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Review Article

CNS Disorders—Current Treatment Options and the Prospects for Advanced Therapies

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The development of new pharmaceutical products has successfully addressed a multitude of disease states; however, new product development for treating disorders of the central nervous system (CNS) has lagged behind other therapeutic areas. This is due to several factors including the complexity of the diseases and the lack of technologies for delivery through the blood–brain barrier (BBB). This article examines the current state of six major CNS disease states: depression, epilepsy, multiple sclerosis (MS), neurodegenerative diseases (specifically Alzheimer's disease [AD]), neuropathic pain, and schizophrenia. Discussion topics include analysis of the biological mechanisms underlying each disease, currently approved products, and available animal models for development of new therapeutic agents. Analysis of currently approved therapies shows that all products depend on the molecular properties of the drug or prodrug to penetrate the BBB. Novel technologies, capable of enhancing BBB permeation, are also discussed relative to improving CNS therapies for these disease states.

Keywords central nervous system; blood–brain barrier; Alzheimer's disease; Parkinson's disease; depression; epilepsy; multiple sclerosis; neuropathic pain; animal models; drug delivery

INTRODUCTION

In recent years, extremely successful progress has been made by the pharmaceutical industry on a number of disease fronts; however, the progress made in the treatment of central nervous system (CNS) disorders has lagged behind. Substantially fewer new drug approvals for CNS disorders compared to other treatment areas are due to several factors including the extended development times, increased drug development costs, higher risk of clinical failure, and an incomplete understanding of both disease biology and requirements for delivery to the CNS. The complexity of CNS diseases in combination with the biological logistics of drug delivery has severely limited development of this area (Pardridge, 2002b).

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While most of the human anatomy is well understood, the CNS has continued to remain a mystery. Although several major advancements in neurobiology have been made in the past few decades, the complicated chemical reactions driving human consciousness are still poorly understood. Diseases of the CNS are also substantially more complicated than other diseases. These disease states, including depression, epilepsy, neurodegenerative disorders, neuropathic pain, multiple sclerosis (MS), and schizophrenia, are complicated disorders affecting mood, memory, and mobility: the true essence of being. Further complicating the treatment of these diseases is a lack of understanding of the causes, confounding treatments to either address the causes or the symptoms. These diseases have potential causes ranging from being genetic predisposition to environmental factors and combinations thereof; however, in most cases, no firm cause has been identified. Additionally, in many cases, the resulting symptoms of the disease are only understood empirically. Schizophrenia and depression, for example, are treated successfully through therapies that use receptor modifying drugs; however, an incomplete understanding of the functionality of these receptors, in combination with the underlying genetic differences of patients, has resulted in variable therapeutic efficacy and significant side effects. Further complicating this is the lack of truly physiologically representative models to study these diseases. Although several of the symptoms have been reproduced effectively in animals by behavioral, genetic, or surgical modification leading to predictive power in treatment, there will always be underlying differences between the species limiting the comparability of these systems (Rockenstein, Crews, & Masliah, 2007).

The CNS, unlike other organs in the human body, is protected by the blood–brain barrier (BBB), a homeostatic defense mechanism designed to protect against pathogens and toxins. This system is effective at preventing the entrance of potentially harmful materials by regulating solute entry via the transcellular route through variations in electrical resistance of endothelial cells at the tight junctions; however, this also limits the ability to deliver therapeutically beneficial compounds as well. Although it is widely believed that small molecules may easily pass the BBB,

their ability to partition is actually regulated by both their size (< 400 Da) and their lipophilicity. Many biological membranes, including the BBB, exhibit a threshold effect where the molecular permeability decreases exponentially as the molecular surface area increases (Fischer, Gottschlich, & Seelig, 1998). These limiting factors have a significant effect on biotechnology products as well, preventing nearly 100% of engineered proteins, monoclonal antibodies (MAb), and enzymes from passing (Pardridge, 2007b).

Materials are allowed to pass this barrier by a variety of mechanisms based on the physical and chemical properties of the substance in question, as shown in Figure 1 (Neuwelt, 2004). Generally, small lipophilic molecules will transit the barrier via paracellular or transcellular mechanisms based on the degree of lipophilicity; however, less than 2% of drug molecules cross the BBB via lipid mediation (Pardridge, 2007a). Other molecules, due to their charge, size, or hydrophilic nature, will be transported via other facilitated mechanisms such as receptor-mediated endocytosis, adsorptive endocytosis, efflux pumps, or via transporter proteins. The endogenous transporters are classified broadly in three major categories: carrier-mediated transport, active efflux transport, and receptor-mediated transport (Pardridge, 2007b). Carrier-mediated transporters actively bring in substances such as vitamins, nutrients, and hormones that are not naturally synthesized in sufficient quantities with the CNS. Active efflux transporters, particularly *p*-glycoprotein in the BBB, remove drugs and metabolites from the CNS, limiting the residence time of these compounds (Kusuhara & Sugiyama, 2001a, 2001b). These transporters also function to bring molecules via coordinated interaction of transporters within the brain capillary endothelial cells.

Given the complexity of delivery across the BBB, it may seem intuitive that delivery directly to the brain would be the best way to provide therapeutic efficacy; however, only limited therapeutic effect can be achieved with delivery routes such as intracranial injection. This is due to the rapid clearance of cerebral fluids, combined with the limited effect of diffusion. Furthermore, microcirculation in the brain occurs along paravascular pathways in proportion to arterial pressure; however, these rates are orders of magnitude smaller than cerebral spinal fluid (CSF) clearance (Krauze et al., 2005). In recent studies of intracranial injections, it was shown that only limited and short lived distribution was achieved in rat models, suggesting the limited effectiveness of this strategy in humans (Krewson, Klarman, & Saltzman, 1995).

As a result of the complexities of drug delivery, many research groups are now focusing on the use of biotechnology and nanotechnology to develop successful delivery strategies. By using molecular engineering to develop complex therapeutic moieties with functional ligands, such as MAbs or receptor binding groups, the BBB permeability of many developmental compounds has been improved significantly. Additionally, nanotechnology has been utilized to develop drug carrier systems capable of delivering high doses of drug in vitro and in animal models. Further combination of these two technologies has allowed for successful delivery of high drug loadings to the CNS, increasing the potential for treating CNS disorders. Although these delivery technologies have shown much promise, pharmaceutical companies have been slow in developing them for commercial gain. Today, no medium or large pharmaceutical company has a BBB drug targeting program (Pardridge, 2007a). It is hoped, however, that with a more complete mechanistic understanding of the CNS disease states, in combination with an ever expanding portfolio of delivery technologies, that the treatment options for these debilitating diseases can be expanded with increased efficacy.

This article discusses six major neurological disease states, encompassing the underlying disease state and current therapies

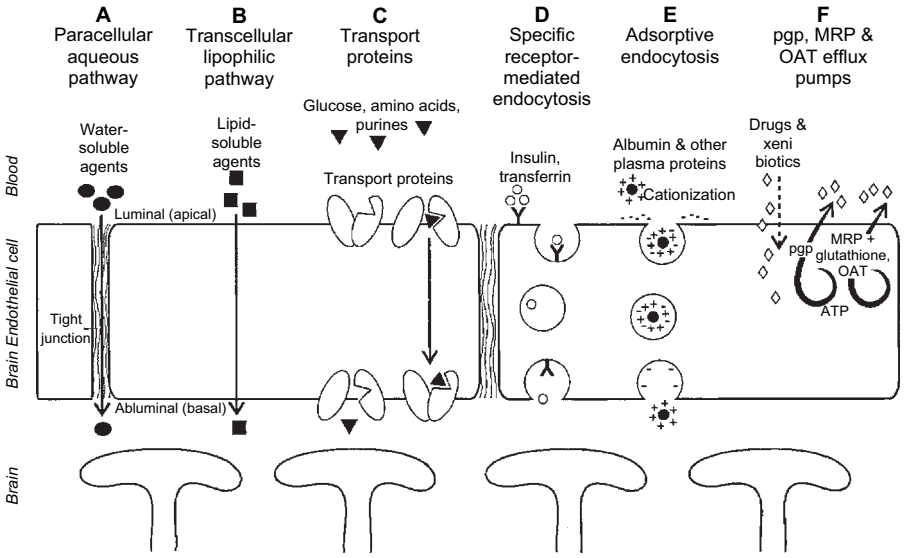

FIGURE 1. Mechanisms and routes of drug transport through the BBB. Reprinted with permission from Neuwelt (2004). Copyright © 2004, with permission from Lippincott Williams & Wilkins. .

available for treatment. The relevant animal models for each disease state are summarized. Finally, new drug delivery technologies for enhanced BBB permeation are identified and discussed in detail to provide more insight into these technologies.

DEPRESSION

Depression is one of the leading areas of research within pharmaceutical companies, due in large part to the high grossing sales of approved products such as Zoloft®, Effexor®, and Lexapro®, each of which grossed over $1.75 billion in 2006 (Pharmaceutical Executive Staff, 2007). The prevalence of major depressive disorder and bipolar disorder has been increasing, with estimated levels of 5.4–8.9% (Narrow, Rae, Robins, & Regier, 2002) and 1.7–3.7% (Kessler et al., 1994), respectively, within the US population. Although the biological mechanisms responsible for depression have not been fully elucidated, current therapies based on selective serotonin reuptake inhibitors and norepinephrine reuptake inhibitors have been effective for the treatment of the disease in many cases. Some suggest, however, that these molecules have reached the point of diminishing returns and that further significant advances will be seen with the development of new molecules and new delivery strategies generated from improved knowledge of the CNS (Thase, 2007).

Disease Biology

No firm cause of depression has been identified in patients; however, there are multiple hypotheses that have been suggested, including deficiencies of serotonin, norepinephrine, dopamine, *g*-aminobutyric acid, brain-derived neurotrophic factor (BDNF), somatostatin, and thyroid-related hormones (Mann, 2005). Additionally, structural changes in the cortical and subcoritcal regions of the brain have been observed by postmortem histopathological studies and neuroimaging studies in individuals diagnosed with depression, suggesting that these changes may be responsible for the mood disorder (Miguel-Hidalgo & Rajkowska, 2002). Although depression has been suggested as a genetic disorder, no firm link has yet been identified. Some recent studies have linked factors such as the presence of the 5-HTTLPR-S and CYP2C9*3 alleles to elevated depression risks (Dorado et al., 2007). Additionally, study of the 5-HTTLPR genotype has shown that it is responsible for variations in resting brain function of mood-related centers, further suggesting an underlying genetic cause for depression (Rao et al., 2007).

Approved Drug Products

Given the lack of fundamental understanding for the causes of depression, available products have focused on mediated receptor interactions, particularly for serotonin and norepinephrine to address the symptoms of the disease. For approved antidepressants, the only method of targeting the CNS relies on the inherent nature of the active pharmaceutical ingredient (API) to transit the BBB. For this review, several major antidepressant systems were selected, and their key properties are presented in Table 1. Based on the properties of the molecules, it is clear that these compounds all exhibit molecular weights and lipophilicities required for BBB permeation.

Bupropion

Bupropion is an aminoketone class selective serotonin reuptake inhibitor (SSRI), marketed under the trade name Wellbutrin® by Glaxo Smith Kline (Brentford, London, UK) as an immediate (IR) and modified release (MR) tablet. The drug substance is a racemic mixture, having a molecular weight of 276.2 g/mol and log *p* of 3.7 (Wishart et al., 2006), allowing the compound to permeate the BBB without the aid of an advanced delivery system.

The IR tablets, produced in 75 and 100mg strengths, are composed of a microcrystalline cellulose and hydroxypropyl cellulose matrix that provides for rapid onset of action, with reported t_{max} values achieved 2 h postadministration. In vivo, bupropion exhibits high plasma binding and is extensively metabolized into three metabolites: hydroxybupropion, threohydrobupropion, and erythrohydrobupropion; however, due to

TABLE 1
Approved Drug Products Indicated in the Treatment of Depression

API	Brand	Manufacturer	MW	log *p*	Class	Dosage Form
Bupropion	Wellbutrin®	Glaxo Smith Kline	276.2	3.7	SSRI	IRT, MRT
Duloxetine	Cymbalta®	Eli Lilly Co.	333.9	5.0	SSNRI	DRC
Escitalopram	Lexapro®	Forest Laboratories Inc.	324.4	4.2	SSRI	OS, IRT
Paroxetine	Paxil®	Glaxo Smith Kline	329.4	3.4	SSRI	IRT, MRT, OSU
Sertraline	Zoloft®	Pfizer Inc.	306.3	5.6	SSRI	OC
Venlafaxine	Effexor®	Wyeth	319.2	3.2	Tricyclic	IRT, MRC

DRC, Delayed release capsule; IMI, intramuscular injection; IRC, immediate release capsule; IRT, immediate release tablet; IVI, intravenous injection; IVIF intravenous infusion; MRC, modified release capsule; MRT modified release tablet; ODT orally disintegrating tablet; OC, oral concentrate; OS, oral solution; OSU, oral suspension; TDP, transdermal patch; SCI, subcutaneous injection.

the lack of an intravenous (i.v.) formulation, no absolute bioavailability data have been reported for this product. Pharmacokinetics of single-dose IR administration indicates that the formulation exhibits dose proportional pharmacokinetics, with steady state dosing achieved after 8 days ("Clinical Pharmacology—Drug Product Monographs," 2007).

Sustained release tablets are produced in strengths of 100, 150, and 200 mg and utilize a hydroxypropyl methylcellulose matrix to provide sustained release of bupropion, providing peak plasma concentrations within 3 h of administration. In a study evaluating BID-dosed Wellbutrin® SR tablets, and 150 mg to TID-dosed Wellbutrin® IR tablets, 100 mg peak plasma concentrations were shown to be 85% of those measured in the reference formulation, with equivalent area under the curves (AUCs), indicating the bioequivalence of the BID MR composition to the TID IR composition ("Clinical Pharmacology—Drug Product Monographs," 2007).

Escitalopram

Escitalopram is an orally administered SSRI marketed under the trade name Lexapro® by Forest Laboratories Inc., as an oral solution and IR tablet. The drug substance is the pure *S*-enantiomer of the racemic bicyclic phthalane derivative citalopram, having a molecular weight of approximately 324.4 g/mol and log *p* of 4.2 (Wishart et al., 2006), meeting the criteria for good BBB permeability. The IR tablet form contains traditional tablet additives, including microcrystalline cellulose (filler), croscarmalose sodium (disintegrant), colloidal silicon dioxide (glidant), and magnesium stearate (lubricant). The core tablets are produced at 10 and 20 mg escitalopram base strength and film coated using a hydroxypropyl methylcellulose-based coating system. The oral solution is produced at a strength of 1 mg/mL (base strength) using traditional oral solution excipients that function as flavorants, diluents, and preservatives ("Clinical Pharmacology—Drug Product Monographs," 2007; "Treatment for Depression and Anxiety: Lexapro (Escilatopram Oxalate) Medication").

