Pharmacogenomics and Personalized Medicine in Parkinsonism

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Trevor Archer and Anders Fredriksson

Abstract

Pharmacogenetic-pharmacogenomic development from a single gene approach to incorporate pathway-based and genome-wide approaches has been benefitted from the emergence of several parallel technologies, such as genomics, transcriptomics, metabolomics, and proteomics which have contributed to and enhanced significantly propensities for generation and testing of pharmacogenomic hypotheses both paralleled and followed by associated developments in the clinical practice for treating Parkinson's disease (PD). The notion of "personalized medicine," incorporating the customization of healthcare, with decisions and practices that suited to each individual patient through application of genetic, biomarker, gene-environment interactive, or other information, involves principles through which drugs, drug combinations, and drug administration properties are optimized for each individual's unique genetic makeup. The personalized medication of antiparkinsonian drug therapy; the symptomatic and regional disruptions; genetic, epigenetic, and biomarkers of the disorder; and the pharmacogenomics of neuroleptic drug-induced parkinsonism provide outlets for eventual understanding and management. As a case study in personalized medicine in the laboratory, physical exercise combined with the electromagnetic wavelength treated *Saccharomyces cerevisiae* yeast, Milmed, was demonstrated to abolish the marked hypokinesia induced by the dopamine (DA) neurotoxin, MPTP, as well as the severe loss of DA in the striatal region of the C57/BL6 mice studied. The Exercise-Milmed coadministration induced also a profound increase in brain-derived neurotrophin levels (BDNF) in the mouse parietal cortex region that included the motor cortex.

T. Archer (✉)
Department of Psychology, University of Gothenburg, Box 500, Gothenburg 40530, Sweden
e-mail: Trevor.archer@psy.gu.se

A. Fredriksson
Department of Neuroscience Psychiatry, Uppsala University, Uppsala 751 85, Sweden

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1 Introduction

Pharmacogenomics is defined by the branch of pharmacology which deals with the influence of genetic variation on drug response in patients, in the present case parkinsonian, by correlating gene expression or single-nucleotide polymorphisms with a drug's efficacy or toxicity (Wang 2010). Weinshilboum and Wang (2006) have defined pharmacogenomics as the study of the role of inherited and acquired genetic variation in response to drug interventions. A major focus of pharmacogenomics is the development of suitable methods that facilitate the efficacy of drug therapy, in association with individuals' genotype, so that maximum efficacy is balanced against minimal adverse effects thereby the attainment of viable therapeutic windows (Becquemont 2009). Current attempts at attainment of bioinformatics, including genomics, proteomics, and metabolomics, should expedite identification of proteins/enzymes, activated proteins, genes, and gene variations facilitating drug therapies (Becquemont et al. 2011), e.g., those that contribute to the etiopathogenesis of Parkinson's disease (PD) and related therapeutic measures (Clayton 2012; Kaiser et al. 2003; Wang et al. 2011). Pharmacogenomics facilitates the identification of biomarkers, not only to facilitate derivation of "disorder staging" but also to allow optimal possibilities for therapeutic drug selection and targets, dose windows, drug dispositions, treatment duration, and projections of adverse reactions that may be avoidable (Evans and McLeod 2003; Weinshilboum 2003; Woodcock 2010). The technologies involved have led greater effectiveness in drug selection and administration accompanied by reductions in adverse/side effect profiles through investigations of neuroscientific, regulatory, and neuropsychological agents (Wang et al. 2000).

PD is a relatively common, idiopathic neurodegenerative movement disorder characterized by impaired motor function, including resting tremors, rigidity, akinesia/bradykinesia, and postural instability as the cardinal symptoms (Gaggelli et al. 2006; Jankovic 2008; Lees et al. 2009). It is a progressive neurodegenerative disorder and, compared with familial forms, is associated most often with advanced age (>55 years of age). The pathophysiology of PD involves dopaminergic neuron death and accumulation of Lewy bodies associated with mutations in α-synuclein, a 14-kDa protein predominantly expressed in the brain and CNS (Rasia et al. 2005). PD patients show decreased levels of presynaptic dopamine (DA) neuron terminal markers in the basal ganglia (Felicio et al. 2009), consistent with loss of dopaminergic terminals due to degeneration of neuronal cell bodies in the substantia nigra pars compacta (Hattori et al. 2006). PD patients exhibit decreased levels of DA transporters (DATs) and vesicular monoamine transporter type 2 (VMAT2), as well as reduced activity of dopa decarboxylase, assessed by striatal conversion of L-dopa to DA, according to PET and SPECT analyses (Al Hadithy et al. 2008; Lewitt et al. 2012). Wu et al. (2012) using MRI showed that the substantia nigra pars compacta expressed a decreased connectivity with several regions, including the striatum, globus pallidus, subthalamic nucleus, thalamus, supplementary motor area, dorsolateral prefrontal cortex, insula, default mode network, temporal lobe, cerebellum, and pons in patients compared to controls. They found that L-dopa administration partially normalized the pattern of connectivity to a similarity such as that expressed by the healthy volunteers involving causal connectivity of basal ganglia networks from the substantia nigra pars compacta. Postsynaptic D_2 DA receptors (D_2Rs) are either unaffected or increased in the striatum of untreated PD patients (Antonini et al. 1994). Oxidative injury appears to be one effect of α-synuclein (α-Syn) aggregates and could ultimately produce neuronal cell death. α-Syn, a 140 residue, intrinsically disordered protein is localized in presynaptic terminals of DA neurons (Yang et al. 2010). Autonomic nervous system involvement occurs at early stages in both PD and incidental Lewy body disease and affects the sympathetic, parasympathetic, and enteric nervous systems. It has been proposed that α-Syn pathology in PD has a distal to proximal progression along autonomic pathways.

