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Editorial

The brain in flux: Genetic, physiologic, and therapeutic perspectives on transporters in the CNS

ABSTRACT

The brain has specific properties that make it uniquely dependent upon transporters. This is the 3rd edition of a biennial special issue that originates from a scientific meeting devoted to studies of transporters and their relationship to brain function and to neurodevelopmental, neurologic, and psychiatric disorders. The field continues to rapidly evolve with advances in studies of structure that inform mechanism, with genetic analyses in humans revealing surprising aspects of biology, and with integrated cellular to whole animal analyses of the role of transporters in their control of physiology and pathophysiology. This special issue includes a sampling of review articles that address timely questions of the field followed by several primary research articles.

1. Introduction

In August of 2017, nearly 70 scientists converged at the Maintenon Hotel Golf and Spa to discuss the latest advances in our understanding of membrane transporters and their roles in brain function and disease. This modern hotel is located in the gardens of Chateau de Maintenon in the Eure-et-Loir *department* of France (~90 km southeast of Paris). Construction of the original castle was started in the 13th century by the Amaury line. In the 17th century, the Chateu was renovated and expanded by Françoise d'Aubigné (Madame de Maintenon) with 'financing' from King Louis XIV (for more information, see http://www.chateaudemaintenon.fr/en/discover-chateau/history-chateau). The chateau with its surrounding moats and pastures provided an idyllic location to convene a group of eminent scientists from Australia, Europe, and both South and North America. The meeting started with a Friday afternoon session and concluded Monday 3 days later; there were 37 20–30 min presentations, two plenary lectures, and 12 data blitzes/poster previews of 5 min each. There were also two poster sessions. As a compliment that is a testament to the quality of the science being presented, there were never any empty seats in the lecture room despite the charming location. This was the 3rd biennial meeting of this group that has been a satellite to the International Society for Neurochemistry. The 4th is being organized by Drs. Sandra Hewett and Vania Prada to occur at La Baluchon (Saint Paulin, Québec, Canada) in August of 2019.

This special issue is the compendium of articles that were submitted by attendees at this meeting. In this editorial, we will give a brief commentary on the state of our understanding of the field and describe the highlights of the articles that are included in this special issue.

2. Brief background of transporters in brain function and linkages to disease

In 1990, the cDNA sequence for the GABA transporter was first reported (Guastella et al., 1990). Shortly thereafter, cDNAs for many of the other neurotransmitter transporters were identified (Arriza et al., 1994; Blakely et al., 1991; Hoffman et al., 1991; Kilty et al., 1991; Pacholczyk et al., 1991; Pines et al., 1992; Shimada et al., 1991; Usdin et al., 1991). Nearly 30 years later, we now know that there are 55 families of transporters with a total of 362 putative transporters in human genome (He et al., 2009). These gene families include transporters that directly utilize the energy generated from ATP hydrolysis to concentrate substrates on either side of the membrane, generally cations (e.g. the Na^+/K^+ ATPase). Many of the gene families utilize the electrochemical gradients generated from these ATPases to concentrate substrates on either side of the membrane (e.g. Na^+-dependent catecholamine and amino acid transporters or the H^+-coupled vesicular neurotransmitter transporters). Finally, many of these families simply facilitate the movement of molecules across a membrane without the capacity to generate a concentration gradient because no energy sources are coupled to the transport cycle (e.g. glucose transporters). The identification of this large family transporters has transformed our understanding of the biology of the nervous system and the relationship of transport to brain disease. Transporters are found on the plasma membrane, on subcellular organelles (e.g. mitochondria and the nucleus), and subcellular compartments (e.g., endosomes, lysosomes, and transmitter-containing vesicles).