Clinical studies of escitalopram have shown the drug to be a highly SSRI with minimal effects on norepinephrine and dopamine reuptake. The *S*-enantiomer is 100 × as potent as the *R*-enantiomer. Single-and multidose studies have demonstrated linear, dose-proportional pharmacokinetics with primarily hepatic biotransformation. Following single-dose administration of the 20 mg IR tablet, t_{max} was achieved after 5 h, achieving 80% absolute bioavailability ("Clinical Pharmacology—Drug Product Monographs," 2007).

Paroxetine

Paroxetine is a SSRI antidepressant, marketed under the trade name Paxil® and produced as an oral suspension, IR tablet and MR tablet. The drug substance has a molecular weight of 329.4 and log *p* of 3.4 (Wishart et al., 2006), allowing the dose to be administered without the aid of an additional formulation BBB transporter. The IR film-coated tablet is produced with a dicalcium phosphate dihydrate matrix, providing similar bioavailabilities to the oral suspension with a t_{max} of approximately 5 h. In vivo, paroxetine does not exhibit any major pharmacologically active metabolites; however, it does exhibit protein binding of approximately 95% ("Clinical Pharmacology—Drug Product Monographs," 2007).

The controlled release, enteric-coated tablets were produced using a technology called Geomatrix™ (SkyePharma), which allows for controlled release over a 4- to 5- h period. Geomatrix™ technology utilizes a novel hydroxypropyl methylcellulose layer containing paroxetine in combination with an additional core tablet barrier layer to provide zero-order drug release kinetics by combing controlled hydration balanced by changing tablet geometries due to erosion (Conte & Maggi, 2000). In vivo testing of this formulation showed the composition provide a t_{max} between 6 and 10 h postadministration ("Clinical Pharmacology—Drug Product Monographs," 2007; "Paxil CR, an SSRI, treats depression, panic disorder, social anxiety disorder, PMDD").

Sertaline

Sertaline is a SSRI antidepressant manufactured under the trade name Zoloft® by Pfizer Inc., (New York, NY, USA) as an oral concentrate and IR tablet at strengths of 25, 50, and 100mg. The drug substance has a molecular weight of 306.3 g/mol and a log *p* of 5.6 (Wishart et al., 2006), allowing for BBB permeability without the use of a secondary transporter system.

The IR tablet is composed of traditional IR tablet excipients, including dicalcium phosphate dehydrate, microcrystalline cellulose, hydroxypropyl cellulose, and hydroxypropyl methylcellulose. The relative bioavailability of the tablet formulation is equivalent to the oral solution, providing a t_{max} of 4.5–8.4 h while the oral concentrate provides a slightly prolonged t_{max}, with onsets of 5.9–7.0 h ("Clinical Pharmacology—Drug Product Monographs," 2007; "Treatment for Depression and Anxiety—Zoloft.com").

Venlafaxine

Venlafaxine is a tricyclic antidepressant manufactured by Wyeth (Madison, NJ, USA) in both an IR tablet formulation and a multiparticulate extended release capsule, marketed under the trade name Effexor®. The drug substance, because of it low molecular weight [319.2 g/mol (Wishart et al., 2006)] and relatively high log *p* (3.2 [Wishart et al., 2006]), does not require a secondary transporter system to penetrate the BBB. The IR tablet formulation contains cellulose and sodium starch glycolate to provide rapid release, with an observed in vivo t_{max} of 2 h. The drug substance is well absorbed and the primary metabolite, *O*-desmethylvenlafaxine, also shows activity as a potent inhibitor of serotonin and norepinephrine. To reduce the dosing frequency, a MR composition, Effexor® XR was developed. This multiparticulate product uses a diffusion controlled release system to provide sustained release through an ethylcellulose membrane that is applied to the pellets. The XR composition is available in strengths of 37.5, 75, and 150 mg,

providing a t_{max} of 5.5 h and 45% absolute oral bioavailability (" Clinical Pharmacology—Drug Product Monographs," 2007).

Duloxetine

Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor (SSNRI), is the newest antidepressant approved for use in the United States and also has applications for neuropathic pain. Marketed as Cymbalta® by Eli Lilly (Indianapolis, IN, USA) as a multiparticulate capsule formulation, each capsule contains 20, 30, or 60 mg of duloxetine. The drug substance has a molecular weight of 333.9 g/mol and log *p* of 5.0 (Wishart et al., 2006), allowing for penetration of the BBB. Duloxetine exhibits poor stability in acid pH, with demonstrated potency reductions of 82% after 2 h (Boot et al., 2004), necessitating an enteric coating of hydroxypropyl methylcellulose acetate succinate. Following oral administration and a 2-h lag time due to the enteric coating, the drug substance is well absorbed with a t_{max} of 6 h ("Clinical Pharmacology—Drug Product Monographs," 2007; "Cymbalta.com").

Animal Models for Testing

Although animal models have been successfully used for the analysis of a number of disease states, the symptoms of depression are complex mental and emotional issues that many animals cannot successfully mimic. Complex emotional symptoms such as suicide, self-esteem, and guilt cannot be reproduced or assessed in traditional animals models due to the differences in brain structure (Cryan & Holmes, 2005; Cryan & Slattery, 2007). Further complicating the study of depression is the fundamental lack of understanding for disease mechanisms preventing the examination of the disease from a pathophysiological perspective; however, genetically engineered animals are beginning to become more prevalent in the field (Cryan & Holmes, 2005; Cryan & Slattery, 2007; Cryan, Valentino, & Lucki, 2005; El Yacoubi & Vaugeois, 2007). Animal models for the study of depression fall into two general categories: behavioral models and genetically modified models.

Behavioral models have been around for many decades to assess the performance of antidepressants and are chiefly responsible for the initial development of currently available products. A review of the literature shows a number of behavioral animal models including the forced swim test (Borsini, 1995; Cryan, Valentino et al., 2005), the tail suspension test (Cryan, Mombereau, & Vassout, 2005), learned helplessness (Maier & Watkins, 2005), olfactory bulbectomy (C. Song & Leonard, 2005), maternal deprevation (Pryce et al., 2005), and the chronic stress model (Willner, 2005). For the purposes of this review, only some of the most prevalent testing methods will be discussed.

The forced swim test is the most extensively used test of antidepressant efficacy in preclinical development due to the observed connection between the duration of swim time for the animal and the efficacy of the antidepressant administered (Cryan, Valentino et al., 2005). The test is performed by administering the drug, 30–60 min prior to immersion, placing a male animal, typically a mouse or rat, into a cylinder filled with water maintained at 20–23°C and recording the time at which the animal stops swimming and maintains only the motions required to keep its head above water level (Borsini, 1995). Numerous antidepressant compounds have been shown to have a correlation between efficacy and reduced immobility time including citalopram (Malinge, Bourin, Colombel, & Larousse, 1988; Mogilnicka, Czyrak, & Maj, 1987, 1988), indalpine (Biziere et al., 1985; Malinge et al., 1988), fluoxetine (Koe, Weissman, Welch, & Browne, 1983), fluvoxamine (Koe et al., 1983; Malinge et al., 1988), sertraline (Koe et al., 1983), zimelidine (Koe et al., 1983); however, this test may have difficulty assessing the efficacy of some SSRIs (Borsini, 1995). To address this, modifications were incorporated into the forced swim test to improve its accuracy. These modifications included increasing the depth of the water, use of a clear tank, and improved assessment of the emotional state of the animal by scoring climbing behavior and swimming behavior using a video tape system instead of real-time scoring. Using this modified system, several other antidepressants, including several SSRIs, were accurately scored to assess their efficacy (Cryan, Valentino et al., 2005). The tested antidepressants included fluoxetine (Detke, Rickels, & Lucki, 1995), sertraline (Detke et al., 1995), paroxetine (Detke et al., 1995), maprotiline (Detke et al., 1995), venlafaxine (Reneric & Lucki, 1998), milnacipran (Reneric & Lucki, 1998), and duloxetine (Reneric & Lucki, 1998). Given the widespread success of this method for predicting antidepressant efficacy, it will continue to see much use throughout the industry; however, because of its empirical basis, it will not offer deeper insights into the cause of depression.

Another model that has seen considerable use in predicting the efficacy of antidepressants is the tail suspension test. This test, developed nearly 20 ago, works on the hypothesis that animals exposed to short-term inescapable stress will develop an immobile posture. The test is performed by hanging the animals vertically from the tail and measuring both the time until the animal becomes immobile and the duration of immobility, as shown in Figure 2. Administration of antidepressants prior to testing has shown longer times to achieve immobility, with shorter durations of immobility (Cryan, Mombereau et al., 2005). The tail suspension test also provides several key advantages over the forced swim test, including absence of hypothermic stress (X. Liu & Gershenfeld, 2003), improved measurements of stress measurements such as the amount of energy exerted, and no requirement for motor skill coordination that may be compromised in genetically modified animals (Lucki, Dalvi, & Mayorga, 2001). As with the forced swim test, this test has been effectively used to characterize the performance of a number of antidepressants including fluoxetine, paroxetine, and venlafaxine (Cryan, Mombereau et al., 2005).

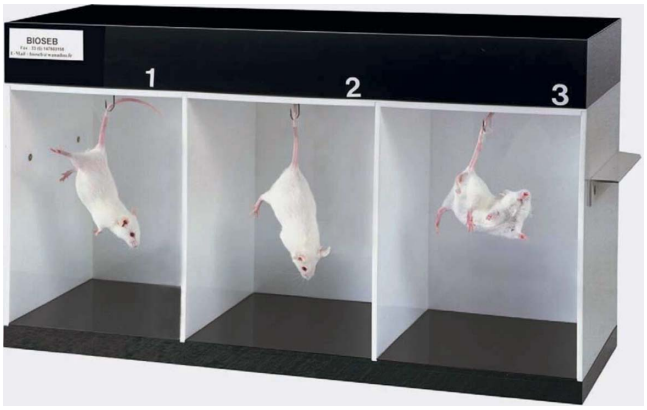

FIGURE 2. Bioseb-automated tail suspension testing apparatus. Reprinted with permission from Cryan, Mombereau et al. (2005). Copyright © 2005, with permission from Elsevier.

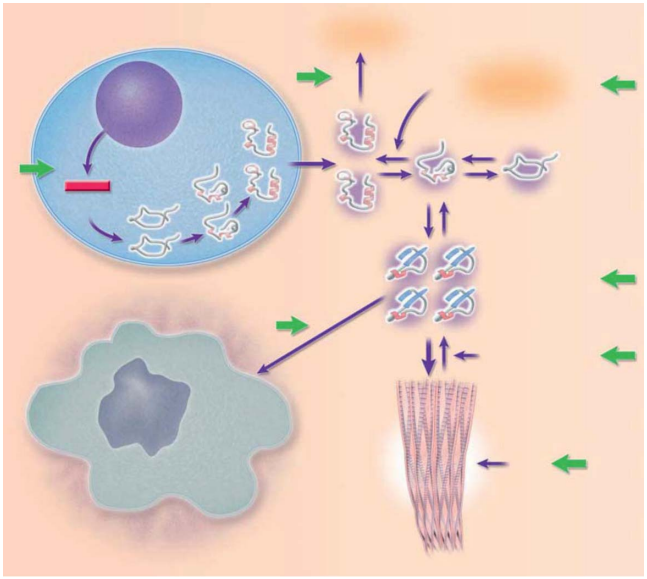

FIGURE 3. Pathway of newly synthesized protein in a patient with amyloidogenic mutation. Reprinted with permission from Merlini and Bellotti (2003). Copyright © 2003, Massachusetts Medical Society. All rights reserved.

A third behavioral model that has been successfully used to assess antidepressant activity is the olfactory bulbectomy model, wherein the olfactory bulb of the animal is removed to induce a depression-like state. Following surgery, the rat suffers from insomnia and looses the ability to detect pheromones, which carry behavioral and physiological information, resulting in irritability and aggression such as cannibalism of pups and territorial dominance (C. Song & Leonard, 2005). The degree to which these behaviors are demonstrated depends on the degree and accuracy of the surgical process. Through the administration of antidepressants, changes in these aggressive behaviors can be monitored and correlated with the efficacy of the test drugs (McArthur & Borsini, 2006).

The learned helplessness model is another successful test for predicting the efficacy of antidepressants. In this model, the animal is subjected to repeated stresses to which it cannot escape, such as electrical shocking of the foot. The repeated stresses result in a learning disability that prevents the animal from escaping when given the opportunity. Through the administration of an antidepressant, the ability of the animal to escape the stress is restored thereby allowing the efficacy of compounds to be assessed (Maier & Watkins, 2005).

Given the apparent hereditary nature of depression, there is a strong indication of a genetic link to the disease. Over the last 20 years, genetic models for the evaluation of antidepressant efficacy in animal models have been developed, some of which have shown remarkable results (Cryan & Holmes, 2005; Cryan & Slattery, 2007; El Yacoubi & Vaugeois, 2007; McArthur & Borsini, 2006). A rat line developed by Overstreet Pucilowski, Rezvani, and Janowsky (1995), the Flinders Sensitive Line, was created by selective breeding of Sprague Dawley rats for differences in the effects of the cholinesterase inhibitor diisopropylfluorophosphate. Utilizing this difference, these rats showed exaggerated immobility, which could be reduced with the administration of an antidepressant. Other animal models such as the Wistar Kyoto rats have shown behavioral and endocrinological similarities to depressed humans, as well as a responsiveness to antidepressant drugs making them an excellent model candidate (Lopez-Rubalcava & Lucki, 2000). CRF receptor-2 (CRFR-2)-deficient mice that show increased stress sensitivity have also been used to study the effect of developmental stress on the potential development of depression symptoms (Goel & Bale, 2007). The animals were exposed to stress-provoking marbles, which altered the burying behavior of the deficient animals and demonstrated that abnormal pubertal stress can be predictive of heightened adult stress sensitivity.

The ability of these models to predict the success of antidepressants has been well documented. Traditional behavioral models allow for rapid and efficient efficacy screening of developmental antidepressants, whereas genetic models allow for a more fundamental understanding of the disease state. By combining these models, there is the potential to significantly improve antidepressant therapy.

