-THP, **19**)

deprivation). In microglial cells, compound **17** suppressed LPS-induced NO release and iNOS expression and also inhibited the release of proinflammatory cytokines (TNF-α, IL-1β, IL-6). In a mouse model of MCAO, it significantly reduced infarct volume. Together, these data suggest that this analogue may be a potential candidate for the treatment of neurodegenerative diseases (69).

Triterpenoids are natural products that resemble steroids and have been traditionally used for medicinal purposes in many Asian countries due to their antiinflammatory activity. TP-224 (**18**), a methyl amide derivative of the triterpenoid analogue CDDO, has been shown to provide significant neuroprotection against neuronal damage in both MPTP and 3-nitropropionic acid (3-NP) animal models, markedly reducing striatal lesions and cell loss (70). *levo*-Tetrahydropalmatine (*l*-THP, **19**) is a tetrahydroprotoberberine alkaloid plant constituent found in many traditional Chinese herbal preparations used for sedation and analgesia, and has been reported to reduce heroin use in recovering addicts in China due to its low-affinity antagonism of dopamine (DA) D2 and D3 receptors, as well as high-affinity antagonism and possible partial agonist effects at D1 receptors and antagonism of several 5-HT receptor subtypes. *In vivo* studies in rats trained to self-administer cocaine showed that *l*-THP significantly attenuates cocaine self-administration and cocaine-induced reinstatement (71). Further studies characterized the neuroprotective effects of *Astragalus membranaceus* (AS), a traditional Chinese medicine that has been used clinically in China for many years. Astragaloside IV (**20**), a purified active ingredient, significantly reduced cell death in PC12 cells exposed to the excitotoxin NMDA, with further evidence for neurite outgrowth (72).



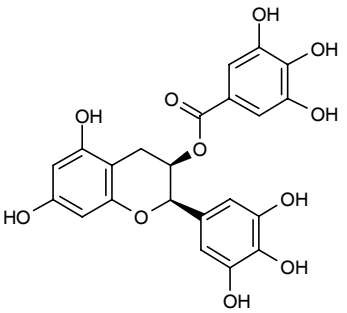
Astragaloside IV (**20**)

Flavonoids

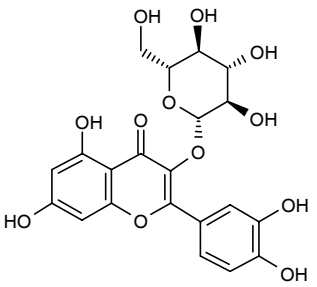
Studies investigating the neuroprotective role of (–)-epigallocatechin-3-gallate (EGCG, **21**) have shown that this polyphenolic constituent of green tea modulates AIDS dementia-like neuronal damage via inhibition of key regulators of proinflammatory signaling through JAK1/STAT1 (73). In rat hippocampal organotypic slice cultures treated with the Aβ protein, EGCG attenuated the neurotoxic action of Aβ protein and improved neuronal survival (74). Further studies demonstrated that oral administration of EGCG to “Swedish” mutant APP-overexpressing mice (Tg2576) reduced Aβ deposition in the cingulate cortex, hippocampus and entorhinal cortex by 43%, 34% and 41%, respectively (75).

Radical-scavenging activity has been proposed as the main explanation for the neuroprotective actions of the dietary components flavonoids. Studies in murine neuronal cultures confirmed that quercetin 3-glucoside (**22**) significantly elevates the induction of antioxidant response element (ARE) and NQO1 (NADPH:quinone oxidoreductase), which plays an important role in the fight against oxidative stress and harmful xenobiotics (76). Additional studies demonstrated that the flavonol (–)-epicatechin (**23**) significantly reduces infarct volumes in a mouse model of MCAO, mediated by upregulation of the heme oxygenase (HO)-1 antioxidant defense system (77). The flavonoid mixture from *Rhus verniciflua* (FM, ratios: kaempferol 85; fustin 10; fisetin 5) improves memory impairment induced by Aβ(1-42) via antioxidant properties, as well as stimulation of muscarinic M_1 receptors (78).

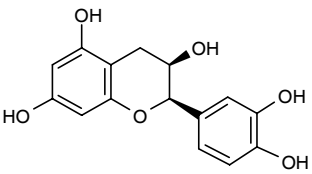
Previous studies have found that the red wine polyphenol resveratrol (**24**) has neuroprotective activity dependent on SIRT1 activation (79). Continuing work has shown that resveratrol augments the cellular antioxidant defense capacity via the induction of HO-1 by ARE-mediated transcriptional activation of NF-E2-related factor 2 (Nrf2), thereby protecting PC12 cells from Aβ-induced oxidative stress (80). Resveratrol protects the neonatal brain against hypoxic-ischemic injury, protecting against axonal degeneration through activation of SIRT1, a class III histone deacetyltransferase (sirtuin) (81). Further studies confirmed that resveratrol can reduce apoptotic neu-



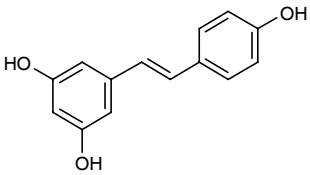
(–)-Epigallocatechin-3-gallate (EGCG, **21**)



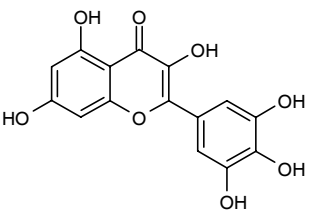
Quercetin 3-glucoside (**22**)



(–)-Epicatechin (**23**)



Resveratrol (**24**)



Myricetin (**25**)

ronal death induced by MPP^+-induced oxidative stress and LPS-induced neuroinflammation by lowering IL-1α and TNF-α mRNA and, at the same time, decreasing apoptotic cell death (82).