According to Braakian notions, the enteric nervous systems are affected before the dorsal motor nucleus of the vagus, and distal axons of cardiac sympathetic nerves degenerate before there is loss of paravertebral sympathetic ganglion neurons. Cersosimo and Benarroch (2012a) have shown that consistent with neuropathological findings, some autonomic manifestations, such as constipation or impaired cardiac uptake of norepinephrine precursors, occur at early stages of the disease even before the onset of motor symptoms (cf. Braak et al. 2007; Cersosimo and Benarroch 2012b; Hawkes et al. 2007).

The evolution of pharmacogenetics-pharmacogenomics from a single gene approach to incorporate pathway-based and genome-wide approaches has been described comprehensively (Wang 2009; Wang and Weinshilboum 2008). Prolifically, several parallel technologies, such as genomics, transcriptomics, metabolomics, and proteomics, have contributed to and enhanced significantly propensities for generation and testing of pharmacogenomic hypotheses followed by associated developments in clinical practice (Lesko and Woodcock 2004; Wang and Weinshilboum 2006). The incorporation of transcriptomic and metabolomic findings has offered an important tactic for assessing and predicting variation in drug-response phenotypes and "translational" variants (Dettmer and Hammock 2004; Hughes et al. 2009; Lindon et al. 2004; Mendes 2006). Studies that focus upon pharmacogenomics involve the rapid scanning of markers across the genome of individuals affected by a certain disorder, e.g., PD, or drug-response phenotype, in comparison with unaffected individuals, with tests for association that compare genetic variations in case–control settings (Manolio 2010). Several oxidative phosphorylation (OXPHOS) system complex activities and quantities are reduced in PD. Toxicogenomics, combining toxicology with genomics, describes the collection, interpretation, and storage of information about gene and protein activity within particular cell or tissue of an organism in response to toxic substances in order to elucidate molecular mechanisms evolved in the expression of toxicity and to derive molecular expression patterns (i.e., molecular biomarkers) that predict toxicity or the genetic susceptibility to PD. OXPHOS functioning is affected by the mutations of PD-linked nuclear genes (Bar-Yaacov et al. 2012), and inactivation of other nuclear genes related to mitochondrial DNA replication and expression leads to PD (Pennington et al. 2010; Orth and Schapira 2001). Lopez-Gallardo et al. (2011) have described the extent to which nuclear and mitochondrial genetic and environmental factors, primary through gene-environment interplay, induce additive/synergistic effects thereby elevating the risk for PD. Population polymorphisms pertaining to mitochondrial DNA replication and expression that influence interactions with different xenobiotics, substances in an individual but which are not normally produced or expected to be there, may present susceptibility factors that contribute to the etiopathogenesis of the disorder.

The notion of "personalized medicine," a model that outlines the customization of healthcare, with decisions and practices that suited to each individual patient through application of genetic, biomarker, gene-environment interactive, or other information (Shastry 2005, 2006), refers in which drugs and drug combinations are optimized for each individual's unique genetic makeup (Squassina et al. 2010). A multitude of factors influence the emergence and progression of parkinsonism, motor symptoms, disability, outcome prognosis, and drug fluctuations, in addition to the clinically significant non-motor features such as depression, anxiety, sleep disturbances, smell and taste loss, compulsive behaviors, and dementia. Disorder staging diagnostic intervention optimizes early identification and accurate diagnosis and management of patients. Therapy of PD is an achievable goal considering the recent advances in neuroimaging, genetic testing, and other evolving diagnostic measures. Successful intervention is facilitated by proteomics, the comprehensive analysis and characterization of proteins and protein isoforms encoded by the human genome. Important biological functions, such as growth and development of the brain and CNS involving migration, differentiation and synaptogenesis, neuronal death, cellular movement, localization and integrity, and

stem cell differentiation, are controlled by signal transduction, an epigenetic process modulated by protein enzyme activity (Clayton et al. 2006). Seventeen regions of the genome are present with common variations that affect the risk of developing Parkinson's disease. Nine genes have been identified that, when mutated, may cause the disorder (Annesi et al. 2011; Cooper-Knock et al. 2012; Dumitriu et al. 2012; Kumar et al. 2012; Lachenmayer and Yue 2012; Maruyama and Naoi 2012). In PD, the range of personalized medicine, from physical exercise schedules (Archer et al. 2011a, b; Schenkman et al. 2012) to personalized deep brain stimulation (Wagle Shukla and Okun 2012) to identification of premotor populations (Streffer et al. 2012), continues to flourish.