EPILEPSY

Epilepsy is characterized by debilitating muscular spasms resulting from neurochemical imbalances in the brain. Over the last several years, many new products have entered the market providing some relief for patients coping with this disease; however, as many as one third of patients still suffer from seizures (Kwan & Brodie, 2000). Furthermore, modern medicine still lacks a fundamental understanding of epileptogenesis, the cellular and molecular mechanisms responsible for the origin of the disease, which limits the ability to develop new chemicals for treatment (Chang & Lowenstein, 2003). With continued study of the origins of the disease, in combination with

advances in drug delivery and genetic technology, it is hoped that new therapies will be developed to threat this disorder.

Disease Biology

The primary feature of epilepsy is uncontrolled seizure, typically of a recurrent type. The disease is characterized into two categories: generalized epilepsy that is characterized by a strong genetic component with seizures that begin in both cerebral hemispheres and localized epilepsy that is primarily caused by neural injury, beginning in localized regions of the brain (Benbadis, 2001). Although the mechanism of epilepsy has not been fully elucidated, it is believed that generalized seizures result from alteration in the circuitry between the thalamus and the cerebral cortex causing neurological imbalances responsible for seizures (Kostopoulos, 2001). To date, numerous genes that are responsible for creating ion channel deviations have been identified in association with these imbalances, including SCN1B (Wallace et al., 1998), SCN1A (Escayg et al., 2000), SCN2A (Sugawara et al., 2001), and GABRG2 (Baulac et al., 2001). In localized epilepsy, physical trauma drives these imbalances. Today, medical treatments focus on developing chemicals capable of correcting these ion channel deviations.

Approved Products

Numerous products for the treatment of epilepsy are currently available, and this section focuses on several of the more recent approvals, presented in Table 2. These compositions all show properties favorable to BBB permeation, and the delivery systems employed for these products do not include any secondary transporter in the formulation. It should also be noted that some drugs, including Lyrica® and Neurontin®, have been indicated for the treatment of neuropathic pain as well as epilepsy. These drugs are discussed in the neuropathic pain section and also exhibit properties favorable for BBB permeation without secondary transport systems.

Felbamate

Felbamate is an anticonvulsant having a molecular weight of 238.2 g/mol and log *p* of 0.8 (Wishart et al., 2006). As with most epilepsy therapies, the molecular mechanism of action is unknown; however, it is believed that felbamate antagonizes the effects of glycine, binding to *N*-methyl-D-asparate (NMDA) receptors preventing seizures. Marketed by Meda Pharmaceuticals (Solna, Sweden) under the trade name Felbatol®, it is produced as an IR tablet and oral suspension. Upon oral administration, peak plasma concentrations are achieved within 1–6 h postadministration with high oral absorption ("Clinical Pharmacology—Drug Product Monographs," 2007).

Levetiracetam

Levetiracetam is a novel anticonvulsant recently approved for use in epilepsy treatment. The properties of the molecule, particularly the negative log *p* (Wishart et al., 2006), do not necessarily indicate an ability of the molecule to transit the BBB. Although the mechanism of action is unknown, it is has been shown to inhibit burst firings in the hippocampus, suggesting that even with its molecular properties it is able to transit the BBB. Marketed as Keppra® by UCB Pharma Inc., (Brussels, Belgium) it is available as an oral solution, IR tablet, and solution for i.v. injection. Orally administered compositions provide 100% bioavailability, achieving peak plasma concentrations within 90 min. Examination of the excipients shows that these formulations do not contain any excipients traditionally identified with increasing BBB permeability, further indicating the ability of the molecule to transit the BBB without secondary transporter systems ("Clinical Pharmacology - Drug Product Monographs," 2007).

Oxcarbazepine

An analog of carbamazepine, oxcarbazepine is an anticonvulsant with a molecular weight of 252.3 g/mol and log *p* of 1.8 (Wishart et al., 2006). Oxcarbazepine exhibits rapid conversion upon oral administration to the 10-monohydroxy metabolite which is believed to provide the majority of the therapeutic effect by blocking voltage-sensitive sodium channels in the brain. Originally developed by Novartis Pharmaceuticals (Basel, Switzerland) as Trileptal® and available as both an IR tablet and oral suspension, several other generic tablet formulations are also available. Upon oral administration, the

TABLE 2
Approved Drug Products Indicated in the Treatment of Depression

API	Brand	Manufacturer	MW	log *p*	Dosage Form
Felbamate	Felbatol®	Meda Pharmaceuticals	238.2	0.8	IRT, OSU
Levetiracetam	Keppra®	UCB Pharma	170.2	–0.5	IRT, IVI, OS
Oxcarbazepine	Trileptal®	Novartis Pharmaceuticals	252.3	1.8	IRT, OSU
Tiagabine	Gabitril®	Cephalon	375.6	3.4	IRT
Topiramate	Topamax®	Ortho-McNeil	339.4	0.7	IRC, IRT

DRC, delayed release capsule; IMI, intramuscular injection; IRC, immediate release capsule; IRT, immediate release tablet; IVI, intravenous injection; IVIF intravenous infusion; MRC, modified release capsule; MRT, modified release tablet; ODT orally disintegrating tablet; OC, oral concentrate; OS, oral solution; OSU oral suspension; TDP, transdermal patch; SCI, subcutaneous injection.

drug is rapidly absorbed and converted to the primary metabolite, with peak plasma concentrations achieved within 4–6 h ("Clinical Pharmacology—Drug Product Monographs," 2007).

Tiagabine

Tiagabine is a gamma aminobutyric acid reuptake inhibitor that is a derivative of nipecotic acid. Having a molecular weight of 375.6 g/mol and log *p* of 3.4 (Wishart et al., 2006), the drug is able to transit the BBB upon administration. Currently marketed as Gabitril® by Cephalon (Frazer, PA), it is available as an IR tablet in potencies of 2, 4, 12, 16, and 20 mg. Upon oral administration, the drug is rapidly and nearly completely absorbed, achieving peak plasma concentrations within 45 min and absolute bioavailability of 95% ("Clinical Pharmacology—Drug Product Monographs," 2007).

Topiramate

While most compounds only raise the seizure threshold, topiramate appears to block the spread of seizures. Although the mechanism of action is unknown, it is believed to function by a combination of reducing abnormal neural discharges, acting as a glutamate receptor antagonist and blocking voltage-sensitive sodium channels. Developed by Ortho-McNeil, the molecular properties of topiramate allow for BBB penetration without the aid of secondary delivery systems. It is marketed as an IR tablet and IR multiparticulate capsule formulation under the trade name Topamax® in a range of potencies. Upon oral administration, it is rapidly absorbed from both compositions with 80% oral bioavailability. The IR capsule formulation is designed for administration by sprinkling the pellets onto a substrate for oral administration and is considered bioequivalent to the tablet formulation ("Clinical Pharmacology—Drug Product Monographs," 2007).

Animal Models

The uses of animal models have a long history in epilepsy research. Many of these models, particularly the earlier models, were based on acute seizures including the two most common ones: the maximal electrical shock model and the pentylenetetrazol seizure test (White, 2003). Each of these models is capable of providing important information on the efficacy of epilepsy drug molecules and are still in use today.

The maximal electrical shock model is performed by using an electric shock to induce seizure in the subject animal and recording the amount of shock required (D. Schmidt & Rogawski, 2002). In a recent study by Luszcki and coworkers, they examined the influence of aminophylline on the antiepileptic effect of gabapentin using the mouse maximal electroshock model. They administered aminophylline for 14 days, followed by administration of gabapentin. The results showed that gabapentin increased the threshold for electrorconvulsion in mice and that there was no significant effect of aminophylline, indicating that aminophylline did not alter the antiepileptic effect of gabapentin (Luszczki, Jankiewicz, Jankiewicz, & Czuczwar, 2007). In another study, conducted by Stöhr et al., they examined the antiepileptic efficacy of lacosamide using a battery of tests including the pentylenetetrazol seizure test and the maximal electrical shock model. In the pentylenetetrazol seizure test, pentylenetetrazol is administered subcutaneously to produce a period of time thereafter with a high probability of chemically induced seizure. By administering an investigational compound and assessing the protection allotted by the chemical in a large group of animals, the efficacy of the drug may be established (White, Wolf, Woodhead, & Kupferberg, 1998). In their testing, results showed that lacosamine improved the maximal electrical shock response; however, it was inactive against clonic seizures produced by pentylenetetrazol (Luszczki et al., 2007). Other kindling models have also been used as seizures in animal models by stimulation of various neural regions. In a study conducted by Tober and coworkers, they assessed the antiepileptic efficacy of an experimental drug, D-23129, using an amygdale kindling model. In their model, surgically modified rats were electrically stimulated to induce seizures, and the efficacy of D-23129 was evaluated. Their results showed that D-23129 reduced seizure severity and duration indicating the potential of this compound in epilepsy therapy (Tober, Rostock, Rundfeldt, & Bartsch, 1996). From these examples, it is clear that these models are effective tools for assessing the therapeutic potential of novel new chemical entities in epilepsy therapy.

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a disease of the immune system that affects the CNS. Overall, the disease has shown to be increasing in frequency and is a chronic crippling syndrome with only partial improvements provided by currently approved therapy, resulting in substantial social and economic effects (Cassan & Liblau, 2007). Current drug products do show limited success in preventing future onsets of the disease; however, the true mechanisms of action for these products are poorly understood and do not restore function following the onset of the disease. At present, there is a substantial need for an improved mechanistic understanding of the disease to allow for successful implementation of neuroprotective therapy.

Disease Biology

MS is caused by the loss of neural functionality stemming from axon damage in the CNS although the mechanisms of the disease have not been fully elucidated. It is hypothesized that immune cells damage myelin surrounding the axons, and the resulting inflammatory response further damages axons and neurons, as some studies have indicated a correlation of inflammation in MS lesions to axon injury (Tanja, Gueanelle, Andreas, Jana, & Wolfgang, 2002). MS begins with formation of acute lesions that break down the BBB, are generally clinically silent, and as much as 10 times more frequent than

episodes of clinical worsening (Stone et al., 1995). Research has indicated that the acute lesions of MS are initiated by the CD4+ T-helper type 1 cells, which is consistent with potential genetic risk with HLA class II molecules. Although not purely a genetic disorder, HLA-DRB* genes of the HLA-DR15 haplotype have been identified as conferring the greatest risk for the disease (McFarland & Martin, 2007). Other factors, such as age, sex, and race may also influence MS, as well as still yet undetermined environmental factors.

Approved Drug Products

Current therapies for MS fall into three basic categories based on the proposed mechanism of action: transition of activated T cells into the Th2 subset, alteration of functional properties of Th1 cells, and prevention of activated T-cell migration into the CNS (McFarland & Martin, 2007). In general, drugs in this class are biotechnology-derived higher molecular weight molecules with mechanisms of actions not fully understood; however, in many cases, research indicates that these products function outside the CNS helping to regulate immune response (Ziemssen, 2005). Furthermore, some research indicates that the BBB may be compromised in cases of MS, allowing for enhanced permeation (Neuwelt, 2004). The drug products discussed in this section are summarized in Table 3.

Dantrolene

Dantrolene is a skeletal muscle relaxant having a molecular weight of 393 g/mol and log *p* of 1.5 (Wishart et al., 2006), indicating potential to transit the BBB. Although not directly designed for treating MS, this product can address some of the symptoms associated with MS, including spasticity. The mechanism of action is unknown; however, it is believed that dantrolene interferes with calcium ion release from the sarcoplasmic reticulum within skeletal muscle cells, uncoupling the excitation–contraction process to attenuate muscle response ("Clinical Pharmacology—Drug Product Monographs," 2007).

Marketed under the trade Dantrium®, it is produced in an oral capsule formulation and as an i.v. injection manufactured by Procter & Gamble (Cincinnati, OH, USA). The i.v. injection formulation is a lyophilized powder designed for reconstitution. The oral capsule formulation, having potencies of 25, 50, and 100 mg is an IR product designed to provide maximum plasma concentrations within 5 h; however, the drug is poorly absorbed with only 35% orally absorbed. Additionally, two generic capsule products are currently available from Amide Pharmaceutical Inc. (Little Falls, NJ, USA) and Global Pharmaceuticals ("Clinical Pharmacology—Drug Product Monographs," 2007).

Glatiramer Acetate

Glatiramer acetate is a synthetic random peptide composed of four basic amino acids: L-alanine, L-glutamic acid, L-lysine, and L-tyrosine. The polypeptide has a molecular weight range of 4,700–11,000 Da and is similar in structure to myelin basic protein. Although the mechanism of action is unknown, it is believed to modify the immune response by functioning as decoy to neutralize antibodies before they can enter the CNS and attack myelin surrounding the axons. Limited information is available on the pharmacokinetics of the product; however, a substantial fraction hydrolyzed locally at the site of injection prior to entering systemic and lymphatic circulation. Manufactured by Sanofi-Aventis (Bridgewater, NJ, USA) and marketed under the trade name Copaxone®, it is available as a prefilled syringe for subcutaneous injection ("Clinical Pharmacology—Drug Product Monographs," 2007; "Copaxone®—Multiple sclerosis therapy helping you manage your relapsing-remitting MS symptoms").

Interferon β-1a

Interferon β-1a is a 166 amino acid glycoprotein of approximately 22,500 Da produced using recombinant DNA technology from Chinese hamster ovary cells. Although the mechanism of action is unknown, it is believed that it inhibits the expression of proinflammatory cytokines including INF-G responsible for triggering the autoimmune reaction of MS. Supplied as lyophilized powder or prefilled syringe under the trade name

TABLE 3
Approved Drug Products Indicated in the Treatment of Multiple Sclerosis

API	Brand	Manufacturer	MW (g/mol)	log *p*	Dosage Form
Dantrolene	Dantrium®	Proctor & Gamble	393	1.5	IRC, IVI
Glatiramer Acetate	Copaxone®	Sanofi-Aventis	4,700–11,000	–	SCI
Interferon β-1a	Avonex®	Biogenic Inc.	22,500	–	IMI
Interferon β-1a	Rebif®	Pfizer	22,500	–	SCI
Interferon β-1b	Betaseron®	Bayer Health Care	18,500	–	SCI
Natalizumab	Tysabri®	Biogen-Idec	149,000	–	IVIF

DRC, delayed release capsule; IMI, intramuscular injection; IRC immediate release capsule; IRT, immediate release tablet; IVI, intravenous injection; IVIF, intravenous infusion; MRC, modified release capsule; MRT, modified release tablet; ODT, orally disintegrating tablet; OC, oral concentrate; OS, oral solution; OSU, oral suspension; TDP, transdermal patch; SCI, subcutaneous injection.

