Lactate administration reproduces specific brain and liver exercise-related changes

In mice, exercise induces liver peroxisome proliferator-activated receptor gamma co-activator 1 alpha (PGC-1α) mRNA, increases gluconeogenesis, but otherwise minimally affects respiration infrastructure. Brain PGC-1-related co-activator (PRC) mRNA, mitochondrial DNA (mtDNA), and vascular endothelial growth factor A (VEGF-A) mRNA increase, whereas tumor necrosis factor alpha (TNF-α) mRNA decreases. Lactate injection reproduces some, but not all, of these effects. Exercise-generated lactate, therefore, likely mediates some exercise-associated liver and brain effects.

Read the Editorial Highlight for this article on page 4 and the full article on page 91.

Formaldehyde in brain: an overlooked player in neurodegeneration?

The neurotoxin formaldehyde is an environmental pollutant that is also generated during normal brain metabolism. The levels of formaldehyde in brain increase with age and in some neurodegenerative disorders. As excess formaldehyde accelerates glycolysis and glutathione export in neural cells, formaldehyde-induced alterations in brain metabolism and oxidative stress may contribute to the pathological progression of neurodegenerative disorders.

Read the full article on page 7.
Binding of the repressor complex REST-mSIN3b by small molecules restores neuronal gene transcription in Huntington's disease models

Dysregulation of REST and its target genes have been implicated in Huntington's disease. We have coupled structured-based virtual screening approaches to biological assays and selected molecules that interfere with the repressor complex REST-mSIN3b. In particular, at the non-toxic dose, compound C91 is able to increase neuronal gene transcription and to reverse low Bdnf mRNA levels in HD models.

Promoter-like sequences regulating transcriptional activity in neurexin and neuroligin genes

Neurexins and neuroligins constitute large families of synaptic cell-surface molecules that play essential roles in neurotransmission and are linked to autism spectrum disorders and schizophrenia. To better understand their gene regulation, we analyze putative promoter regions for transcriptional activity. Expression involves the brain-specific regulator MeCP2 and methylation frequency, suggesting an unexpected pathway for regulating their distribution, splicing or activity-dependent plasticity.

Read the full article on page 22.

Read the full article on page 36.
Amyloid precursor proteins are constituents of the presynaptic active zone

We deciphered the precise subcellular localization of APP at the nerve terminal. We demonstrate that APP and its family members, APLP1 and APLP2, are constituents of the presynaptic active zone, albeit virtually absent in synaptic vesicles (SV). Our findings open new avenues for understanding the physiological role of the mature APP proteins at synaptic contacts, implying a function in the physiology of neurotransmitter release.

Arrestin-dependent but G-protein coupled receptor kinase-independent uncoupling of D2-dopamine receptors

The classical model for the uncoupling and desensitization of G-protein coupled receptors (GPCRs) involves the phosphorylation of the agonist-bound receptor by G protein coupled receptor kinases (GRK), followed by the binding of arrestin to the GRK phosphorylated agonist-activated receptor. We reconstituted D2-dopamine receptor (D2R) signaling in Xenopus oocytes to show that arrestin-mediated uncoupling of D2R from associated G proteins (Gαβγ) occurs independently of GRKs.

Read the full article on page 48.

The classical model for the arrestin-mediated uncoupling of GPCRs involves prior agonist-dependent phosphorylation of the GPCR by GRKs

GRKs are not necessary for the arrestin-mediated uncoupling of D2R

Read the full article on page 57.
AMP-activated protein kinase counteracts brain-derived neurotrophic factor-induced mammalian target of rapamycin complex 1 signaling in neurons

Here, we report that growth factor-induced mTORC1 activity is dependent on glucose sufficiency, but not on amino acids in neurons. The mechanism underlying this phenomenon is AMP-activated protein kinase (AMPK) activation. AMPK activation inhibits BDNF-induced mTORC1 activity through TSC2 and raptor.

![Diagram of AMPK and mTORC1 signaling]

Read the full article on page 66.

Depolarization-induced suppression of a glycinergic synapse in the superior olivary complex by endocannabinoids

We report retrograde endocannabinoid modulation of synaptic strength in auditory brainstem nuclei of the Mongolian gerbil. Utilising electrophysiological recordings and immunohistochemistry, we found endocannabinoid-dependent suppression of excitatory and inhibitory glycinergic currents in the same neurone types. We propose that retrograde endocannabinoid signalling contributes to adapting inputs to sound environment in the time period around the onset of functional hearing.