Several unique features of the brain make it exquisitely dependent upon transporter function. First, the brain is anatomically unique. Neurons are both long and functionally somewhat asymmetric with both axons and dendrites. Many transporters are targeted to specific locations to provide better spatial control of substrate. For example, catecholamine transporters are enriched on the presynaptic nerve terminal to both clear transmitter from regions enriched in receptors and to recycle transmitter for repackaging in vesicles (Ciliax et al., 1995; Liu et al., 1994; Pickel and Chan, 1999). Second the brain contains diverse populations of cell types, including neurons and glia. Many neurotransmitters are trafficked between neurons and astrocytes; this trafficking is critically dependent upon transporters. For example, glutamate is primarily cleared into astrocytes where some fraction of this glutamate is converted to glutamine and then glutamine is exported from astrocytes (Chaudhry et al., 2002; Danbolt, 2001b). Third, the

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brain is highly vascularized and the endothelia of blood vessels form tight junctions that separate the brain from the periphery forming the basis of the blood brain barrier. Endothelia and vascular smooth muscle cells that underlie arteriole anatomy in the brain are almost exclusively sheathed by astrocytic endfeet (Abbott et al., 2006; Obermeier et al., 2013; Saunders et al., 2014; Zhao et al., 2015). Transporters are organized to facilitate directional flux of substrate into or out of the brain. For example, ATP-binding cassette transporters are organized on the basolateral and apical sides of the endothelial cells that line brain blood vessels ensuring directional flux of substrate across of the blood brain barrier (Abbott et al., 2010; Loscher and Potschka, 2005; Miller, 2010, 2015 Shawahna et al., 2011). Finally, the electrical activity of the brain imposes unique transporter-dependent challenges. The repolarization of neurons after synaptic transmission or action potential generation is dependent upon appropriate positioning of transporters and imposes unique energetic demands. In fact, the human brain only represents 2% of body weight, but it consumes ~20% of the basal metabolic rate (Attwell, 2000; Attwell and Laughlin, 2001; Barros et al., 2018). The brain is thought to be almost completely dependent upon glucose for energy production and except for the modest stores of glycogen that are found in astrocytes, requires that this glucose be delivered from the circulating blood on a continuous basis. In addition, although still controversial, there is evidence that lactate is shuttled between cells to provide 3 carbon backbone for oxidative phosphorylation; this shuttling is dependent on monocarboxylate transporters (Diaz-Garcia et al., 2017; Dienel, 2012, 2017; Funfschilling et al., 2012; Hertz, 2004; Machler et al., 2016; Pellerin et al., 1998).

Given these unique features and the fact that the brain controls essentially all behaviors, it should not be surprising that hundreds of transporter gene variants have been identified that are associated with neurodevelopmental, neurodegenerative, and psychiatric disease (Cartier et al., 2015; Hamilton et al., 2013; Heils et al., 1996; Ilie et al., 2016; Marshe et al., 2017; Murphy and Moya, 2011; Prasad et al., 2009; Ruel et al., 2008; Scott et al., 2011; Siemann et al., 2017; Veenstra-VanderWeele et al., 2012; Zike et al., 2017 Ng et al., 2014 for reviews, see Lin et al., 2015; O'Donovan et al., 2017). This realization is both informing critical aspects of biology and raising hope that treatments are not far away.

3. Summary of special issue

Investigators in the field continue to utilize a variety of approaches to study the function, biology, and pathophysiology of transporters, but the level of sophistication has dramatically escalated. In this special issue, we combine a number of timely review articles with primary research articles that typify many of the advances being made in studies of brain transport.

The special issue starts with a review of the K^+ - Cl^- co-transporters (KCC) that cooperate with Na^+ - Cl^- - K^+ (NKCC) and Na^+ - Cl^- (NCC) to regulate distribution of these ions across the plasma membrane by Bianca Flores and her colleagues (Flores et al., 2018). This article nicely showcases how the discovery of mutations in the KCC3 gene cause Hereditary Motor Neuropathy with Agenesis of the Corpus Callosum led to the generation of several mouse models of the disease and a better understanding of the role of KCC3 in control of neuronal function. Interestingly both gain- and loss-of-function mutations cause peripheral nerve disease, suggesting that inhibitors of KCC3 may provide a useful therapeutic when there is gain-of-function mutation. This speaks to the complexity of understanding how mutations in a single gene can present with different phenotypes and underscores the need to characterize the effects of each gene variant on function(s) of the transporter. The review ends with a summary of the many questions that still need to be resolved to truly understand the function of KCC3 under physiologic conditions and how KCC3 causes this form of neuropathy.