Avonex® and manufactured by Biogenic Idec for intramuscular injection, this composition achieves peak serum concentrations between 3 and 13 h. Rebif® manufactured by Pfizer Inc. is a subcutaneous formulation, supplied in prefilled syringes for injection that achieves peak serum concentration after approximately 16 h. For both compositions, biological response markers, including neopterin and $beta_2$-microglobulin, remained elevated for at least 4 days post injection ("Clinical Pharmacology—Drug Product Monographs," 2007; "Rebif").

Interferon β-1b

Interferon β-1b is manufactured by bacterial fermentation of *Escherichia coli* with a genetically engineered plasmid for human interferon beta ser17, interferon β-1b 165 amino acid, 18,500 Da non-glycosolated polypeptide. As with the 1a form, the mechanism of action is unknown, however, it is believed that it inhibits the expression of pro-inflammatory cytokines such as interleukin-6 (IL-6) and down-regulates the interferon gamma to reduce inflammatory response. It may also increase in vivo levels of nerve growth factor, assisting with the healing process. Marketed by Bayer Health Care (Wayne, NJ, USA) under the trade name Betaseron, it is supplied as a reconstituteable lyophilized powder designed for subcutaneous injection ("BETASERON.com | Your Resource for Information on Multiple Sclerosis and BETASERON Treatment,"; "Clinical Pharmacology—Drug Product Monographs," 2007).

Natalizumab

Natalizumab is a selective adhesion molecule inhibitor and the first FDA-approved alpha-4-integrin inhibitor. Marketed as Tysabri® by Biogen-Idec (Cambridge, MA, USA), it is a recombinant humanized IgG4k MAb produced in murine myeloma cells and intended for use an i.v. infusion. Although the formulation contains polysorbate 80, a known BBB permeation enhancer, no documentation was found identifying this as a mechanism for allowing the MAb to transit the BBB. The mechanism of action is unknown; however, it is believed to prevent transmigration of leukocytes across the endothelium into the inflamed parenchymal tissue. Functioning outside the BBB by inhibiting a4b1 integrin from binding to VCAM-1, it is believed that it prevents T lymphocytes from entering the CNS. In 2004, when the product was initially approved, three patients developed multifocal leukoencephalopathy requiring the manufacturer to remove the product from the market. The FDA-approved remarketing of the product, however, because of the increased risk of progressive multifocal leukoencephalopathy, this product is recommended as a second-line therapy ("Clinical Pharmacology—Drug Product Monographs," 2007; "Monotherapy Treatment for MS"; "Natalizumab (marketed as Tysabri) Information"; Ransohoff, 2007).

Animal Models for Testing

Given the lack of understanding regarding the causes and disease mechanisms for MS, there is no true animal model currently available for studying all facets of the disease (Cassan & Liblau, 2007; Gold, Linington, & Lassmann, 2006; Yong, Giuliani, Xue, BarOr, & Metz, 2007). Accepting this, models based on experimental autoimmune encephalomyelitis (EAE), a similar inflammatory demyelinating disease of the CNS, have been developed, which are capable of replicating some of the most common symptoms of MS in animal models (Bolton, 2007; Cassan & Liblau, 2007; Gold et al., 2006; Kieseier & Hartung, 2007; McFarland & Martin, 2007; Yong et al., 2007). EAE has been induced in a number of animals, including rodents and primates (Hohlfeld & Wekerle, 2001), and is accomplished by immunization of animals with myelin antigens such as myelin basic protein, proteolipid protein, and myelin oligodendrocyte glycoprotein with the antigen determining, in part, the location of the responses (Bettelli, 2007). Applying the EAE model has been essential for the development of several approved MS therapies and continues to be critical in the developing understanding of MS (Cassan & Liblau, 2007). During the initial development of the model, steroids showed significant in vivo effect, which was subsequently confirmed in human subjects. This similarity between EAE and MS laid the ground work for its acceptance as a pharmaceutically relevant model (Bolton, 2007). Additionally, developmental products such as LF 15-0195 continue to be tested in EAE rat model (Duplan et al., 2006), demonstrating its continued utility for assessing pharmacological activity.

The use of EAE for evaluating the pathogenesis and pathology of MS has been questioned by some, however, the common characteristics of EAE and MS have allowed this model to be adequately used to screen and evaluate emerging therapies (Bolton, 2007). Even with the ability to modify the region of response to better study the disease, there are still substantial differences between EAE and MS, in particular the induced nature of EAE compared to the spontaneous nature of MS and the genetic heterogeneity of the MS population compared to the genetic homogeneity of the investigated animal model. To this end, several research groups have focused on developing transgenic animal models that better express the underlying genetics of the disease. Cabarrocas et al. (2006) studied the effect of thymus-derived regulatory T cells expressing CD4, CD25, and the transcription factor Foxp3 in preventing autoimmunity in transgenic astroglial selfantigen mouse model which more accurately represents the underlying genetics of the disease. Their work showed that the hemagglutinin (HA) transgene in thymic epithelial cells can contribute to induction or expansion of regulatory T cells, potentially contributing to MS. Bettelli and coworkers generated T cell antigen receptors (TCR) transgenic mice (2D2) specific for the myclin/oligodendrocyte glycoprotein (MOG) 35–55 peptide on the C57BL/6 background having MOG-specific T cells to better study MS (Bettelli et al., 2003). Their work showed that MOG-specific T cells entered the CNS preferentially

through the optic nerve compared to the spinal cord. Additionally, the development of MAbs to fight MS based on the insights gained these studies have also been reported, including the use of orally administered anti-CD3 (Ochi et al., 2006) and anti-CD28 (Tischner et al., 2006) MAbs. From the results of these studies, more effective drugs may be developed targeting the underlying physiological mechanisms of the disease, further illustrating the importance of transgenic models.

Adding to the complexity of studying MS in EAE animal models is the nature of the therapeutic agent. With there being a number of biologically derived compounds in the therapeutic portfolio of MS, the question arises whether it is more appropriate to develop treatments based on the animal biology or based on the human body. An excellent example of this is EAE induced with recombinant rat MOGIgd and treated with human interferonβ-1a, where mixed results have been observed using interferon from human and animal sources. Sättler et al. (2006) concluded that Interferonβ-1a was a suitable candidate for treatment of axonal and neuronal degeneration; however, retinal ganglion cells cultured in vitro and tested with interferonβ-1a showed no difference in survival, indicating that the effect was actually indirect. Interferon has been shown to-differ significantly between human and rats, with interspecies homologies of 68 and 49% at the nucleotide and amino acid levels, respectively (Yokoyama, Ohishi, Shamoto, Watanabe, & Yagi, 1997), suggesting that the administration of rat-based interferon may have illustrated the difference.

NEURODEGENERATIVE DISORDERS

Neurodegenerative disorders are one of the disease states for CNS disorders encompassing a variety of ailments including Alzheimer's disease (AD), Parkinson's disease, Lewy body disease, multiple system atrophy, and fronto-temporal dementia. Of these disease, AD is the most prevalent of these diseases, effecting an estimated 4.5 million Americans, with costs estimated at $100 billion annually and predicted to spread to over 12 million Americans by the year 2050 (Roney et al., 2005). Given the continued increase in lifespan today, in combination with the increasing rates of AD, much research has focused on both identifying the specific disease mechanisms and developing drugs capable of addressing both the causes and the symptoms. This section focuses on developments in addressing and treating AD.

Disease Biology

Amyloidoses is a disease state wherein proteins misfold to create insoluble aggregates, as shown in Figure 3, resulting in damage to surrounding tissue, with AD being the most prevalent of this type (Merlini & Bellotti, 2003). In AD, β-amyloid (Aβ) proteins misfold in the intracellular and extracellular spaces resulting in inflammation and neuronal damage. The mechanism by which this occurs is proteolytic remodeling of the Aβ precursor protein. Amyloidogenic and normal counterparts are synthesized and secreted as native proteins where the variants reach a state of equilibrium between the folded states. Changes in microenvironmental state shift this equilibrium in favor of the misfolded proteins in AD, resulting in large areas of insoluble aggregates. These aggregates cannot be removed under normal CNS physiologically, resulting in swelling and neuronal damage (Ghiso & Frangione, 2002; Koistinaho & Koistinaho, 2005). While the exact cause of AD onset is unknown, it is believed to originate from a combination of both environmental and genetic factors. Numerous genes and mutations have been identified for both familial and late stage AD (Wolfe, 2001). The *ApoE* gene has been identified as a major predictor of late onset AD, with the ApoE4 allele conferring a major risk factor (Corder et al., 1993). Also, in a small number of cases, autosomal dominant mutations in APP or presenilin genes have been identified that lead to the elevation of Aβ plaque levels (Koistinaho & Koistinaho, 2005). While much has been learned about AD in the last few decades, a need for fundamental mechanistic understanding of the disease and CNS pathology is still required to develop more efficient strategies of treating and preventing the disease.

Approved Drug Products

Very few drug products are currently available for the treatment of AD, and these products fall into two classes: cholinesterase (ChE) inhibitors and NMDA receptor agonists. These products, listed in Table 4 with their respective attributes, all show favorable properties for BBB permeability. Additionally, a review of the available dosage forms clearly shows that no secondary mechanisms of permeation are used in the delivery of these compounds to the CNS.

Donepezil

Donepezil is piper dine-type reversible ChE inhibitor that enhances cholinergic function through inhibition of acetylcholine hydrolysis. With a molecular weight of 379.4 g/mol and log *p* of 4.1 (Wishart et al., 2006), the chemical properties meet the criteria for BBB permeation independent of a secondary transporter. Marketed by Pfizer Inc. as Aricept®, it is the only medication approved for mild to severe AD. Produced as an IR tablet, orally disintegrating tablet, and oral solution, these formulations are designed to achieve rapid drug release. The IR tablets, available in 5 and 10 mg potencies, consist of drug-loaded cores containing lactose, corn starch, microcrystalline cellulose, hydroxypropyl cellulose, and magnesium stearate that are film coated with a hydroxypropyl methylcellulose coating. In all cases, the drug is well absorbed with a relative bioavailability of 100%, and peak plasma concentrations are reached in 3–4 h ("Aricept® (donepezil HCl)—Official Site—Aricept—Alzheimer's"; "Clinical Pharmacology—Drug Product Monographs," 2007).

TABLE 4
Approved Drug Products Indicated in the Treatment of Alzheimer's Disease (Neurodegenerative Diseases)

API	Brand	Manufacturer	MW	log *p*	Class	Dosage Form
Donepezil	Aricept®	Pfizer, Inc.	379.4	4.1	ChE inhibitor	IRT, ODT, OS
Galantamine	Razadyne®	Ortho-McNeil	287.4	2.4	ChE inhibitor	IRT, MRC, OS
Memantine	Namenda®	Forest Laboratories Inc.	179.3	2.2	NMDA antagonist	IRT, OS
Rivastigmine	Exelon®	Novartis Pharmaceuticals	250.3	2.6	ChE inhibitor	IRC, OS, TDP
Tacrine	Cognex®	Sciele Pharma	198.3	2.3	ChE inhibitor	IRC

DRC, delayed release capsule; IMI, intramuscular injection; IRC, immediate release capsule; IRT, immediate release tablet; IVI, intravenous injection; IVIF, intravenous infusion; MRC, modified release capsule; MRT, modified release tablet; ODT, orally disintegrating tablet; OC, oral concentrate; OS, oral solution; OSU, oral suspension; TDP, transdermal patch; SCI, subcutaneous injection.

Galantamine

Galantamine is a reversible acetylcholinesterase inhibitor having a molecular weight of 287.4 g/mol and log *p* of 2.4 (Wishart et al., 2006) functioning similarly to Aricept®. Marketed by Ortho-McNeil (Titusville, NJ, USA), it is available as an oral solution, IR tablet, and MR capsule formulation under the trade name Razadyne®. The IR tablet formulation, available in 4, 8, and 12 mg strengths, shows comparable bioavailability to the oral solution, with 90% absolute bioavailability and maximum concentrations achieved within 1 h; however, because of the elimination, the product must be administered BID. The extended release capsule formulation was developed to provide once daily dosing using a diffusion-controlled ethylcellulose-coated multiparticulate composition to provide sustained release. Using the extended release composition, QD dosing can be achieved ("Clinical Pharmacology—Drug Product Monographs," 2007; "In the treatment of mild to moderate dementia of Alzheimers Disease").

Memantine

Memantine is a NMDA receptor antagonist having a molecular weight and log *p* of 179.3 g/mol and 2.2 (Wishart et al., 2006), respectively. Namenda®, marketed by Forest Laboratories (New york, NY, USA), is approved for moderate to severe AD and functions by blocking the NMDA receptors to slow the intracellular damage of calcium accumulation in the CNS. Namenda is available as an oral solution and film-coated IR tablet in potencies of 5 and 10 mg. Both compositions provide near 100% bioavailability, with the IR tablet formulation providing rapid release of drug in vivo and achieving a t_{max} between 4 and 6h ("Clinical Pharmacology—Drug Product Monographs," 2007; "Namenda Alzheimer's Symptoms Treatment—Namenda.com").

Rivastigmine

Approved for mild to moderate AD, rivastigmine is a reversible ChE inhibitor with a molecular weight of 250.3 g/mol and log *p* of 2.6 (Wishart et al., 2006). It is weakly bound to human plasma and can readily cross the BBB because of its chemical properties. Marketed under the trade name Exelon® by Novartis Pharmaceuticals as an oral solution IR capsule and transdermal patch, it functions by inhibiting the hydrolysis of cholinesterase. The IR capsules are powder filled with a blend of microcrystalline cellulose, hydroxypropyl cellulose, silicon dioxide, and magnesium stearate to provide rapid drug release. For oral administration, absorption occurs rapidly; however, absolute bioavailability is only 36% due to first pass metabolism. Although some food effect was observed, and it is recommended that oral compositions be taken with food, a transdermal system was developed to circumvent the first pass effect. The transdermal patch is available in two 24 strengths of 4.6 and 9.5 mg, with drug exposure between a 9.5-mg/24-h patch and BID 6 mg IR capsules equivalent. Lower intersubject variability for the transdermal system was also observed; however, body weight may affect exposure ("Clinical Pharmacology—Drug Product Monographs," 2007; "Exelon® Patch").