![Diagram of cannabinoid signaling and synaptic modulation]

Read the full article on page 78.
Polyglucosan neurotoxicity caused by glycogen branching enzyme deficiency can be reversed by inhibition of glycogen synthase

Knockdown of glycogen branching enzyme in neurons led to accumulation of an insoluble form of glycogen called polyglucosan, to apoptosis and to activation of glycogen synthase. These effects were reversed by glycogen synthase inhibition through starvation and rapamycin treatments, suggesting a potential therapeutic value of glycogen synthase inhibition for treating glycogen storage disorders.

Read the full article on page 101.

Novel systemically active galanin receptor 2 ligands in depression–like behavior

We utilize several chemical modifications to increase in vivo usability of peptide-based ligands, acting upon CNS. Accordingly, we introduce a series of novel systemically active galanin analogues, with modest preferential binding towards GaIR2, and demonstrate their ability to attenuate depression–like behavior via brain GaIR2 in different mouse models of depression.

Read the full article on page 114.

PrP<sup>C</sup> regulates epidermal growth factor receptor function and cell shape dynamics in Neuro2a cells

In this study, we analyzed the PrP<sup>C</sup>-dependent gene expression signature of neuroblastoma (N2a) cells after transient acute up-regulation and down-regulation of PrP<sup>C</sup>. We demonstrate that PrP<sup>C</sup> plays roles in proliferation and neuritogenesis through modulation of EGFR activity. This approach will give new insights into the molecular mechanisms by which PrP<sup>C</sup> regulates key cellular functions in cell physiology.

Read the full article on page 124.
PI3Kγ contributes to MEK1/2 activation in oxidative glutamate toxicity via PDK1

Glutamate induces extracellular $\text{H}_2\text{O}_2$ generation by NADPH oxidase 4 (Nox4), leading to cell death in neurons. Our experiments, using siRNAs and chemical inhibitors, showed the PI3Kγ-PDK1–MEK axis but not Akt1, mTOR, or S6K to be involved in the glutamate-induced $\text{H}_2\text{O}_2$ generation and the subsequent toxicity in neurons.

Read the full article on page 139.

Amyloid beta$_{1-42}$ (Aβ$_{42}$) up-regulates the expression of sortilin via the p75$^\text{NTR}$/RhoA signaling pathway

Sortilin is the co-receptor of p75$^\text{NTR}$ which signals the cell death induced by Aβ and proneurotrophins. We found that sortilin is increased in the AD brain and up-regulated by Aβ and pro-brain-derived neurotrophic factor (proBDNF). Aβ-induced upregulation of sortilin is mediated by p75$^\text{NTR}$ and the down-streaming RhoA-ROCK signaling pathway. The Aβ/Sortilin/p75$^\text{NTR}$ signaling may play a role in the pathogenesis of AD.

Read the Editorial Highlight for this article on page 149 and the full article on page 152.

Crosstalk between Dopamine D2 receptors and cannabinoid CB$_1$ receptors regulates CNR1 promoter activity via ERK1/2 signaling

Cannabinoid CB$_R$ and dopamine D$_2$R cross-talk at ERK12 signal. Activation of D$_2$R increases the CB$_R$ transcription, which is ERK12 dependent and enhances CB$_R$ promoter activity that requires up-stream 1 to 222 region. The results implicate pre-synaptic D$_2$R could functionally regulate the retrograde cannabinoid signal in the striatum.

Read the full article on page 163.
GZ-793A, a lobelane analog, interacts with the vesicular monoamine transporter-2 to inhibit the effect of methamphetamine

GZ-793A inhibits methamphetamine-evoked dopamine release from synaptic vesicles through a surmountable allosteric mechanism and interacts with several sites on the vesicular monoamine transporter-2 (VMAT2), including high- and low-affinity intravesicular dopamine release sites, high-affinity extravesicular dopamine uptake sites and low-affinity extravesicular dihydrotetrabenazine binding sites. VMAT2 interactions likely underlie the ability of GZ-793A to attenuate the neurochemical and behavioral effects of methamphetamine.

Effects of VMAT2 inhibitors lobeline and GZ–793A on methamphetamine–induced changes in dopamine release, metabolism and synthesis in vivo

We determined if inhibition of the vesicular monoamine transporter (VMAT2) alters METH-induced changes in dopamine (DA) release, metabolism, and synthesis in vivo. Our results suggest that selective inhibition of VMAT2 produces a time-dependent decrease in DA release as a result of alterations in tyrosine hydroxylase (TH) activity, which may play a role in the ability of the VMAT2 inhibitor GZ–793A to decrease METH reward.
**Galanin stimulates neurite outgrowth from sensory neurons by inhibition of Cdc42 and Rho GTPases and activation of cofilin**

Galanin plays a key role in neurite outgrowth from adult sensory neurons via activation of the second galanin receptor (GalR2). Our results demonstrate the galanin decreases the activation state of Rho and Cdc42 and markedly increases the activation of cofilin. These changes lead to alterations in growth cone motility. These findings have important implications for the treatment of peripheral sensory neuropathies.