Next Beatriz López-Corcuera and her colleagues review the relationship between the neuronal glycine transporter (GlyT2 or SLC6A5) and hyperekplexia or “startle disease” (Lopez-Corcuera et al., 2018). As a bit of background, there are two glycine transporters. The first, GlyT1, is distributed to excitatory synapses where glycine functions as a co-agonist at the NMDA subtype of glutamate receptor, and thus thought to be more important for limiting excitatory signaling (Hansen et al., 2018). The second, GlyT2, is enriched in spinal cord and brainstem, locations where glycine functions as an inhibitory neurotransmitter through its actions at glycine-gated ion channels (Bowery and Smart, 2006; Callister and Graham, 2010; Eulenburg et al., 2005). While mutations in the glycine receptor are the most common cause of hyperekplexia, mutations in GlyT2 may be the cause in up 25% of cases. These patients present with a slightly different phenotype than that observed in individuals with receptor mutations; they present with infantile apnea and developmental delay. The review synthesizes information gleamed from basic science studies of structure, oligomerization, and maturation (endoplasmic, Golgi, to plasma membrane trafficking) of GlyT2 with the analyses of mutations that affect these fundamental aspects of GlyT2 function. It closes with a description of approaches that might be used to facilitate maturation of functional GlyT2 in subsets of these patients.

The third review of this special issue is from Moriah Hovde and colleagues who describe the advantages and disadvantages of the various *in vitro* model systems that have been employed to study dopamine transporter (DAT) activity and regulation (Hovde et al., 2018). The model systems include brain slices, synaptosomes, primary cultures, cell lines that endogenously express DAT and cell systems that have been used to exogenously express DAT. There is an extensive list of references to kinetic values for DAT that have been obtained in these various systems. In the final section of this article, the relationships of kinetic values to cholesterol content are discussed along with the evidence that cholesterol regulates DAT function.

The fourth review by Paul Gasser describes the role of the organic cation transporter, OCT3, in the clearance of dopamine (Gasser, 2018). As described, the data for the concentration-dependence of dopamine transport were best fit to two different sites when this transport was originally characterized (Iversen, 1965; Iversen and Salt, 1970). The first had a higher affinity (K_m value < 1 μM) and the second had a lower affinity (K_m value > 200 μM), but the capacity of the high affinity site was ~1% of that for the low affinity site, so these two sites were called high-affinity low capacity and low-affinity high capacity. Most early investigations focused on the high-affinity sites because many of the psychoactive drugs target these sites. This review summarizes the contributions of various OCTs and plasma membrane monoamine transporters (PMATs) to the clearance of monoamines in the brain; it then focuses on OCT3. This transporter is expressed by several different cells in the nervous system, including neurons, astrocytes, microglia, oligodendroglia, and endothelial cells. Like some of the other organic cation transporters, OCT3 is inhibited by corticosterone and not blocked by classical inhibitors of dopamine transport (e.g. cocaine). This review also describes the evidence that OCT3 contributes to the regulation of cocaine seeking behavior. The functional redundancy of PMATs and OCT3, or perhaps complementarity is a better word, is likely to impact our understanding the clearance of many neurotransmitters. It will be important to determine the conditions under which both systems are utilized. One presumes that the low-affinity sites have an important contribution to clearance when the high-affinity sites are blocked or saturated.

In the final review, Susan Underhill and her colleagues discuss the somewhat under-appreciated glutamate transporter called EAAT3 or EAAC1 which is encoded by the SLC1A1 gene (Underhill et al., 2018). Understanding the functional significance of this neuronal glutamate transporter has been somewhat enigmatic for a variety reasons. First, in contrast to mice deleted of the astroglial glutamate transporter, EAAT2 or GLT-1, mice deleted of EAAT3/EAAC1 transporter didn't have a remarkable phenotype when they were first characterized (Peghini et al., 1997; Tanaka et al., 1997). Second, the levels of EAAT3 protein are much lower than those of EAAT2, ~1% (Holmseth et al., 2012).