Tacrine

Tacrine, a ChE inhibitor with a molecular weight of 198.3 g/mol and log *p* of 2.3 (Wishart et al., 2006), was the first drug approved for improving cognitive symptoms associated with AD and is approved for mild to moderate AD. Tacrine works by inhibiting acetylcholinesterase and butylcholinesterase to enhance cholinergic effect. Marketed under the trade name Cognex®, the drug product is supplied as an IR capsule at strengths of 10, 20, 30, and 40 mg. Manufactured as a powder-filled IR capsule formulation containing inactive ingredients including microcrystalline cellulose, silicon dioxide, sodium lauryl sulfate, lactose, and magnesium stearate, the composition provides rapid release with peak plasma concentrations achieved within 2 h. Absolute bioavailability is low however, ranging from 5 to 30% ("Clinical Pharmacology—Drug Product Monographs," 2007).

Animal Models for Testing

Given the substantial research into AD, numerous animal models have been reported in the literature, ranging from rodents to primates; however, the most commonly tested

model is the rodent because of the ease of genetic modification and study (Albert, 2007). The animal models can be broadly classified into two categories: performance models, which assess the performance of the trained animal in certain tasks such as the water maze, and pathological models, which characterize the physical changes to subject following replication of all or part of the AD disease state.

Effective pathological models are dependent on the ability to accurately recreate part or all of the disease symptoms in the model. This can be accomplished through the use of transgenic animal where the AD disease state can be replicated by genetic modification and overexpression of genes associated with familial AD, specifically modification of APP and PS genes. Using a mouse model with overexpression of mutated human amyloid precursor protein (hAPP717VF), Masliah et al. (1996) were able to generate amyloid deposition and complex cellular degeneration similar to AD. Similarly, Games et al. (1995) demonstrated that transgenic mice overexpressing human mutant APP exhibited symptoms characteristic of AD.

The utility of these models has been highlighted recently in the evaluation of several currently approved products for the development of more rapid screening techniques and more efficient therapies. Hu and coworkers (2007) evaluated the neuroprotective effects of memantine and a developmental drug, PNU-282987, in APP transgenic mice. Both compounds exhibited a neuroprotective effect that was also correlated with a cell-based high-throughput assay for rapid screening of neuroprotection. Chacard-Chastel et al. used transgenic mice to study the effect of donepezil and prucalopride on the 5-HT4 receptor, demonstrating the beneficial use of 5-HT4 agonists in AD therapy.

Although transgenic models can provide insight into the mechanisms of the disease, performance models are required to assess the rate of cognitive decline in the animals. One test, the Morris water maze, has been used extensively in animal models of AD. This test consists of conditioning an animal, typically a rodent, to swim in a pool of water with a small clear floating platform inside and locate the platform within a set period to free itself from the water. The water in the pool will remove any scent markers that the animal could use to track the platform during the test, requiring it to use its memory of the test procedure. After conditioning, testing is performed by placing the animal inside the pool without the floating platform and recording the trajectories of the animal during the test period and the number of passes through the target location. Several other variations of the water maze test have been reported in literature along with other tests, such as computer-aided matching and lever actuation. These tests are also excellent metrics for cognitive function assessment, however, this will not be discussed in detail here.

The use of performance test models in combination with transgenic models is an excellent way to assess current AD therapies for both cellular and cognitive functionality. Sood, Beach, Webster, Terry, and Buccafusco (2007) evaluated an experimental AD candidate, JWB1-84-1, on the cognitive function of transgenic AD mice in computer-aided matching studies and water maze testing. Their results showed that task accuracy was significantly improved at all but the lowest dose of drug, indicating the therapeutic potential of the investigational compound. In another study, Bachuring and coworkers (2007) investigated the behavioral and neuroprotective properties of glutamate receptor ligands, specifically the novel investigational compound NT1505 using a water maze test to assess cognitive function. Their results also demonstrated the utility of the investigational compound for the improvement of cognitive function.

NEUROPATHIC PAIN

Neuropathic pain is defined as pain resulting from lesions in the CNS (Woolf, 2004). To address these lesions, it is important to understand how they originate. Numerous conditions, including degenerative spine disease, diabetes, herpes zoster, AIDS, surgery, stroke, and trauma, have been identified as causes of lesions resulting in neuropathic pain (Raja & Haythornthwaite, 2005). Given the prevalence of these diseases, it is not surprising that the number of cases of neuropathic pain are increasing, with an estimated three million people in the United States suffering from diabetic neuropathy alone (Schmader, 2002). Even with the growing increase in this disease, there are a limited number of CNS compounds for treating this disease currently approved by the FDA, with opium therapy being the primary option for pain management (Dworkin et al., 2003).

Disease Biology

Although the disease is caused by lesions of the CNS, the varying origins for these lesions make developing a fundamental disease model difficult. The pain may generally be classified into two categories: positive symptoms, which result from changes in peripheral nerves, and negative symptoms, which result from axonal damage and neuronal loss (Raja & Haythornthwaite, 2005). During the course of the initiator disease, the CNS is damaged, resulting in the presence of lesion with several effects. Physical damage to the cells can result in changes in sensory flow input, stimulating the sensory experience of pain (C. -N. Liu, Devor, Waxman, & Kocsis, 2002). Additionally, changes in the levels of transcripts occur, re-regulating hundreds of neuron genes including those associated with regeneration and survival (Costigan et al., 2002). Over time, these injuries result in a variety of painful sensory inputs creating the neuropathic pain condition.

Approved Drug Products

Although many products have been used for the treatment of neuropathic pain through off label use, very few approved therapies are available for this indication, highlighting the need

TABLE 5
Approved Drug Products Indicated in the Treatment of Neuropathic Pain

API	Brand	Manufacturer	MW	log *p*	Class	Dosage Form
Gabapentin	Neurontin®	Pfizer	171.2	0.8	Anticonvulsant	IRC, IRT, OS
Duloxetine	Cymbalta®	Eli Lilly Co.	333.9	5.0	SSNRI	DRC
Lidocaine	Lidoderm®	Endo Pharmaceuticals	234.3	2.5	Ib antiarrhythmic	IMI, TDP
Pregabalin	Lyrica®	Pfizer	159.3	0.8	ChE Inhibitor	IRC

DRC, delayed release capsule; IMI, intramuscular injection; IRC, immediate release capsule; IRT, immediate release tablet; IVI, intravenous injection; IVIF, intravenous infusion; MRC, modified release capsule; MRT, modified release tablet; ODT, orally disintegrating tablet; OC, oral concentrate; OS, oral solution; OSU, oral suspension; TDP, transdermal patch; SCI, subcutaneous injection.

for development in this area. Of the compounds approved for this indication, many of them have uses in other therapeutic areas such as epilepsy or depression. Duloxetine, one of the approved therapies for depression, has been discussed in the depression section. A complete list of these products is provided in Table 5. Based on the molecular properties and the information provided on the delivery systems, it is clear that these compositions depend on the molecular properties of the API to penetrate the BBB.

Gabapentin

Gabapentin is a gamma-aminobutyric acid agonist, having a molecular weight of 171.2 g/mol and log *p* of 0.8 (Wishart et al., 2006), and readily partitions into the CNS. In vivo, it functions by modulating voltage-sensitive calcium channels and preventing neuron death. Produced in both tablet and capsule forms, these compositions are designed to provide rapid drug release. Orally administered drug is rapidly absorbed, however, limited and dose-dependent bioavailability has been reported ("Clinical Pharmacology—Drug Product Monographs," 2007).

Lidocaine

Lidocaine is type 1b antiarrhythmic typically used as a topical anesthetic; however, it is available for treatment of neuropathic pain associated with postherpetic neuralgia. In 1995, the drug received orphan drug status for neuropathic pain and was marketed as Lidoderm®, a transdermal patch. Manufactured by Endo Pharmaceuticals (Cnadds Ford, PA, USA), this patch is intended for local treatment of pain because of nerve agitation, functioning by penetrating the skin to interact with regional nerve cells ("Lidoderm® (Lidocaine Path 5%)—Targets the Lingering Pain After the Shingles").

Pregabalin

Structurally similar to gabapentin, pregabalin is indicated in a variety of disease states including epilepsy. Pregabalin has been shown to reduce neuronal calcium currents by binding to calcium channels, which is believed to be responsible for neuropathic pain reduction. Developed by Pfizer and marketed under the trade name Lyrica®, it is available as an IR capsule in strengths from 25 to 300 mg. Upon oral administration, drug is rapidly absorbed (90% bioavailability), achieving peak plasma concentrations within 90 min. Once in systemic circulation, the molecular properties allow pregabalin to enter the CNS without the aid of secondary transporter ("Clinical Pharmacology—Drug Product Monographs," 2007; "Welcome to the official site of LYRICA—Find more information about Nerve Pain, DPN, PHN and P").

Animal Models for Testing

Pain models have been extensively studied in literature for the last hundred years, and although neuropathic pain exhibits many of the same symptoms of pain induced by physical injury, the biological mechanism of the pain is quite different. To study neuropathic pain in animal models, it is necessary to induce a state of neuropathic pain before conducting traditional pain measurement studies such as mechanical sensitivity tests to external stimuli. As these stimuli tests are extensively covered in traditional pain therapy evaluation reviews, this section will focus on the different methods for inducing the neuropathic condition.

Many different methods are available creating neural damage characteristic of neuropathic pain by both surgical alteration and administration of damaging agents. The most commonly applied technique used for induced neuropathy is surgical alteration of sciatic nerve that innervates the hind limbs. Several different techniques, including the Chung spinal segmental nerve (Kim & Chung, 1992), the Bennett chronic constriction injury (Bennett & Xie, 1988), and the Seltzer partial sciatic nerve injury model (Seltzer, Dubner, & Shir, 1990), are available for the modification with each resulting in varying degrees of injury. A novel method developed by Decosterd and Woolf, (2000), the spared nerve injury model, provides the ability for behavioral study with improved sensitivity by limiting axon degeneration in distal regions. Other methods of reproducing neuropathic pain conditions include the use of neurologically damaging materials. Chemotherapeutic

compounds capable of producing allodynia in rodents, such as paclitaxel, have been used to induce neuropathic states (Higuera & Luo, 2004). Similarly, administration of streptozotocin can induce a state of diabetic neuropathy through the destruction of pancreatic β-cells (Fox, Eastwood, Gentry, Manning, & Urban, 1999). Using these models, neuropathic conditions are successfully replicated for study in well-established clinical models.

SCHIZOPHRENIA

Generally associated with extreme and dangerous behavior, schizophrenia is a debilitating mental condition, estimated to effect 1% of the people world wide (Capuano, Crosby, & Lloyd, 2002). It was not until the first antipsychotic drugs in 1952 that effective methods for treating this illness were developed. Other previous treatments, such as electroconvulsive therapy, lobotomy, and institutionalization, met with limited success (Capuano et al., 2002). Today, modern medicine has coupled therapeutic drugs with psychiatric counseling, providing patients with the opportunity to regain their life, although even today, many of the drugs have substantial side effects due to a lack of understanding of the disease biology.

Disease Biology

The present understanding of schizophrenia is still largely empirical. The symptoms of schizophrenia can be classified into two distinct categories: positive and negative (Capuano et al., 2002; Freedman, 2003; Lieberman et al., 2005; Wassef, Baker, & Kochan, 2003). Positive symptoms include hallucinations, delusions, incoherent speech, passivity, thought modification, and incongruity of affect (Capuano et al., 2002). Negative symptoms include scarcity of speech, reduced emotional responsiveness, inability to feel pleasure, inability to feel intimacy, apathy, and impaired attention (Capuano et al., 2002). Further defining the patient, they can be categorized in one of five subtypes based on the type and degree of the symptoms. These subcategories include catatonic, paranoid, disorganized, simple, and residual.

Although evidence suggests a hereditary link to schizophrenia, no specific genes have been identified, and additional evidence suggests some effect of environmental factors as well. Currently, there are several leading theories for the cause of schizophrenia, each identifying different aspects of the receptor-mediated basis of the disease. The dopamine and serotonin receptor hypothesis identifies imbalances in these two receptors as the primary mechanism for positive and negative symptoms (van Veelen & Kahn, 1999). Another leading theory for the cause of the disease is the dopaminergic overactivity theory, which identifies overactive dopamine receptors in the mesolimbic system as the source of schizophrenia symptoms (McKenna, 1987). Other theories postulate that mesolimbic system becomes overactive due to prefrontal cortex dysfunction, accounting for both environmental and genetic traits of the disease (Weinberger, 1987).

Approved Drug Products

Antipsychotic drugs can be classified into two broad categories: typical antipsychotics, which are first-generation drugs having a high affinity for dopamine D_2 receptors with significant side effects, and atypical antipsychotics, which are second-generation drugs having a broader pharmacological activity with reduced side effects. Given the extensive number of drug products available for schizophrenia, a complete review of all formulations was not possible; however, several of the most recent atypical drugs were evaluated along with a few typical drugs and described based on their delivery systems. These products, listed in Table 6 with their respective attributes, all show favorable properties for BBB permeability. Additionally, a review of the available dosage forms clearly shows that no secondary mechanisms of permeation are used in the delivery of these compounds to the CNS; however, several

TABLE 6
Approved Drug Products Indicated in the Treatment of Schizophrenia

API	Brand	Manufacturer	MW	log *p*	Class	Dosage Form
Aripiprazole	Abilify®	Otsuka America Pharmaceuticals	448.4	4.5	Atypical	IRT, ODT, OS
Chlorpromazine	Thorazine®	Glaxo Smith Kline (Discontinued)	318.9	5.5	Typical	IRT, IVI
Clozapine	Clorazril®	Novartis Pharmaceutical Company	326.8	2.5	Atypical	IRT, ODT
Haloperidol	–	Multiple Generic Companies	375.9	4.4	Typical	IMI, IRT, IVI, OS
Risperidone	Risperdal®	Janssen Pharmaceutica Products, LP	410.5	2.7	Atypical	IMI, IRT, ODT, OS
Olanzapine	Zyprexa®	Eli Lilly	312.4	2.2	Atypical	IMI, IRT, ODT
Quetiapine	Seroquel®	AstraZeneca	383.5	2.3	Atypical	IRT, MRT
Ziprasidone	Geodon®	Pfizer	412.9	3.8	Atypical	IMI, IRC

DRC, delayed release capsule; IMI, intramuscular injection; IRC, immediate release capsule; IRT, immediate release tablet; IVI, intravenous injection; IVIF, intravenous infusion, MRC, modified release capsule; MRT, modified release tablet; ODT, orally disintegrating tablet; OC, oral concentrate; OS, oral solution; OSU, oral suspension; TDP, transdermal patch; SCI, subcutaneous injection.

delivery systems were designed to maximize the duration of action or reduce first pass metabolism.