Myricetin (**25**), another wine polyphenol, exerted neuroprotective efficacy against Aβ-induced toxicity, reducing Aβ-induced calcium influx, and subsequently the activation of caspase-3, and preventing the structural change of Aβ from random coil to a β-sheet structure (83).

Further studies have focused on identifying an alcohol-free alternative for the treatment of AD. MegaNatural® Gold Grape Seed Extract significantly reduces the generation of Aβ peptides by primary corticohippocampal neuron cultures prepared from Tg2576 mice and *in vivo* administration (200 mg/kg/day) over a period of 3 months significantly reduced the accumulation of Aβ(1-40) and Aβ(1-42) peptides and amyloid neuritic plaques in the brain (84).

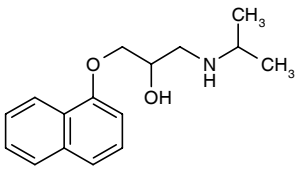
Drug repositioning

Finding new therapeutic uses for drugs that are already marketed, or for safe drug candidates that failed in clinical trials, is an emerging strategy known as drug repositioning. We highlight newly proposed uses for propranolol, sildenafil, (*R*)-flurbiprofen and AC-253, an amylin receptor antagonist, in AD.

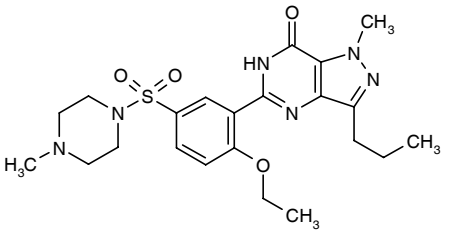
Cardiovascular risk factors including hypertension have been associated with cognitive impairment and AD. Researchers from the Mount Sinai School of Medicine and the University of British Columbia found that levels of Aβ(1-40), Aβ(1-42) and neuritic plaque were significantly reduced in the transgenic Tg2576 mouse model of AD following propranolol (**26**) treatment (10 mg/kg/day for 4 months). *In vitro*, propranolol decreased Aβ production in primary corticohippocampal neurons from Tg2576 mice. In addition, propranolol treatment caused a reduction in the proinflammatory cytokines IL-1β and interferon gamma, known to induce Aβ production, in Tg2576 astrocytes. Further *in vivo* studies are ongoing (85).

Hippocampal LTP has been found to be profoundly impaired by Aβ via several signaling pathways. In particular, downregulation of the NO/cGMP/CREB memory pathway by Aβ has been demonstrated by Italian researchers at the University of Catania in collaboration with Columbia University (86). Moreover, NO donors and cGMP analogues protected against Aβ-induced impairment of LTP. Therefore, this research team found that the phosphodiesterase type 5 (PDE5) inhibitor sildenafil (**27**), which prevents cGMP degradation, rescued synaptic and cognitive deficits in APP/PS1 transgenic AD mice. Sildenafil treatment re-established normal LTP and CREB phosphorylation in 3-month-old APP/PS1 brain slices. Also, 3-week treatment with sildenafil (3 mg/kg/day i.p.) improved contextual learning and spatial working memory over a prolonged period of time (3 months). Moreover, sildenafil-treated mice showed augmented basal synaptic transmission and LTP (87).

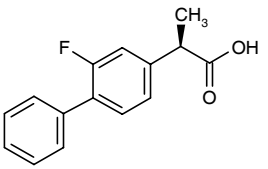
(*R*)-Flurbiprofen (MPC-7869, tarenflurbil, **28**; Myriad Genetics), a single enantiomer of the nonsteroidal antiinflammatory drug (NSAID) flurbiprofen, has been shown to selectively reduce brain levels of Aβ42 in transgenic Tg2576 AD mice. *In vitro*, clinically relevant concentra-



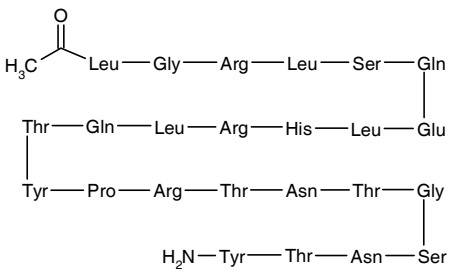
Propranolol (**26**)



Sildenafil (**27**)



(*R*)-Flurbiprofen (MPC-7869, tarenflurbil, **28**)



AC-253 (**29**)

tions of (*R*)-flurbiprofen (*i.e.*, 1 μM) protected both SH-SY5Y cells and primary neurons from Aβ42 cytotoxicity. (*R*)-Flurbiprofen also upregulated nerve growth factor (NGF) gene expression, thus increasing its synthesis and secretion and suggesting an underlying mechanism for its neuroprotective action (88). (*R*)-Flurbiprofen is in phase III clinical trials at Myriad Genetics for the prevention and treatment of Alzheimer's-type dementia.

Amylin, a pancreatic hormone involved in glucose metabolism, was first isolated from amyloid protein deposits in the pancreas of patients with type 2 diabetes mellitus. Structurally similar to Aβ, amylin also shares a similar neurotoxicity profile. Furthermore, Aβ neurotoxicity in basal forebrain neurons appears to be mediated by the amylin receptor. The amylin receptor antagonist AC-253 (**29**; Amylin Pharmaceuticals) has been shown to attenuate Aβ-induced neurotoxicity in human cultured neurons via the inhibition of apoptotic pathways involving mitochondrial (caspase-9) and endoplasmic reticulum (caspase-4 and -12)-associated proteins (89).

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