2 Personalized Medication and Anti-PD Treatment

Anti-PD compounds, such as L-dopa and direct-acting DA agonists, show an efficacy dependent upon patient characteristics in reducing symptoms of movement disorder (Devos et al. 2009; van Hilten et al. 2000). The pharmacotherapy of PD has focussed upon dopaminergic compounds, largely the DA precursor, L-dopa (L-3,4-dihydroxyphenylalanine), which is very much the treatment of choice for the disorder (Fahn 1999). Orally administered L-dopa is absorbed by the intestine, enters the bloodstream, crosses the blood–brain barrier, and enters dopaminergic neurons in the brain where it is converted to DA through the action of the aromatic amino acid decarboxylase (AADC) enzyme. In general, it is administered in combination with a decarboxylase inhibitor to prevent conversion to DA peripherally. Large to very large fluctuations in the responses of individual patients to anti-PD drug medication have been observed (Fabbrini et al. 1988), not least due to the correlation between motor performance and plasma concentration of L-dopa (Jankovic and Stacy 2007; Pahwa and Lyons 2009). Similar extent of fluctuation has been described with regard to the development of motor complications, e.g., L-dopa-induced dyskinesia and side effects such as hallucinations and sleepiness, up to 45 % of users within 5 years (Graham et al. 1997). Additionally, the likelihood of ischemic complications presents another symptom for consideration (Arbouw et al. 2012). The notion of personalization medication emerges in the context of compounds designed to reduce fluctuations in PD: Lewitt et al. (2000) assessed the pharmacokinetic profile, efficacy, and safety of XP21279 administered with carbidopa (CD) in subjects with Parkinson's disease (PD) experiencing motor fluctuations and explore dose correspondence between CD-levodopa and XP21279 administered with carbidopa. They observed that XP21279 provided significantly less variability in LD concentration compared with carbidopa-levodopa in 10 PD patients presenting motor fluctuations, consistent with a lower peak-to-trough fluctuation for XP21279. The expressed patterns of percentage of patients' "OFF-periods" were consistent with the levodopa concentration-time profiles for each respective treatment. Compared with carbidopa-levodopa treatment, 6 of 10 study completers experienced reduction of 30 % or greater in average daily OFF time during the last 4 days in the XP21279 treatment period. XP21279 resulted in an increase in the time spent during "ON-periods" without functionally blocking dyskinesias, and the mean time to ON after the first morning XP21279 dose was not delayed, as compared with carbidopa-levodopa.

It is likely that genetic variations in gene coding for drug metabolism and drug availability contribute to a large extent towards the interindividual variability experienced in response to drugs of therapy (Swen et al. 2007), not least regarding the pharmacogenetics of anti-PD compounds (Arbouw et al. 2007). The genetic variability, together with gender and reproductive factors (Nicoletti et al. 2011), of each individual determines largely the interindividual variability in the responses to anti-PD drug therapy (Zappia et al. 2005). Although the findings emerging from several genetic association studies implying links between anti-PD drug-induced dyskinesias and polymorphisms are conflicting, several genes appear to be involved, including the *DRD2* gene, the *DRD4* gene, the DA transporter (*DAT*)

gene, the μ1-opioid receptor (*OPRM1*) gene, the cholecystokinin (*CCK*) gene, the apolipoprotein E (*APOE*) gene, the preprohypocretin (*HCRT*) gene, and the catechol-o-transferase (*COMT*) gene (Arbouw et al. 2009; Liu et al. 2009a, b; Paus et al. 2008; Williams-Gray et al. 2008). Lin et al. (2007) in a study of 251 PD patients observed that the frequency of the angiotensin I-converting enzyme gene homozygote ACE-II genotype with L-dopa-induced psychosis was significantly higher than that in PD patients without the adverse effect. Additionally, the possible role of brain-derived neurotrophic factor (BDNF) in L-dopa-induced dyskinesias has been considered since the factor is involved in synaptogenesis, synaptic plasticity and efficacy (Chase 2004; Woo et al. 2005), modulation of receptor systems underlying L-dopa-induced dyskinesias (Guillin et al. 2003), and the pathogenesis of dopaminergic neurotransmission in PD (Fumagalli et al. 2006; Momose et al. 2002). Foltynie et al. (2009) studied the influence of a common functional polymorphism of the BDNF gene on the risk for development of L-dopa-induced dyskinesias in a cohort of 315 PD patients, independently and variably treated with L-dopa and/or other DA interventions. PD patients with the met allele of BDNF, linked with lower activity-dependent secretion of BDNF, presented significantly higher risk of developing dyskinesia earlier in the course of dopaminergic agent therapy. Pharmacogenetic-pharmacogenomic studies facilitate the description and definition of genetic variations in gene coding and the regulation of the proteins involved in the pathways underlying dyskinesic expressions evolving from the pathophysiology of PD (Arbouw et al. 2010).