Aripiprazole

Aripiprazole is an atypical antipsychotic drug, classified as a dopamine system stabilizer, having a molecular weight of 448.4 g/mol and log *p* of 4.5 (Wishart et al., 2006). Ariprazole is a partial agonist at the dopaminergic D_2 and serotonergic 5-HT_{1A} receptors and is an antagonist at the serotonergic 5-HT_{2A} receptor, allowing for treatment of schizophrenia-related symptoms. Produced as an oral solution, intramuscular injection, IR tablet, and orally disintegrating tablet, it is marketed under the trade name Abilify®. The IR tablet composition contains drug in a matrix of corn starch, hydroxypropyl cellulose, lactose, microcrystalline cellulose, and magnesium stearate, along with the appropriate colorants to provide rapid drug release and is available in potencies of 2, 5, 10, 15, 20, and 30 mg. An orally disintegrating composition was also developed, Abilify® Discmelt™, to provide more rapid release and therapy for patients unwilling or unable to swallow tablets. The orally disintegrating product is available in 10 and 15 mg strengths. After oral administration, it is well absorbed having a bioavailability of 87%, and peak plasma concentrations are usually obtained within 3–5 h after administration. The intramuscular injection provides even greater absolute bioavailability (100%) with an improved onset of action ($t_{1/2}$ is 1–3 h) ("Abilify® (aripiprazole)—A Treatment for Bipolar Disorder and Schizophrenia,"; "Clinical Pharmacology—Drug Product Monographs," 2007; Kelleher, Centorrino, Albert, & Baldessarini, 2002).

Chlorpromazine

Chlorpromazine is an aliphatic phenothiazine having a molecular weight of 318.9 g/mol and log *p* of 5.5 (Wishart et al., 2006) meeting the criteria for unassisted BBB transport. Discovered in 1952, it was one of the first drugs to treat the positive symptoms of schizophrenia (Capuano et al., 2002). Chlorpromazine functions by blocking postsynaptic dopamine receptors in the mesolimbic system and increasing dopamine turnover by blocking the D_2 somatodendritic autoreceptor. Although Thorazine® has been discontinued, numerous generic products are available as both i.v. injection formulations and IR tablet formulations. The tablet formulations, available in potencies of 10, 25, 50, 100, and 200 mg, provide rapid drug release with peak plasma concentrations achieved 3–4 h postadministration; however, orally administered drug exhibits significant patient variation due to first pass metabolism, with oral bioavailability ranging from 19 to 51% ("Clinical Pharmacology—Drug Product Monographs," 2007).

Clozapine

Clozapine is classified as an atypical antipsychotic agent and is a dibenzodiazepine derivative with a molecular weight of 326.8 g/mol and log *p* of 2.5 (Wishart et al., 2006) meeting the requirements for BBB transit. Cloazpine functions by blocking dopamine receptors (D_1, D_2 to a lesser extent, and D_4), thereby countering schizophrenic problems. The blocking action of alpha$_1$-adrenergic receptors produces sedation, muscle relaxation, and cardiovascular effects. The innovator product, Clorazil® marketed by Novartis Pharmaceutical Company, is an IR tablet composition produced in 25 and 100 mg strengths. Additional generic IR tablets are produced by a variety of manufacturers in potencies ranging from 12.5 to 200 mg. An orally disintegrating tablet product, produced by Azur Pharma Inc. (Philadelphia, PA, USA) and marketed under the name Fazaclo®, provides rapid drug release in the buccal cavity. Upon oral administration, the drug is rapidly absorbed but exhibits an extensive first pass metabolism having two metabolites with minimal pharmacological activity and providing bioavailbilities of 27–50%. The orally disintegrating tablets are considered bioequivalent to the IR tablet composition ("Clinical Pharmacology—Drug Product Monographs," 2007).

Haloperidol

Haloperidol is a high-potency antipsychotic with a molecular weight of 375.9 g/mol and log *p* of 4.4 (Wishart et al., 2006). The drug functions by blocking postsynaptic dopamine receptors, specifically D_2 in the mesolimbic system. Produced in a variety of dosage forms and salt forms by numerous companies, the drug is primarily administered orally and parenterly. The IR tablet formulation is available in range of potencies, from 0.5 to 20 mg, allowing for rapid absorption (t_{max} is 2–6 h) with reported bioavailabilities of 60% due to first pass metabolism. The intramuscular injection provides for more rapid onset of action and also avoids the first pass metabolism increasing the bioavailability to 75% ("Clinical Pharmacology—Drug Product Monographs," 2007).

Risperidone

Risperidone is an atypical antipsychotic agent having a molecular weight of 410.5 g/mol and log *p* of 2.7 (Wishart et al., 2006). The drug is a selective monoaminergic antagonist with a high affinity for both serotonergic 5-HT_2 and dopaminergic D_2 receptors and functions by synergistically blocking serotonin and dopamine transmission. Marketed under the trade name Risperdal® by Janssen Pharmaceutica Products (Titusville, NJ, USA), LP is available in a variety of dosage forms including an IR tablet, orally disintegrating tablet, oral solution, and reconstitutible powder for intramuscular injection. The oral solution and tablet formulations are bioequivalent, providing rapid and complete absorption within 1–2 h postadministration. Risperidone is metabolized by CYP 2D6 enzymes to 9-hydroxyrisperidone, an active metabolite that also crosses the BBB. The intramuscular formulation, Risperdal® Consta™ is a microsphere-based drug delivery system that provides extended release of the drug over a 7-week period. Risperidone-loaded poly (lactic-co-glycolic acid) (PLGA) microspheres

are produced using microencapsulation technology as described in US patent 6,544,559 B2 and provide sustained release because of the gradual hydrolization of the carrier (Mesens, Rickey, & Atkins, 2003; Sah & Lee, 2006; Swainston & L, 2004) ("Clinical Pharmacology—Drug Product Monographs," 2007; "Risperdal"; "RISPERDAL CONSTA—For Healthcare Providers").

Olanzapine

Olanzapine is an atypical antipsychotic having multiple receptor binding activities, molecular weight of 312.4 g/mol, and log *p* of 2.2 (Wishart et al., 2006). The molecule functions by binding to alpha$_1$, dopamine, histamine H_1, muscarinic, and serotonin type 2 (5-HT_2) receptors, exerting antischizophrenic effect through antagonism of dopamine and serotonin type 2 receptors. Marketed under the trade name Zyprexa®, it is available in a variety of dosage forms including IR tablets, orally disintegrating tablets, and intramuscular injections. The orally disintegrating tablet and the IR tablet show rapid drug release, achieving peak plasma concentrations within 6 h postadministration and are considered bioequivalent. Because of extensive first pass metabolism that converts the drug into inactive metabolites, oral bioavailability is significantly reduced. The intramuscular injection provides rapid release of drug, achieving peak plasma concentrations 15–45 min postadministration and provides enhanced bioavailability due to reduced first pass effect ("Clinical Pharmacology—Drug Product Monographs," 2007; "The Official ZYPREXA Olanzapine Site").

Quetiapine

Marketed by AstraZeneca (Wilmington, DE, USA) under the trade name Seroquel®, quetiapine is an atypical antipsychotic agent capable of functioning as a serotonin 5-HT_2-receptor antagonist with moderate dopamine (D_2)-receptor antagonism. The compound is indicated for use in the treatment of schizophrenia and related disorders. The chemical properties of the drug, specifically the low molecular weight (383.5 g/mol [Wishart et al., 2006]) and lipophilicity (log p = 2.3 [Wishart et al., 2006]), allow the drug to penetrate the BBB. The molecule functions by combined dopamine D_2 and serotonin 5-HT_2 receptor antagonism. Seroquel® is available as in both IR and MR tablet formulations at varying potencies using the fumarate salt form. Seroquel® IR tablets are produced in potencies of 25, 50, 100, 200, 300, and 400 mg using a tablet core composed of calcium phosphate dibasic, lactose, microcrystalline cellulose sodium starch glycolate, povidone, and magnesium stearate. The film-coated tablets are capable of providing rapid drug release, with maximum concentrations achieved in vivo within 1.5 h and are generally prescribed for bipolar mania. The extended release compositions use a hydroxypropyl methylcellulose matrix to provide controlled drug release, with maximum plasma concentrations achieved after 6 h. The extended release tablets are prescribed for schizophrenia ("Clinical Pharmacology—Drug Product Monographs," 2007; "SEROQUEL—Home").

Ziprasidone

Developed by Pfizer and marketed as Geodon®, ziprasidone is an atypical antipsychotic having a molecular weight of 412.9 g/mol and log *p* of 3.8 (Wishart et al., 2006) that exerts a pharmacological effect due to its dopamine and serotonin receptor antagonist properties. The drug product is produced as an IR capsule formulation for oral delivery and also an intramuscular injection. The IR capsule formulation is produced by powder filling a mixture of API, lactose, pregelatinized starch, and magnesium stearate into gelatin capsules, with the product being available in several strengths (20, 40, 60, and 80 mg). The oral formulation does show reduced bioavailability, and administration with food is recommended. The intramuscular injection shows 100% bioavailability, achieving peak plasma concentrations within 1 h of injection ("Clinical Pharmacology—Drug Product Monographs," 2007; "Schizophrenia and Bipolar Mania Treatment—Geodon").

Animal Models for Testing

The study of schizophrenia in animal models is complicated by the complex emotional symptoms the disease elicits and the lack of a fundamental mechanism for its cause. Current models focus on reproducing the observed receptor-mediated problems or behavioral traits through the use of drugs or external stimuli to quantify the efficacy of a developmental drug molecule. In addition to the way in which the disease symptoms are induced, the animal model selected may play a significant role in the testing. Although smaller animals such as rodents have the advantage of being small, easy to handle, and readily available for genetic alteration, they lack the development in complex regions of the brain that humans have. Nonhuman primates are an excellent alternative for mimicking the complex brain patterns observed in humans, however, they can be difficult to work with and expensive to house. This section will discuss the use of animal and nonhuman primate models for the study of schizophrenia, including techniques for inducing the disease state, as well as procedures for assessing efficacy.

Rodent models are easy to work with and easily modified on a genetic level; however, they lack the complex neuroarchitecture characteristic of humans. To induce pseudoschizophrenic states, the animals are given drugs such as amphetamine and phencyclindene, in a variety of procedures reported in literature to stimulate dopamine and serotonin receptors. Animals can then be subjected to a battery of physical tests to evaluate their behavior, including climbing, maze testing, and electrical shock. In several earlier studies conducted by Costall and coworkers, they demonstrated that the addition of apomorphine-induced wall climbing responses could be eliminated by the administration of antipsychotic drugs such as haloperidol (Costall, Naylor, & Nohria, 1980a, 1980b). In more recent research articles, several experimental drugs have also been investigated. Hirst et al. (2006) investigated the potential application of SB-399885, a potent 5-HT6

receptor antagonist, for use in AD and schizophrenia using the rat maximal threshold shock test, water maze test, and prefrontal cortex microdialysis. The electrical shock testing was conducted by dosing the animal with the investigational drug, applying a mild shock current to the foot and measuring the response. This testing demonstrated a minimum effective dose of 1 mg/kg orally. Water maze testing results showed that animals dosed with the experimental compound demonstrated improved task recall. Microdialysis studies demonstrated that SB-399885 effectively crosses the BBB without the aid of a secondary delivery system. They concluded that this compound could have potential therapeutic value to AD and schizophrenia. Ishiyama et al. (2007) also recently investigated the use of lurasidone, an atypical antipsychotic, as a potential schizophrenia candidate in rats using the passive avoidance response model. In this model, animals are placed in the lighted chamber of a cage with a sliding door leading to a dark cage. They are then allowed to explore the lighted chamber, the door opens and the time for the animals to enter the darkened chamber is recorded, at which time the door closes and the animal receives an electric shock. The animals are then rested for a period, given the required dose based on study protocol, and the procedure is repeated without the electric shock. For this study, animals were administered dizoclipine, an NMDA receptor antagonist to mimic the schizophrenic condition. The results of this study showed that lurasidone did not alter the passive aggressive response and eliminated reduced the dizoclipine impairment, indicating the potential of the investigational compound.

Nonhuman primates provide a much similar model to the human brain than other smaller animals, allowing for more representative testing. While small animals can be trained to perform only the simplest of tasks, nonhuman primates can perform much more complicated tasks, allowing for the assessment of cognitive function. A battery of tests have been developed, generally following the same protocol for inducing the disease state. These tests are capable of assessing many of the cognitive aspects associated with schizophrenia and include the spatial delayed response test, delayed to match sample test, and attentional set shifting test. For a complete review of primate testing procedures, the reader is referred to a recent review by Castner, Goldman-Rakic, and Williams (2004).

ADVANCED DRUG DELIVERY ROUTES FOR CNS DISORDERS

Many successful therapies have been developed for treating CNS disorders; however, the delivery systems employed by these products are extremely simplistic and/or essentially nonexistent when targeting the CNS. Several new strategies focused on molecular design, nanotechnology, and complexation with targeting moieties have recently been investigated, demonstrating promising results for CNS delivery. This section describes recent advances in targeted CNS delivery.

Molecular Drug Design

When a drug is unable to penetrate the BBB due to its chemical properties, modification of the molecular structure may be necessary. Two types of chemical modifications have been traditionally employed to enhance BBB permeation of an active moiety: development of a prodrug capable of permeation or attachment of lipophilic groups to compound of interest to induce transport.

A prodrug is defined as a pharmacologically inert form of an active drug that must undergo transformation to the parent compound in vivo by either a chemical or an enzymatic reaction to exert its therapeutic effect (Kumar & Banker, 1996). The prodrug strategy relies on synthesizing prodrugs capable of entering the CNS by virtue of their chemical properties where they undergo metabolism to the pharmacologically active form. As many potentially CNS active drugs are unable to enter the CNS due to their chemical structure, prodrugs are actually designed to exploit BBB transporters responsible for the uptake of nutrients (Pardridge, 2002a).