Finally, *in vitro* and *in vivo* studies demonstrated that a substantial pool of EAAT3 is found inside cells and not on the plasma membrane (Davis et al., 1998; Holmseth et al., 2012; Robinson, 2002). This review describes the evidence that this transporter likely has a significant impact on function. In fact, several mutations in SLC1A1 have been associated with diseases including dicarboxylic amino aciduria, schizophrenia, or obsessive-compulsive disorder. In a subsequent analysis of the EAAT3/EAAC1 knock-out mice, a different group observed an age-dependent loss of neurons consistent with depletion of glutathione (Aoyama et al., 2006). Several studies have supported a role of EAAT3 in providing glutamate as a precursor for the synthesis of GABA in inhibitory interneurons and in regulating the activation of glutamate receptors (Nieoullon et al., 2006; Sepkuty et al., 2002). In the final section of this review, evidence that amphetamine regulates the trafficking of EAAT3 and that supports a role for EAAT3 in amphetamine-induced behaviors is described.

These reviews are followed by a series of primary research articles. Michael Tomlinson and his colleagues seek to use structural information to understand why some inhibitors of DAT, such as cocaine, have psychostimulant effects while others (benztropines) do not (Tomlinson et al., 2018). They use a photoaffinity activated benztropine, substituted cysteine accessibility method protection analyses, and computational modeling to demonstrate that both classes of compounds have overlapping binding sites, suggesting that the differential behavioral effects are likely related to downstream signals induced by structural changes. Osama Refai and Randy Blakely continue their analyses of dopamine signaling in *C. elegans* based on loss of DAT function mutations that display a remarkable, paralytic phenotype when exposed to water (Refai and Blakely, 2018). Normally adding water to the animals induces swimming; animals with no functional DAT display paralysis, termed swimming-induced paralysis (Swip). This laboratory has used genetic screens and pharmacological approaches to identify and characterize genes whose mutation induce swip (Hardaway et al., 2012). In the current study, they demonstrate that the antipsychotic, azaperone, suppresses Swip in animals that express non-functional DAT or animals treated with a DAT inhibitor. This study paves the way for these investigators to screen for genes involved in azaperone-induced behavioral effects, an important step to further dissect the roles and protein interactions of D2-type dopamine receptors and possibly their contributions to brain disorders such as schizophrenia and attention-deficit/hyperactivity disorder.

As described by Paul Gasser in the review described above (Gasser, 2018), there is evidence that there are multiple transport sites for monoamines that may function complementarily. Alyssa West and her colleagues use fast-scan cyclic voltammetry (FSCV) and fast-scan controlled absorption cyclic voltammetry (FSCAV) to study the kinetics of serotonin clearance *in vivo* (West et al., 2018). These approaches have the advantages of impressive spatial selectivity (microelectrodes are 7 μm in diameter), relatively fast kinetics, and high chemical selectivity. They combine these approaches with modeling and pharmacological approaches to investigate the kinetics of serotonin release/clearance in medial prefrontal cortex. Their data are consistent with the notion that different transporters are engaged in serotonin clearance under different conditions (e.g. they have complementary roles). Along a similar theme, Felix Mayer and his colleagues characterize the interactions of cathinone derivatives, a group of psychoactive compounds found in bath salts, with the classical monoamine transporters and OCT3. The show that cathinones can induce efflux of substrates through OCT3; they also show that two different cathinones work synergistically to both block uptake of monoamines through the classical dopamine, serotonin, or norepinephrine transporters and stimulate efflux through OCT3.