Genetic predispositions modulating factors causing anti-PD drug therapy fluctuations bedevil both treatment prognosis and outcome appraisals. In order to investigate more closely whether or not genetic predispositions may contribute to the pathophysiological development of medication-related complications in PD, Paus et al. (2009) reassessed the impact of the *DRD3* Ser9Gly polymorphism on development of motor complications in a large-scale association study based on the gene bank of the German Competence Network on Parkinson's disease, using stepwise regression analysis. Despite incorporating established clinical risk factors to avoid overlooking an effect of genotype, no effect of DRD3 Ser9Gly on chorea, dystonia, or motor fluctuation expressions in PD was observed. They confirmed that duration of PD was confirmed as the most important clinical risk factor, followed by age of disease onset and female gender. Furthermore, it was not possible to identify any effect of *DRD3* Ser9Gly on tremor in PD, even when regarding various symptom combinations to avoid missing a weak effect on the phenotype (Paus et al. 2010). AADC provides the major pathway for decarboxylation of L-dopa to DA. Thus, the relationship between subregional AADC activity in the striatum and the PD symptoms, using high-resolution PET with an AADC tracer, 6-[^{18}F]fluoro-L-m-tyrosine (FMT), has been assessed (Asari et al. 2011). They found that FMT uptake was decreased in the posterior putamen regardless of predominant motor symptoms and disease duration in all 101 patients and that severity of bradykinesia, rigidity, and axial symptoms was correlated with the decrease of FMT uptake in the putamen, especially in the anterior part. L-Dopa is metabolized to 3-O-methyldopa by catechol-O-methyltransferase (COMT) under conditions of AADC inhibition that involve L-dopa complications (Alachkar et al. 2010). COMT inhibitors, e.g., entacapone, increase the duration of motor responding by PD patients 30–40 %, decreasing the motor fluctuations, and effectively elevating the ON period (Kaakkola 2010; Rinne et al. 1998; Ruottinen and Rinne 1996a, b). The extent and definition of COMT polymorphisms, particularly the *COMT* gene (rs4608) resulting in Val157Met, and related DA and L-dopa metabolism and symptom profiles have been described (e.g., Kiyohara et al. 2011; Vallelunga et al. 2012; Wu et al. 2012). Corvol et al. (2011) determined the consequences of COMT polymorphisms upon 58 PD patients' responses to entacapone (200 mg) coadministered with L-dopa (50 mg), with regard to high (Val/Val, $COMT^{HH}$), intermediate (Val/Met, $COMT^{HL}$), and low (Met/Met, $COMT^{LL}$) COMT activity (Hernán et al. 2002). They observed that

the gain in the best ON-period time was higher in *COMT*^{HH} patients than in *COMT*^{LL} patients. Area under the concentration over time curve of L-dopa increased more after entacapone in *COMT*^{HH} patients than in *COMT*^{LL} patients, and COMT inhibition by entacapone was higher in *COMT*^{HH} patients than in *COMT*^{LL} patients. They concluded that the *COMT*^{HH} genotype enhanced the effect of entacapone on the pharmacodynamics and pharmacokinetics of L-dopa in PD patients.

It has been observed that the benefits of levodopa therapy become less marked over time, possibly due to the degeneration of nigrostriatal dopaminergic neurons inducing a progressive loss of AADC, the enzyme that converts levodopa into dopamine (Contin et al. 1994). Gene transfer of dopamine-synthesizing enzymes into the striatal neurons and/or neuroprotective interventions has led to behavioral recovery in animal models (Harms et al. 2011; Huo et al. 2012; Laganiere et al. 2010; Zhou et al. 2011). Muramatsu et al. (2010) have provided evidence for the safety and efficacy of AADC gene therapy in Phase I study of PD treatment. Using PET imaging with [(18)F]fluoro-L-m-tyrosine tracer was used for evaluation of AADC expression and the UPDRS; Mittermeyer et al. (2012) observed elevated PET signal in the first 12 months that persisted over 4 years in both dose (high and low) groups. The elevated PET value, compared with the presurgery baseline, was maintained over the 4-year monitoring period. The UPDRS off medication for 12 h improved in the first 12 months for all the patients, but deteriorated slowly in subsequent years. These studies implied that a therapy strategy involving manipulation of the AADC gene may prove a viable alternative. In a primate model of PD, intrastriatal infusion of an adeno-associated viral type 2 vector containing the human AADC gene (AAV-hAADC) results in robust response to low-dose levodopa without the side effects associated with higher doses. In a clinical trial, patients with moderately advanced PD received bilateral intraputaminal infusion of AAV-hAADC vector (Christine et al. 2009). Although gene therapy was well tolerated, 1 symptomatic and 2 asymptomatic intracranial hemorrhages followed the operative procedure. Total and motor rating scales improved in both cohorts. Motor diaries also showed increased on-time and reduced off-time without increased ON-period time dyskinesia. At 6 months, FMT PET showed a 30 % increase of putaminal uptake in the low-dose cohort and a 75 % increase in the high-dose cohort. It appears that bilateral intrastriatal infusion of adeno-associated viral type 2 vector containing the human AADC gene improves mean scores on the Unified Parkinson's Disease Rating Scale by approximately 30 % in the on and off states, but the surgical procedure may be associated with an increased risk of intracranial hemorrhage and self-limited headache.