Numerous studies have been conducted illustrating the utility of this strategy. Bonina et al. evaluated the potential of novel glycosyl derivatives of dopamine and L-dopa link by a succinyl linker at varying positions. Their work showed that compositions linked via the C-3 glucose position provided greater effect in reversing hypolocamotion in rats with minimal vascular effects of the derivatives (Bonina et al., 2003). In another recent study, Denora et al. investigated the feasibility of linking L-dopa and dopamine to L-dopa ethyl ester to 2-phenyl-3-carboxymethyl-imidazopyridine compounds. These dopimid compounds were characterized in MDCKII-MDR1 monolayer studies and in vivo with rats using brain microdialysis. Results showed that these dopimid compounds were capable of providing in vitro and in vivo permeability (Denora et al., 2007), highlighting their potential use for targeted delivery.

In addition to numerous research studies conducted, Sinemet® is an approved therapy for Parkinson's disease based on this strategy. Each tablet contains 100 mg of levodopa, the metabolic precursor of dopamine, which is able to transit the BBB for conversion in the CNS. To prevent the decarboxylation of levodopa, each tablet also contains 10 mg of carbidopa, allowing the drug to enter the CNS unchanged ("Clinical Pharmacology—Drug Product Monographs," 2007).

The other drug modification strategy is the attachment of lipophilic compounds to increase BBB permeability. It has been shown that increasing the lipophilicity of a compound strongly correlates with BBB permeability (Levin, 1980), making this a potentially attractive delivery strategy for a number of developmental compounds. There are several difficulties with this approach for targeting the CNS, specifically the increased permeation across all biological membranes, increased molecular weight potentially reduces BBB permeability and increased plasma clearance results in reducing systemic AUC (Batrakova & Kabanov, 2007; Pardridge, 2007b). Furthermore, no products have been approved using this technology (Pardridge, 2007b).

Several researchers have investigated lipophilic modification for the delivery of macromolecules. Kozova et al. developed hydrophobic α-chymotrypsin derivatives for targeted delivery. Their work demonstrated that reverse micelle-based reactions could successfully modify the hydrophobic nature of proteins (Kozlova, Bruskovskaya, Melik-Nubarov, Yaroslavov, & Kabanov, 1999). In another study, Chopineau et al. studied the effect of regiospecific monoacylation of RNase A on BBB permeability. Using a reverse micelle-based reaction, they showed a single fatty acid could be linked to the RNase A, which improved BBB in an in vitro model (Chopineau et al., 1998). These studies demonstrate the utility of lipophilization for targeted delivery, specifically with macromolecules.

BBB Modification

The ability of materials, specifically solvents, to modify the permeability of the BBB has been known for many years. Many solvents such as sodium dodecyl sulfate (SDS), ethanol, dimethylsulfoxide (DMSO), glycerol, and polysorbate-80 have been utilized to disrupt the BBB, enhancing permeability of molecules which do not normally transit the barrier. Hanig et al. investigated the effect of ethanol on the uptake of norepinephrine and epinephrine in neonate chickens. Their research showed that ethanol did not alter endogenous levels of either amine in the brain; however, they did significantly increase the uptake of these molecules (Hanig, Morrison, & Krop, 1972). The researchers hypothesized that the increased permeability was due to the polar and nonpolar solvent characteristics of ethanol. The functionality of SDS as a BBB permeability enhancer has also been investigated by several researchers. Ellison et al. studied the effects of systemic human recombinant interleukin-2 (rIL-2) infusion upon BBB status and cerebral vascular ultrastructure in cats. Their research showed that formulations containing SDS enhanced BBB permeability (Ellison, Povlishock, & Merchant, 1987). Kobiler, Lustig, Gozes, Ben-Nathan, and Akov (1989) also demonstrated that SDS increased BBB permeability, highlighting the potentially dangerous use of this material in i.v. injections by increasing the penetration of pathogens as well. Polysorbate-80 has also been used extensively as a BBB permeation enhancer. Florence et al. demonstrated the utility of polysorbate-80 for enhanced brain uptake of methotrexate following oral delivery in mice (Azmin, Stuart, & Florence, 1985). Polysorbate-80 also functioned as a gastrointestinal permeation enhancer and did not significantly damage the intestinal mucosa. Additionally, Sakane and coworkers investigated the effect of polysorbate-80 on brain uptake of D-kyotorphin. In mice, D-kyotorphin showed no analgesic activity; however, when coadministered with polysorbate-80, significant analgesic activity was observed, which was attributed to improved BBB permeation induced by the additive (Sakane et al., 1989).

Additives that modified the permeability of the BBB may also allow potentially harmful pathogens to transit the barrier as well, elevating the risk of significant injury or death to patient. To minimize the risk to patients, a new generation of BBB permeability modifiers is being developed to function locally. These systems, based on vasoactive leukotrienes, modulate transpeptidases in normal capillaries, resulting in a decreased endothelial barrier. Using these systems, changes in the BBB occur rapidly after beginning infusion with normal function restored after 5 min (Batrakova & Kabanov, 2007). This novel BBB permeability modifying system may allow for therapeutic delivery of advanced compounds without the risks associated with other permeability modifying compounds.

Stealth Systems

Although many compounds are prevented from entering the CNS, it is possible to complex target molecules or carriers (i.e., nanocontainers) with a material capable of passing the BBB, in a strategy termed “Trojan horse,” to provide successful delivery.

The use of MAbs as complexing agents to allow for successful delivery to the CNS has been employed recently in a number of applications by exploiting pre-existing mechanisms of BBB transit. Coloma and coworkers developed a Trojan horse system based on the murine 83-14 MAb—human insulin receptor as a brain drug targeting vector. Using genetic engineering, they developed chimeric human insulin receptor monoclonal antibodies (HIRMAb) and characterized their misdistribution in a radio labeling study. The results demonstrated that CNS uptake of the radiolabeled HIRMAb was extensive, as shown in Figure 4, demonstrating the utility of this delivery platform (Coloma et al., 2000).

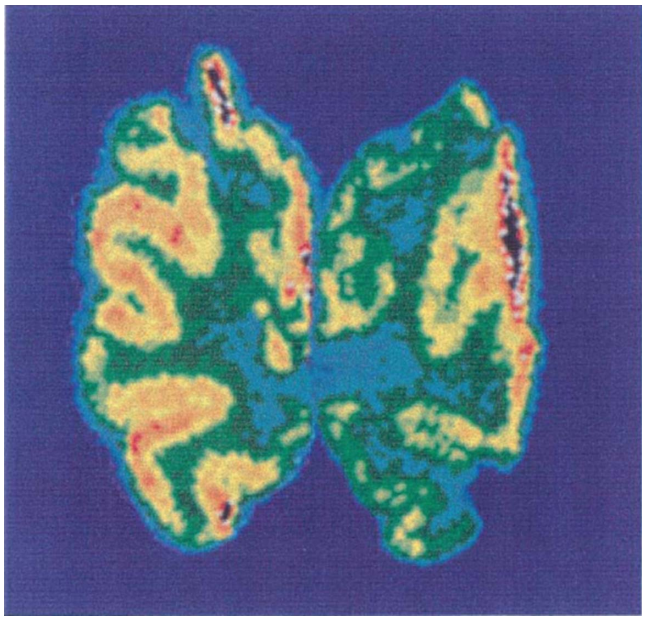

FIGURE 4. Film autoradiography of coronal brain sections obtained from a Rhesus monkey 2 h after the intravenous injection of [111In-DTPA] chimeric HIRMAb. With kind permission from Springer Science & Business Media: Reprinted with permission from Coloma et al. (2000), Figure 7. Copyright © 2000, Plenum Publishing Corporation.

Boado, Zhang, Zhang, and Pardridge (2007) also successfully demonstrated the utility of complexing HIRMAb to therapeutics by complexing -BDNF for targeting of the CNS in vitro and in vivo. BDNF proteins are highly neuroprotective in acute ischemia; however, they are not pharmacologically active following i.v. administration because of their inability to transit the BBB. The study demonstrated that the affinity of the fused protein was identical to BDNF and also exhibited 100-fold increases in mean residence time when tested in Rhesus monkeys, as shown in Figure 5. In another recent study, this research group used a tri-functional fusion antibody to treat AD (Boado, Zhang, Zhang, Xia, & Pardridge, 2007). The delivery strategy employed, and presented schematically in Figure 6, was based on binding of HIRMAb to the human insulin receptors for transit of the BBB, utilizing the Aβ fibril to disaggregate the amyloid plaque followed by efflux from the brain to the blood via the Fc receptor. This fusion antibody was shown to rapidly transit the primate BBB in vivo, shown in Figure 7, and also demonstrated 40% clearance of Aβ plaque with 48 h of single intracerebral injection in a double-transgenic AD mouse brain, as shown in Figure 8.

Another commonly reported Trojan horse system is the OX26 MAb. In a recent study by Song et al., they examined the potential of the MAb to improve CNS delivery of basic fibroblast growth factor, which has minimal pharmacological activity in the absence of a secondary system for BBB transit, using a regional brain ischemia model. In vivo results showed an 80% reduction in infract volume following doses as low as 25 μg/kg (B. -W. Song, Vinters, Wu, & Pardridge, 2002). This indicated that the use of a BBB targeting system could greatly improve the efficacy of basic fibroblast growth factor, further illustrating the utility of Trojan horse technology.

The use of MAb complexation can also be used to deliver nanocontainers of drug, such as nanoparticles or liposomes, further enhancing therapeutic efficacy. Several recent studies have developed immunoliposomes, liposomes complex with PEG and MAb, to provide site-targeted drug delivery to the CNS. In an attempt to isolate exogenous gene expression to the brain, Shi, Zhang, Zhu, Boado, and Pardridge (2001) used pegylated immunoliposomes to deliver β-galactosidase and luciferase utilizing the 8D3 MAb and OX26 MAb (Shi & Pardridge, 2000). Both studies demonstrated the utility of the targeted systems to provide site-specific delivery.

Nasal Delivery

While delivery to the CNS is regulated by the BBB, it has been shown that delivery of low molecular weight lipophilic compounds can be achieved through nasal delivery by passing the nasal epithelial barrier and the arachnoid membrane, these compounds are able to enter the olfactory CSF in proportion to lipid solubility (Sakane et al., 1991). Ross et al. (2004) investigated the applicability of an intranasal delivery system of interferon-β-1b for the treatment of MS. They compared the intransal delivery of IFN-β-1b solutions to the i.v. injection, evaluating tissue concentrations and biodistributions. Their results, shown in Figure 9, indicated that the IFN-β-1b was distributed successfully in the CNS, having statistically higher concentrations compared to the i.v. formulation while maintaining lower levels of distribution in other body tissues. In another interesting study, Vyas et al. investigated nasal delivery of a mucoadhesive microemulsion system to provide delivery of clonazepam in a rabbit model. Using the mucoadhesive system, gamma scintigraphy and measured drug concentrations within the brain demonstrated that the system provided more rapid and CNS-specific delivery of drug, suggesting a potential utility of the system in humans (Vyas, Babbar, Sharma, Singh, & Misra, 2006).

Numerous authors have demonstrated potentially successful systems in animal models; however, variations in animal model anatomy have led some to question the validity of these models for extrapolation to human subjects. Anatomical studies have shown that the olfactory region of the nasal epithelium is 50% of the total nasal surface area in the rat, while the olfactory region is only 3–8% in the human nose (Pardridge, 2007a). These differences further confound extrapolation of animal studies to the potential in human subjects. Numerous studies have suggested that nasal delivery can be used to circumvent the BBB; however, to date, no studies have conclusively

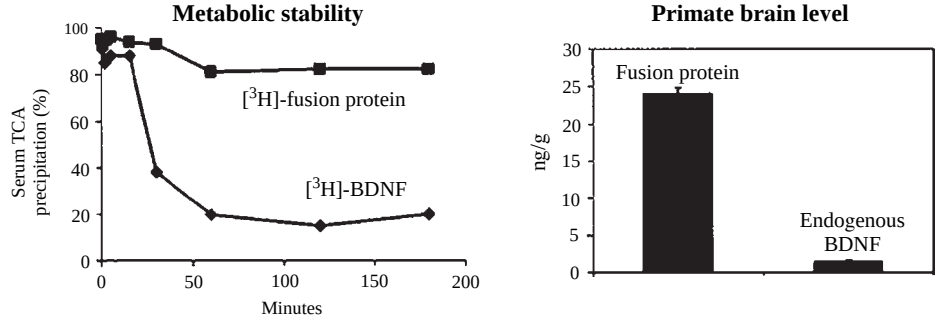

FIGURE 5. Metabolic stability and primate brain levels of fusion protein and BDNF. Reprinted with permission of Wiley-Liss, Inc., a subsidiary or John Wiley & Sons, Inc., from Boado, Zhang, Zhang, & Pardridge (2007). Copyright © 2007.

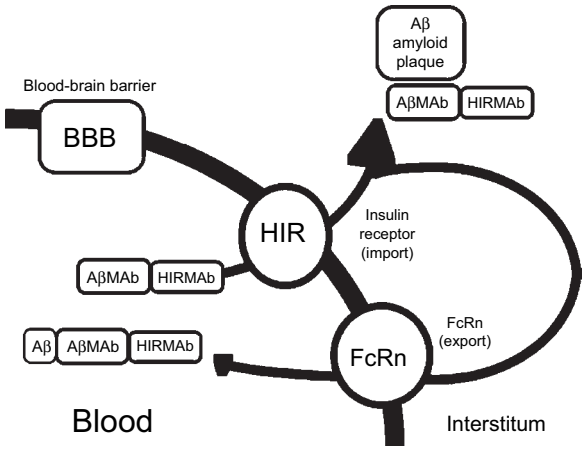

FIGURE 6. Import–export model of β-amyloid (Aβ) antibody therapeutics using a three stage delivery: influx, binding, and efflux. Reprinted with permission from Boado, Zhang, Zhang, Xia et al. (2007). Copyright © 2007, American Chemical Society.

demonstrated that this will be an effective strategy for delivery in humans (Merkus & van den Berg, 2007).

Nano Systems Targeting the Blood Brain Barrier

Nanotechnology is best defined as the development of a system or device having functional organization in at least one dimension on the nanometer scale (Silva, 2007). Although nanotechnology has made great strides in the last decade, percolating everything from electronics to paints, this technology has perhaps seen its greatest application in medical devices. The use of nanoparticle systems for enhanced drug delivery systems has been explored extensively in the last decade, finding a variety of uses including bioavailability enhancement, medical imaging, pulmonary delivery, ocular delivery, and site-targeted drug delivery within the body, specifically the CNS (Kabanov & Gendelman, 2007; Kreuter, 2007).