Glutamate transport is mediated by five members of the SLC1A gene family, including EAAT1 (GLAST), EAAT2 (GLT-1), EAAT3 (EAAC1), EAAT4, and EAAT5 (for reviews, see Beart and O'Shea, 2007; Danbolt, 2001b; Robinson, 1999; Vandenberg and Ryan, 2013). Several lines of evidence suggest that the bulk of glutamate uptake in forebrain is mediated by EAAT2/GLT-1, including the fact the total knock-out of this gene results in a lethal phenotype (Tanaka et al., 1997). Original studies suggested that EAAT2 expression was almost exclusively restricted to astrocytes (Chaudhry et al., 1995; Rothstein et al., 1994). Several groups used synaptosomes or crude synaptosomal membrane preparations to characterize the properties of glutamate uptake and found that the pharmacology of uptake matched that observed for EAAT2/GLT-1 (Arriza et al., 1994; Ferkany and Coyle, 1986; Robinson et al., 1991 for review, see Robinson and Dowd, 1997). Based on these observations, it was assumed that the uptake in synatosomal membranes was actually into resealed astrocytic membranes that are found in these preparations (Henn et al., 1976). More recently, Paul Rosenberg's group has used cell-specific gene deletion approaches to demonstrate that hippocampal synaptosomal uptake is mediated by a mixture of both neuronal and astrocytic pools of GLT-1 (Petr et al., 2015). In this special issue, Yun Zhou and colleagues used a similar strategy to delete GLT-1 from neurons (Zhou et al., 2018b). They show that deletion of neuronal pools of GLT-1 using a synapsin-1-driven Cre recombinase results in essentially no change in total GLT-1 protein (~95% of control), but reduces accumulation of glutamate into crude synaptosomal membranes to ~50% of control in several different forebrain regions (see cover figure for schematic). They also demonstrate that this loss of neuronal glutamate uptake subtly shifts the incorporation of carbon backbone from glucose into both glutamine and GABA. This is followed by an article from Robert Laprairie and colleagues in which they test the hypothesis that glutamatergic dysfunction caused by selective deletion of GLT-1 from neurons can induce changes in gene expression similar to that observed in Huntington's Disease (Laprairie et al., 2018). Using synapsin Cre to delete neuronal pools of GLT-1, they observed decreased expression of some of the genes known to be dysregulated in Huntington's Disease, including cannabinoid receptors, preproenkaphalin, and phosphodiesterase 10A. The differences are specific to striatum and are age-dependent, providing an interesting model to understand the role of glutamate/GLT-1 in transcriptional dysregulation that occurs in Huntington's disease.

Like many of the other neurotransmitter transporters, the levels of glutamate transporters on the plasma membrane can be regulated by a variety of signals (Robinson, 2002). In this special issue, Ignacio Ibáñez and his colleagues have followed up on the observation that glutamate, itself, causes a redistribution of GLT-1 from the plasma membrane to an internal pool (Ibanez et al., 2018). They show that this glutamate-dependent redistribution of GLT-1 is dependent upon extracellular Ca^{2+}. In the next series of studies, they demonstrate that glutamate evokes a rapid increase in intracellular Ca^{2+} as detected using a genetic Ca^{2+} indicator and show that this increase in Ca^{2+} is attenuated by inhibitors of glutamate transport, by an inhibitor of reversed Na^{+}/Ca^{2+} exchange, or by an inhibitor of TRP channels. Finally, they show that two different inhibitors of reversed Na^{+}/Ca^{2+} exchange block glutamate-induced redistribution of GLT-1. Together, these studies suggest that the influx of Na^{+} that accompanies glutamate uptake triggers a reversal of the Na^{+}/Ca^{2+} exchangers, an increase in intracellular Ca^{2+}, and internalization of GLT-1.

It has been known for over 30 years that excessive activation of glutamate receptors can cause neuronal loss through a process called excitotoxicity (Choi, 1992; Doble, 1999; Greene and Greenamyre, 1996; McDonald and Johnston, 1990; Olney, 2003). It has also been clear that blocking or deleting glutamate transporters can cause an increase in extracellular glutamate and cell death (Danbolt, 2001a; Demarque et al., 2004; Rothstein et al., 1996; Tanaka et al., 1997). In this special issue, Tatiana Olivares-Bañuelos and her colleagues demonstrate that the organophosphate, diethyl dithiophosphate (DEDTP), alters the V_{max} of D-aspartate uptake measured in chick Bergmann glial cells (Olivares-Banuelos et al., 2018). The effects of DEDTP are both time and concentration-dependent with shorter incubations causing a decrease in V_{max} and longer incubations causing an increase in V_{max}. They find no evidence of cellular toxicity, and the effects of DEDTP on uptake are dependent upon Ca^{2+}. These studies highlight the importance of

understanding how these commonly used pesticides may have effects on various species that are inadvertently exposed.