3 Pharmacogenomics of Neuroleptic-Induced Parkinsonism

Neuroleptic-induced parkinsonism (NIP), secondary parkinsonism, presents a movement disorder occurring in 15–40 % of patients treated with antipsychotic medication, with accompanying adverse effects on drug compliance, self-esteem, and quality of life (Gerlach 1999; Hirose 2006). It tends to develop slowly, over days to weeks, expressing high levels of variability in individual sensitivity/susceptibility to all the extrapyramidal side effects as a function of the pharmacological and pharmacodynamic profiles of the compounds applied (Friedman 2006, 2010; Thomas and Friedman 2010). Several risk factors affect the predisposition to development of NIP, including advanced age, gender (female), type of neuroleptic drug, age at diagnosis, and dose levels of drugs applied (Caligiuri et al. 1999, 2000; Jabs et al. 2003). Nevertheless, the high levels of variation in incidence have prompted attempts to identify genetic predisposition (e.g., Lencer et al. 2004). Using logistic regression and controlling for population stratification, age, gender, Simpson-Angus scale score at baseline, and concomitant use of anticholinergic drugs, Alkelai et al. (2009) identified several single-nucleotide polymorphisms associated with NIP severity.

They identified a number of candidate genes that were likely to contribute to the pathophysiology of the syndrome.

Pharmacogenetic studies have generalized the several expressions of NIP, i.e., tardive dyskinesias, akathisia, and dystonia, into a single clinical syndrome (Gunes et al. 2007; Guzey et al. 2007; Nakazono et al. 2005). The etiopathogenesis could involve the antagonistic actions of neuroleptic compound upon dopamine DA D2 receptor gene, the DRD2 gene (Lidow 2000; Reynolds 2004; Mihara et al. 2000). However, Chong et al. (2003) failed to obtain evidence that the D2 genotype was involved in the pathophysiology of tardive dyskinesias in Chinese patients with schizophrenia. Instead, they pointed out that the association of tardive dyskinesias with the serine/serine genotype of the DRD3 may be an epiphenomenon of patients with a subtype of schizophrenic patients with greater exposure to neuroleptic drugs (see also Lee et al. 2008, 2010; Tan et al. 2003). Additionally, the modulating effects of the serotonin 2A and 2C receptor genes, HTR2A and HTR2C, respectively, have been considered (Hamdani et al. 2005; Lerer et al. 2005). Grønbaek et al. (2008) studied the association between polymorphisms for DRD3, HTR2A, and HTR2C and NIP, rigidity, bradykinesia, and rest tremor in 117 African-Caribbean inpatients at the D.R. Capriles clinic (Curacao, Netherlands Antilles). Inclusion criteria were (1) absence of organic and neurological disorders that could cause movement disorders, (2) a history of neuroleptic use over at least 3 months, and (3) informed consent. Determination of polymorphisms was performed according to standard protocols, the Unified Parkinson's Disease Rating Scale (UPDRS) for assessment of NIP, rigidity, bradykinesia, and rest tremor. In the male patients, significant associations between DRD2 (the *-141CDel*-allele carriership) and rigidity, and HTR2C (*23Ser*-allele carriership) and bradykinesia, were obtained. Their overall conclusions pertained to symptom-specific pharmacogenomic, personalized medicine analyses (see also Bakker et al. 2006).

4 Milmed-Exercise Combination as Personalized Intervention in PD

Physical exercise has been described as any and all activity that generates force through muscular activity that disrupts a homeostatic state (McArdle et al. 1974; Scheuer and Tipton 1977). Although daily physical activity holds benefits for general measures of function, quality of life, and physical strength, as well as increasing endurance (Dechamps et al. 2010; Marks et al. 2009, 2010), much evidence presents the manifest advantages for cerebral integrity during aging (Kramer et al. 1999; Lustig et al. 2009; Marks et al. 2011). Any bodily activity that enhances or maintains physical fitness implies the involvement of regular and frequent exercise. Morris and Schoo (2004) have defined exercise as a planned, structured physical activity with the purpose of improving one or more aspects of physical fitness and functional capacity. Physical exercise offers a nonpharmacologic, noninvasive intervention that enhances brain health and plasticity (Cotman and Berchtold 2002). It has been characterized on the basis of type, intensity, frequency, and duration, with either endurance or resistance as the training end point (Mougios 2010). Long-term exercise benefits brain functioning by increasing cerebral blood flow and oxygenation (Linkis et al. 1995), mobilizing growth factors and synaptic plasticity (Hunsberger et al. 2007), and facilitating performance through neurotransmitter release (Morishima et al. 2006; Waters et al. 2008). Regular physical exercise holds particular benefits for older individuals, whether under conditions of normal aging or affected by neurodegenerative disorders (Archer 2011; Archer et al. 2011a, b).