Nanoparticles have been used extensively in research to deliver both drugs and genes to the CNS. These particles, characterized as having a solid core or core shell structure less than 1000 nm in diameter and preferably less than 100 nm for delivery to the CNS, utilize biocompatible materials to provide small size, high surface materials capable of penetrating a number of biological tissues. However, a number of factors can influence the performance of these systems in vivo, including particle size, surface energy, and surface composition. Furthermore, because of their small size, these particles may be rapidly cleared by the reticuloendothelial system, limiting the residence time in vivo. To maximize BBB permeation and minimize clearance, many researchers have studied nanoparticles.

Illustrating the effect of nanoparticle properties on in vivo performance, Jallouli et al. recently investigated the binding, uptake, and transcytosis of 60-nm porous nanoparticles based on surface charge and inner composition. Using maltodextrins, they

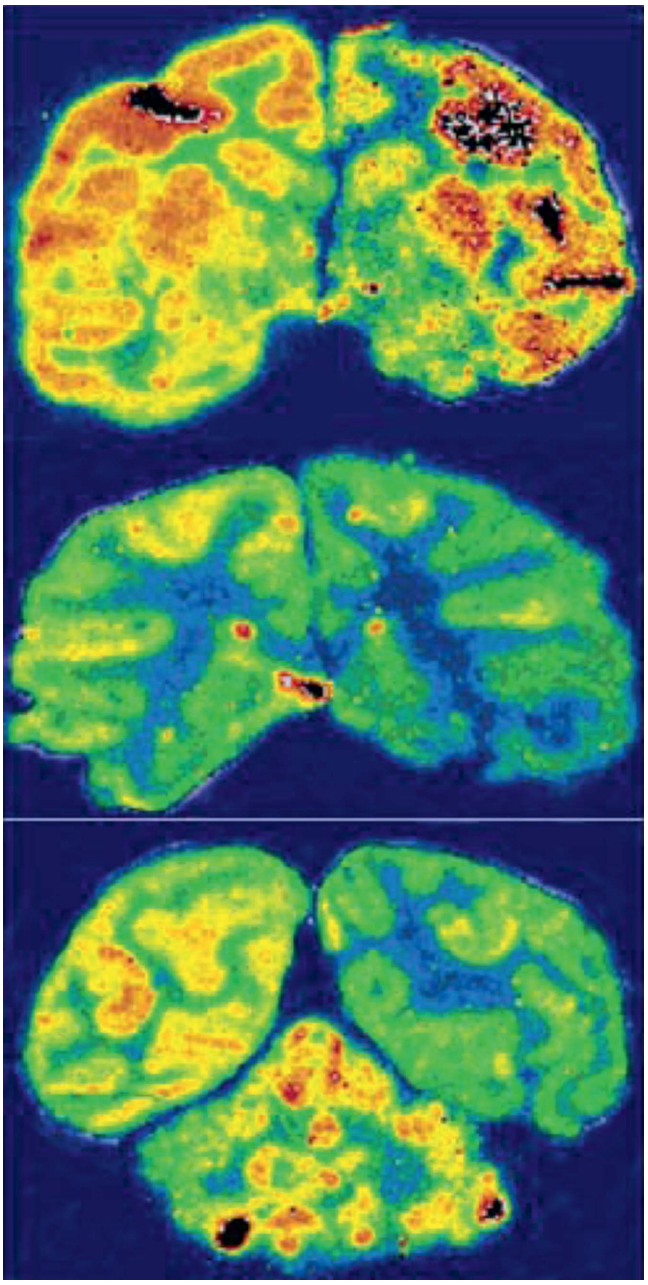

FIGURE 7. Global distribution of fusion antibody in adult Rhesus monkey 3 h postintravenous administration. Samples were labeled with [^{125}I]. Reprinted with permission from Boado, Zhang, Zhang, Xia et al. (2007). Copyright © 2007, American Chemical Society.

produced highly porous particles with and without surface charge. Studying their behavior in cell cultures, they were able to show differences in the mechanism of transport based on surface charge, as seen in Jallouli, Paillard, Chang, Sevin, and Betbeder (2007), presented in Figure 10. Particle composition may also affect the behavior of nanoparticles based on the carrier selected. In one study evaluating the in vitro performance of nanoparticles made of solid lipids, methylmethacrylate-sulfopropylmethylacrylate,

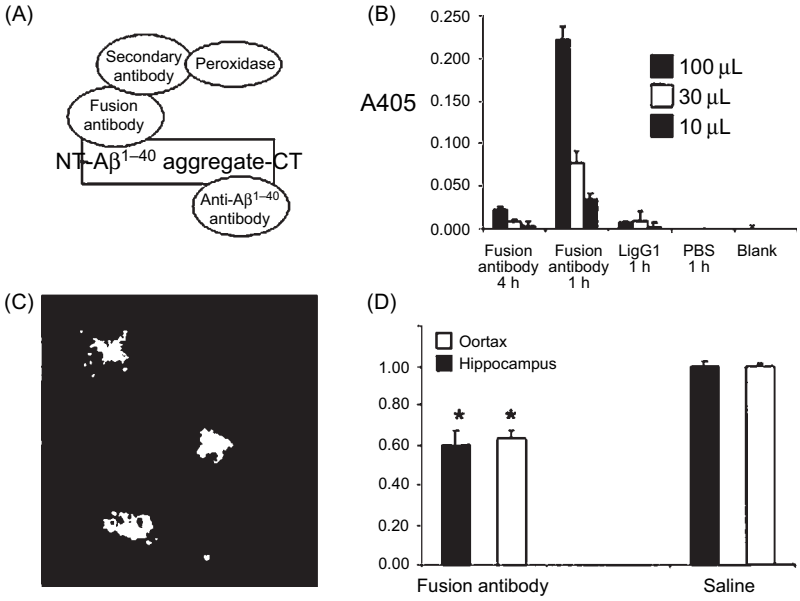

FIGURE 8. In vitro and in vivo results from fusion β-amyloid (Aβ). (A) Outline of Aβ plaque disaggregation assay. (B) Disaggregation of Aβ fibrils. (C) Amyloid plaque in brain of double transgenic APPswe/PS1dE9 mice stained with thioflavine-S. (D) Percent of brain occupied by amyloid plaque. Reprinted with permission from Boado, Zhang, Zhang, Xia et al. (2007). Copyright © 2007, American Chemical Society.

and polybutylcyanoacrylate, it was shown that the carrier material functioned synergistically with the drug loading to influence BBB permeation (Kuo & Su, 2007). A commonly used technique to avoid such effects is PEGylation, the processes of applying chemical linked polyethylene glycol chains to the nanoparticles to reduce agglomeration and increase in vivo circulation. In comparison studies of PEGylated and non-PEGylated nanoparticles, PEGylated nanoparticles showed improved physico-chemical characteristics with reduced cycotoxicity, highlighting the importance of the process (Peracchia et al., 1998). Nanoparticle delivery and targeting can be further enhanced through the use of Trojan horse technologies discussed previously.

Another novel class of drug delivery systems which exists in the nanodomain is the liposome. While nanoparticles have a solid core, liposomes have a lipid bilayer encapsulating the contents that are typically in a liquid state. These systems, as with their nanoparticle counterparts, have been studied extensively recently for applications to CNS targeting. Schmidt et al. recently examined the use of PEGylated liposomes for the delivery of glucocorticosteroids for the treatment of MS in an EAE rat model. Using the model drug prednisolone, their work showed that the PEGylated liposome formulation achieved greater therapeutic efficacy than a 5-fold higher does of drug alone (J. Schmidt et al., 2003).

Through the use of nanocarrier technology, including liposomes and nanoparticles, it is possible to achieve excellent delivery with high therapeutic loadings. These systems demonstrate high efficiencies in targeting the CNS, especially when combined with targeting mechanisms such as the Trojan horse system. It is hoped that these novel technologies will allow for improved therapies in the future.

CONCLUSIONS

CNS disorders exhibit debilitating symptoms that significantly impact the patient's quality of life. Because of the complex nature of these diseases in combination with the biology of the BBB, development of new compounds is currently limited to molecules or prodrugs capable of entering the CNS without the aid of a secondary transporter mechanism. Examination of drug products for six major CNS disease states shows that the formulations were designed to maximize therapeutic efficacy; however, none of the FDA-approved products were designed with systems to enhance BBB permeability. To improve the development process, numerous animal models have been developed and successfully employed to evaluate the developmental drug products. The expanding knowledge of the fundamental mechanisms of CNS diseases has also allowed for continued development of more complex and realistic animal models, capable of providing greater insight into the disease state and developmental therapies. Additionally, the expanding portfolio of BBB drug delivery technologies is providing significant opportunities to design novel therapeutics that are incapable of transiting the BBB individually because of their chemical properties by providing new mechanisms of transport. Using the combination of refined animal models and novel delivery technologies, the pharmaceutical industry will be able to develop new compounds capable of addressing the

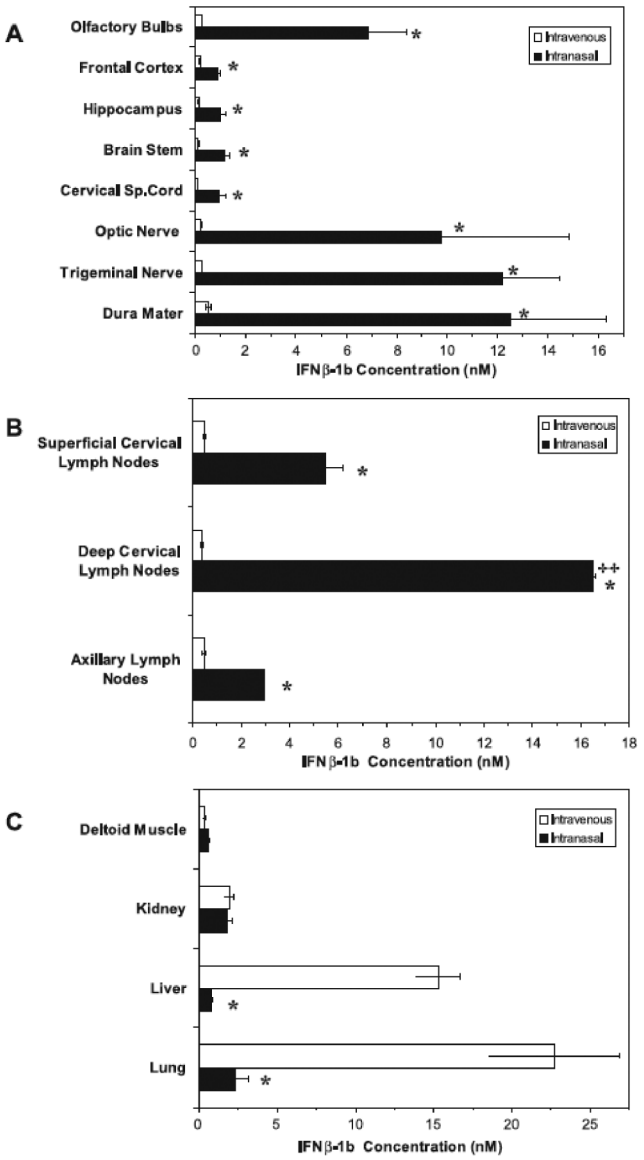

FIGURE 9. Comparison of IFN-b-1b levels for intranasal and intravenous formulations. * indicates statistically significant difference. Reprinted with permission from Ross et al. (2004). Copyright © 2004, with permission from Elsevier.

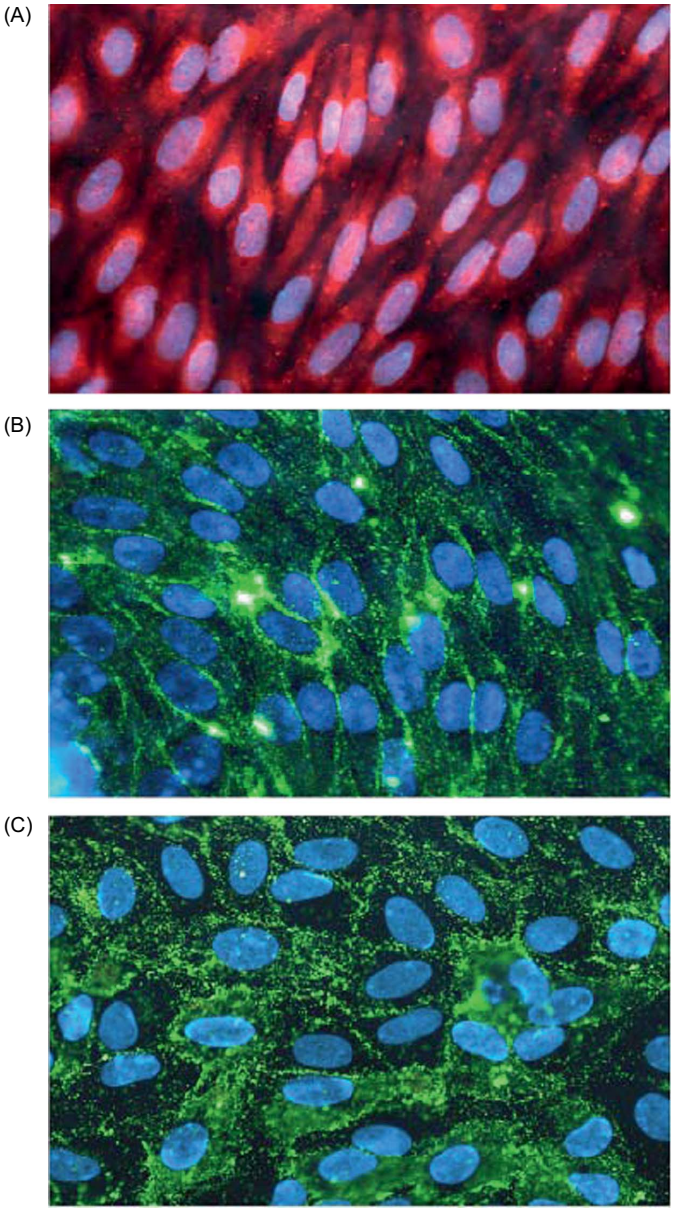

FIGURE 10. Evaluation of NPs binding on blood–brain barrier (BBB) at 4°C using fluorescence microscopy. Neutral nanoparticles (NPs) were labeled with rhodamine (A), and cationic NPs (B) and DPPG-NPs (C) were labeled with FITC. The nucleus was labeled with Hoechst. Reprinted with permission from Jallouli et al. (2007). Copyright © 2007, with permission from Elsevier.

needs of CNS patients, ultimately improving the quality of life for those afflicted with these diseases.

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