**GalR3 activation promotes adult neural stem cell survival in response to a diabetic milieu**

Adult neurogenesis impairment in diabetes could play a role in the development of neurological complications. GalR3 activation counteracts glucolipotoxicity in adult neural stem cells (NSCs) in the subventricular zone (SVZ) by decreasing apoptosis. At least part of the protective effect mediated by GalR3 activation occurs through modulation of the unfolded protein response (UPR) signaling in the endoplasmic reticulum. The data support a potential therapeutic development for treatment of diabetic brain disorders, based on increased neurogenesis by GalR3 activation. CB, cerebellum; LV, lateral ventricle; OB, olfactory bulb.

**Mitochondrial dynamics modulate the expression of pro-inflammatory mediators in microglial cells**

LPS induced excessive mitochondrial fission through mitochondrial localization of de-phosphorylation of Ser637 Drp1. Interestingly, inhibition of LPS-induced mitochondrial fission and mitochondrial ROS generation by Mdivi-1 and Drp1 shRNA attenuate the production of pro-inflammatory mediators via reduced NF-κB and MAPK signaling. Our results suggest that mitochondrial dynamics may be essential for understanding pro-inflammatory mediator expression in activated microglial cells.
Interleukin-1 β orchestrates underlying inflammatory responses in microglia via Krüppel-like factor 4

IL-1β is a potent pro-inflammatory cytokine which regulates inflammation in brain via activation of microglia. In this regard, we unravelled mechanisms for IL-1β mediated regulation of downstream Cox-2, iNOS (inducible nitric oxide synthase) as well as other cyto-chemokines in microglia and have established a role for Klf4 in mediating microglial activation. We further report that Klf4 mediates the production of endogenous IL-1β in response to exogenous IL-1β stimulation. We hereby propose a novel transcription factor underlying IL-1β mediated modulation of inflammation in the CNS.

Microglia in juvenile neuronal ceroid lipofuscinosis are primed toward a pro-inflammatory phenotype

Juvenile neuronal ceroid lipofuscinosis (JNCL) is a lysosomal storage disease caused by an autosomal recessive mutation in CLN3. Regions of microglial activation precede and predict areas of neuronal loss in JNCL; however, the functional role of activated microglia remains to be defined. In this report, primary microglia from CLN3<sup>Δ;ex7/8</sup> mutant mice over-produced numerous inflammatory cytokines in response to stimuli that are present in the JNCL brain, whereas wild-type microglia were relatively non-responsive. In addition, activated microglia induced significant cell death in CLN3<sup>Δ;ex7/8</sup> but not wild-type neurons, demonstrating that intrinsically diseased CLN3<sup>Δ;ex7/8</sup> neurons are less equipped to withstand cytotoxic insults. Collectively, aberrant microglial activation may contribute to the pathological chain of events leading to neurodegeneration during later stages of JNCL.

Minocycline reduces remyelination by suppressing ciliary neurotrophic factor expression after cuprizone-induced demyelination

To examine the role of microglia in remyelination, mice were treated with minocycline after cuprizone-induced demyelination. Minocycline treatment reduced the number of oligodendrocytes and CNTF expression in the remyelination phase. In vitro, CNTF directly affected the differentiation of oligodendrocytes. These findings suggest that minocycline reduces remyelination by suppressing CNTF expression by microglia after cuprizone-induced demyelination.

Read the full articles on pages 233, 245, and 259.
Diethylmaleate and iodoacetate in combination caused profound cell death in astrocytes

Energy failure and oxidative stress have been implicated in the pathogenesis of ischemia and cell death. Through the application of the glycolytic inhibitor iodoacetate and the glutathione chelator diethylmaleate, we report a potential link between cytosolic phospholipase A₂ (cPLA₂) activation and energy failure/oxidative stress-induced astrocyte damage involving reactive oxygen species (ROS), signaling through the kinases PKC-α, Src, Raf, and ERK and concurrent elevation of endogenous chelatable zinc.

Kallikrein 6 signals through PAR1 and PAR2 to promote neuron injury and exacerbate glutamate neurotoxicity

Here, we show kallikrein 6 (Klk6) and thrombin contribute to the proteolytic imbalance that occurs in CNS injury. Activation of the G-protein coupled receptor PAR1 was sufficient to mediate the neurotoxic effects of thrombin while KLK6 neurotoxicity involved activation of PAR1 and PAR2. In addition, both proteases exacerbated glutamate neurotoxicity. These data suggest Klk6, thrombin and PARs each represent new targets for the development of neuroprotective therapies.