Repeated administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to C57/BL6 mice induces selective and long-lasting lesions of dopamine (DA) in nigrostriatal regions of the brain (Jackson-Lewis et al. 1995; Jones-Humble et al. 1994). The susceptibility of mice to the neurotoxic actions of MPTP can be quite

variable, depending on gender and strain differences, expressed in functional, neurochemical, and histochemical analyses (Schwarting et al. 1999; Sedelis et al. 2000a, b, 2001, 2003). C57/BL6 and Swiss Webster strains were shown to differ in c-Jun N-terminal kinases (JNKs) and c-JUN activation in response to MPTP. JNKs, of the mitogen-activated protein kinase family, are responsive to stress stimuli, such as cytokines, ultraviolet irradiation, heat shock, and osmotic shock; c-Jun is the name of a gene and protein that, in combination with c-Fos, forms the AP-1 early response transcription factor. MPTP induced COX-2, an enzyme responsible for inflammation and pain, responding exclusively in C57/BL6 mice (Boyd et al. 2007). MPTP, administered systemically, induces parkinsonism in human and nonhuman primates (Langston 1985) that results in the loss of *substantia nigra* cells in the *pars compacta* of adult animals (Chiueh et al. 1985). It destroys selectively nigrostriatal neurons thereby inducing acute, subacute, long-lasting, and even permanent effects that resemble certain features of PD, particularly the hypokinesic effects (Schultz et al. 1989). Systemic administration of MPTP (2×40 mg/kg, s.c.) caused L-dopa reversible hypoactivity (Fredriksson et al. 1990; Sundström et al. 1990). A less rigorous dose regime, e.g., 2×20 or 25 or 30 mg/kg, of MPTP has been found not to reduce motility in the C57 black mice, although DA brain concentrations may indicate up to 50–80 % reductions (Heikkila et al. 1989; Sonsalla and Heikkila 1986), unless given much more repeatedly (cf. Kurz et al. 2007). The parameters of MPTP treatment neurotoxicity in mice are extremely long-lasting (up to and beyond 52 weeks after treatment) with strong correlations between the functional deficits, particularly hypokinesia, the main biomarker, severe DA depletions, and a dose- and time-dependent recovery of several parameters of motor behavior following treatment with the DA precursor, L-dopa (Archer and Fredriksson 2003; Fredriksson and Archer 1994; Fredriksson et al. 1999).

In the unilateral 6-hydroxydopamine rat model of Parkinson's disease (PD), Tillerson et al. (2001) abolished the lesion-induced motor asymmetry by forcing the rats to use affected (contralateral) limb, whereas forced nonuse exacerbated the injury (Tillerson et al. 2002). Both dopamine (DA) and 3,4-dihydroxyphenylacetic acid (Dopac) were elevated markedly in "casted" 6-OHDA-treated rats (forced to use the contralateral limb) compared with "non-casted" rats (Cohen et al. 2003). Archer and Fredriksson (2010) found that daily running-wheel activity attenuated the hypokinesic effects of MPTP in both a concentrated (2×40 mg/kg, 24-h interval) and progressive (1×40 mg/kg, weekly doses over 4 weeks) schedule with regard to spontaneous motor behavior and activity following a subthreshold dose of L-dopa. The loss of DA in each case was attenuated by exercise also (Experiment I, 61 % of control rather than 17 %; Experiment II, 24 % rather than 11 %). Using the progressive schedule of MPTP treatment and extending the exercise intervention from 7 to 14 weeks, it was shown that spontaneous motor activity after MPTP was close to restoration, whereas activity after subthreshold L-dopa was completely recovered (Fredriksson et al. 2011); DA levels were restored from 17 % (non-exercised) to 64 % in the 14-week exercise intervention, and levels of brain-derived neurotrophic factor were increased significantly. It was shown also that both the functional and DA deficits by MPTP were attenuated even by delayed introduction of exercise (Archer and Fredriksson 2012).

Brain-derived neurotrophic factor (BDNF) is a neurotrophin with widespread expression in the brain and is connected intimately with brain metabolism and homeostasis (Chaldakov 2011). It is associated with neurogenesis, neuronal survival, and neuroreparation in the brain and CNS (Cui 2006; Numakawa et al. 2010). Treatment interventions that enhance BDNF-related signaling have the potential to restore neural connectivity (Kaplan et al. 2010). Physical exercise induces improvements in motor ability and enhances BDNF expression (Macias et al. 2009). It is linked to elevated BDNF levels in the hippocampus (Neeper et al. 1996; Oliff et al. 1998). Voluntary running, as physical activity, amplifies the BDNF signal that augments neurogenesis through diverse molecular pathways (Stranahan