After it is cleared into astrocytes, at least some fraction of glutamate is converted to glutamine by glutamine synthetase (McKenna, 2013; Sonnewald, 2014). In brain, expression of glutamine synthetase is essentially restricted to astrocytes (Norenberg and Martinez-Hernandez, 1979). Glutamine does not activate glutamate receptors; so after synthesis, it is released into the extracellular space (Chaudhry et al., 2002). Although the specific transporters responsible for the uptake of glutamine into the presynaptic terminus have not been identified to date (Varoqui et al., 2000), but see (Erickson, 2017), this glutamate-glutamine cycle is generally accepted as a major pathway for conserving the carbon backbone required for glutamate-mediated neurotransmission (McKenna, 2013; Sonnewald, 2014). In the final article of this special issue, Yun Zhou and colleagues generated a new line of mice in which several introns of the glutamine synthetase gene are deleted upon cre recombinase-induced excision (Zhou et al., 2018a). They used Emx1 to drive expression of Cre recombinase during early development and observe a loss of glutamine synthetase in hippocampus and cortex. This loss of glutamine synthetase causes dramatic reductions (> 50%) in aspartate, glutamate, glutamine, and GABA in these brain regions. It also results in an age-dependent glial pathology, seizures, and neurodegeneration. These changes are also associated with altered expression of glial glutamate transporters and some of the subtypes of glutamate receptors. As the field continues to evolve, one expects that we will develop a better understanding of the functional significance of the co-compartmentalization/physical coupling of metabolic enzymes with transporters.

4. Conclusion, awards, and most importantly thanks

In summary, our understanding of transporter function has continued to advance at a rapid pace. As captured by both the presentations and the papers in this special issue, this has been fueled by a variety of technological advances, including the ability to manipulate gene function in a pathway specific manner in intact systems, the density of sequencing information that is obtained in the clinical arena, and the ability to monitor transporter function and circuit activity in the intact nervous system. We look forward to hearing about more of these advances at the next meeting of this group in 2019.

The organizers of this regular event are committed to show-casing and acknowledging the outstanding contributions of the trainees and junior faculty who are pursuing careers in the area. The organizing committee selected the following trainees for awards based on their presentations (talks and/or posters): Rachel Cliburn, Bianca Flores, Jennie Garcia-Olivares, Felix Mayer, Nako Nakatsuka, Meagen Quinlan, Rachel Saylor, Adele Stewart, Carolyn Sweeney, and Suzanne Underhill. The committee also selected several early stage faculty investigators for awards including: Jorge Campusano, Lucia Carvelli, James Foster, Parry Hashemi, Ali Salahpour, and Sonja Sucic.

Of course, a meeting like the Brain in Flux conference is not possible without the help of many others. It starts with a group of scientists who recognize that it is the right time to share advances in a field. We thank all of the attendees for bringing such great scientific stories to share with the group, for asking insightful and stimulating questions, and for doing this is a respectful and friendly style. Without the support of the International Society for Neurochemistry, whose program committee selected this meeting as a satellite to the general meeting, along with the generosity of The American Physiological Society, Cellexbio, the Florida Atlantic University Brain Institute, Labex BioPsy, Neurocrine, Nikon, and Neurochemistry International (Elsevier), this meeting would never have happened. Importantly, none of the sponsors imposed constraints on the organization of the meeting nor on the choice of speakers. We were also ably led by a superior organizing committee, including Susan Amara, Phillip Beart, Lynn Daws, Eric Delpire, Ulrik Gether, Bruno Giros, Arturo Ortega, and Robert Vandenberg, who provided assistance with selecting abstracts for oral presentation and identifying trainees for travel awards.

Finally, we wish to express sincere thanks to Sheilah Jewart of the *American Society for Neurochemistry* (ASN), who worked with us from first concept to subsequent stages of meeting organization including selection of venue, negotiation of contracts, setting up of the website, working with budgets, and coordination of donation and reimbursements. That she managed to do all of this while maintaining a cheerful attitude is simply amazing.

Based on the success of our venture, a sequel to our meeting will assemble at the International Society for Neurochemistry Meeting in Montreal in August of 2019, once again devoted to the dynamic state of research of the brain in flux.

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