et al. 2009). BDNF mediates several essential morphological changes at neuronal levels that include dendritic arborization (Imamura and Greer 2009; Zhou et al. 2008), axonal and dendritic remodeling (Jeanneteau et al. 2010; Menna et al. 2003), synaptogenesis (Liu et al. 2009b; Tchantchou et al. 2009), and synaptic efficacy (Boulanger and Poo 1999; Sallert et al. 2009). Faherty et al. (2005) have shown that a combination of exercise, social interactions and learning, or exercise alone during adulthood gave total protection against MPTP-induced parkinsonism. They found also that changes in mRNA expression suggested that increases in glial-derived neurotrophic factors, coupled with a decrease of dopamine-related transporters (e.g., dopamine transporter, DAT; vesicular monoamine transporter, VMAT2), contributed to the observed neuroprotection of dopamine neurons in the nigrostriatal system following MPTP exposure. Tajiri et al. (2010) observed that exercise induced behavioral recovery in an animal model of PD and caused increased BDNF and glial-derived neurotrophic factor (GDNF) in the striatum of 6-OHDA-treated rats.

The production of Milmed is a patent-protected treatment of yeast cultures, but for any synergistic antiparkinson effect, a regime of physical exercise must be incorporated: the basis of "personalized medicine" builds upon this particular combination, whereas the pharmacogenetic aspect involves the selective susceptibility of the C57/Bl6 mouse strain for the DA neurotoxin, MPTP. The yeast cultures, *Saccharomyces cerevisiae* or *Saccharomyces carlsbergensis*, have been utilized as industrially important cell factories (Nielsen and Jewett 2008), with many regulatory pathways conserved between these yeasts and humans (Zhang et al. 2010). Cell death studies using yeast apoptosis increasingly provide a model for analyzing the cascade of molecular events that contribute to neurodegenerative disorders (Carmona-Gutierrez et al. 2010; Petranovic et al. 2010). Several features of PD have been reproduced in yeast with cell death promotion in a concentration-dependent manner (Outeiro and Lindquist 2003) with possibilities for facilitating the development of both therapeutic targets and compounds (Braun et al. 2009; Teneiro and Outeiro 2010). This experiment illustrates, for the purposes of this review, that the treatment of yeast cell cultures themselves provides an agent that provides an antiparkinson effect. The treatment and preparation of *Saccharomyces cerevisiae* or *Saccharomyces carlsbergensis* with electromagnetic waves in the extreme high frequency (EHF) range of 30–300 GHz produces a treated yeast extract, given the name Milmed (i.e., Milmed®). This treatment was developed through the pioneering work of MB Golant (Golant 1994; Golant et al. 1994; Ragimov et al. 1991) upon the genesis and reparation of cells. The coadministration of Milmed with daily physical exercise has been reported to induce plasticity in attenuating MPTP-induced motor deficits (Oscarson et al. 2009).

This following experiment illustrates that, as an example of "personalized medicine," physical exercise in a running wheel combined with administration of the treated Milmed (yeast extract) under conditions where the extract was charged or uncharged would ameliorate the functional and DA deficits induced by MPTP under Milmed regimes. Additionally, BDNF levels in the parietal cortex (including the motor cortex) were assayed in order to assess the effects of MPTP, MPTP + Exercise, and MPTP + Exercise combined with charged or uncharged Milmed ("yeast extract"). Here, the notion of "personalized medicine" derives from the particular combination of physical exercise regime with twice weekly doses of Milmed. In the case of the mice studied here, daily 30-min bouts of running-wheel activity constituted the exercise regime.

4.1 Description of Exercise-Milmed Intervention

4.1.1 Animals

Male C57 Bl/6 mice were purchased from B&K, Sollentuna, Sweden, and were maintained, five to a cage, in plastic cages in a room at temperature of 22 ± 1 °C and a 12/12 h constant light/dark cycle (lights on between 06.00 and 18.00 h). They were placed and maintained in groups of

four to six animals in a room maintained for male mice only following arrival at the laboratory for about 2 weeks in order to acclimatize. Free access to food and water was maintained throughout, except for the day previous to the initiation to wheel-running exercise which occurred at the end of the second week following arrival. They were housed in groups of six animals, wheel-running exercised and activity chamber tested only during the hours of light (08.00–15.00 h). All exercising and testing was performed in a normally lighted room. Half of the mice in each treatment condition (MPTP-Exer, MPTP-Exer-Milmed, and Vehicle) were given wheel-running exercise, whereas the other half were placed in a clean laboratory cage for the same period in a room in which the running wheels were placed. Motor activity was tested in a specially arranged test room. This test room, in which all 12 ADEA activity test chambers, each identical to the home cage, were placed, was well secluded and used only for this purpose. Each test chamber (i.e., motor activity test cage) was placed in a soundproofed wooden box with 12-cm-thick walls and front panels and a small double-glass window to allow observation; each box had a dimmed lighting.

Three weeks following arrival, four groups ($n = 10$) of DSP4-treated and two groups of vehicle-treated mice were administered with either MPTP (2×40 mg/kg, s.c., 24 h between injections) or vehicle (0.9 % physiological saline injected s.c. in a volume of 2 ml/kg body weight). Milmed (see below for details of preparation) or vehicle was administered twice weekly.

Experiments were carried out in accordance with the European Communities Council Directive of 24 November 1986 (86/609/EEC) after approval from the local ethical committee (Uppsala University and Agricultural Research Council) and by the Swedish Committee for Ethical Experiments on Laboratory Animals (license S93/92 and S77/94, Stockholm, Sweden).

4.1.2 Drugs

MPTP (Research Biomedical Inc., MA, USA, 2×20 mg/kg or 2×40 mg/kg, s.c., with a 24-h interval between injections in each case) was dissolved in saline and administered s.c. in a volume of 2 ml/kg body weight. Milmed was obtained through treatment and preparation of Saccharomyces cerevisiae with electromagnetic waves in the extreme high frequency (EHF) range of 30–300 GHz to produce the treated yeast extract (cf. Golant 1994). Saline was used as vehicle in each case.

4.1.3 Behavioral Measurements and Apparatus

Activity test chambers. An automated device, consisting of macrolon rodent test cages (40×25×15 cm) each placed within two series of infrared beams (at two different heights, one low and one high, 2 and 8 cm, respectively, above the surface of the sawdust, 1 cm deep), was used to measure spontaneous motor activity (RAT-O-MATIC, ADEA Elektronic AB, Uppsala, Sweden). The distances between the infrared beams were as follows: the low-level beams were 73 mm apart lengthwise and 58 mm apart breadthwise in relation to the test chamber; the high-level beams, placed only along each long side of the test chamber, were 28 mm apart. According to the procedures described previously (Archer et al. 1986), the following parameters were measured: *locomotion* was measured by the low grid of infrared beams. Counts were registered only when the mouse in the horizontal plane is ambulating around the test cage. *Rearing* was registered throughout the time when at least one high-level beam was interrupted, i.e., the number of counts registered was proportional to the amount of time spent rearing. *Total activity* was measured by a sensor (a pickup similar to a gramophone needle, mounted on a lever with a counterweight) with which the test cage was constantly in contact. The sensor registered all types of vibration received from the test cage, such as those produced both by locomotion and rearing as well as shaking, tremors, scratching, and grooming. All three behavioral parameters were measured over three consecutive 20-min periods. The motor activity test room, in which all 12 ADEA activity test chambers, each identical to the home cage, were placed, was well secluded and used only for

Table 14.1 Chronological and experimental design for MPTP treatment, exercise schedule, and Milmed (charged/uncharged) administration over the 14-week experiment

Time and test	Day	Vehicle	MPTP	MPTP + Exer	MPTP + Exer + Milm(1)	MPTP + Exer + Milm(0)
	Monday	Cage	Cage	Exer	Exer	Exer
	Tuesday	Cage	Cage	Exer	Exer	Exer
Weeks 1–4	Wednesday	Cage	Cage	Exer	Exer	Exer
	Thursday	Cage	Cage	Exer	Exer	Exer
Tests 1–4[a]	Friday	Test + sal	Test + MPTP[b]	Test + MPTP[b]	Test + MPTP[b]	Test + MPTP[b]
	Monday	Cage	Cage	Exer	Exer	Exer
	Tuesday	Cage	Cage	Exer	Exer	Exer
Weeks 5–8	Wednesday	Cage	Cage	Exer	Exer	Exer
	Thursday	Cage	Cage	Exer	Exer	Exer
Tests 5–8[a]	Friday	Test + sal	Test	Test	Test	Test
	Monday	Cage	Cage	Exer	Exer	Exer
	Tuesday	Cage	Cage	Exer	Exer	Exer
Weeks 9–14	Wednesday	Cage	Cage	Exer	Exer	Exer
	Thursday	Cage	Cage	Exer	Exer	Exer
Tests 9–14[a]	Friday[c]	Test + sal	Test	Test	Test	Test

[a]Spontaneous activity over 60 min
[b]MPTP (40 mg/kg) injected during the first 4 weeks
[c]L-dopa (5 mg/kg, s.c.) tests after 60-min habituation to test cages 6, 8, 10, 12, and 14 weeks

this purpose. Each test chamber (i.e., activity cage) was placed in a soundproofed wooden box with 12-cm-thick walls and front panels and day lighting. Motor activity parameters were tested on one occasion only, over three consecutive 20-min periods, at the age of 3–4 months. Groups of mice were treated with MPTP and then given access to running wheels (30 min/day, 4 times/week), with or without concomitant treatment with Milmed ([Milm(1)-charged] or [Milm(0)]-uncharged = yeast itself), as displayed in Table 14.1.

4.1.4 Neurochemical Analysis

Mice were killed by cervical dislocation within 2 weeks of completion of behavioral testing. Determination of DA was performed using a high-performance liquid chromatograph with electrochemical detection (HPLC-EC), according to Björk et al. (1991), as modified by Ye Liu et al. (1995). Striatal regions were rapidly dissected out and stored at −80(C until neurochemical analysis. DA concentration was measured as follows: the frozen tissue samples were weighed and homogenized in 1 ml of 0.1 M perchloric acid, and alpha-methyl-5-hydroxytryptophan was added as an internal standard. After centrifugation (12,000 rpm, i.e., 18,600 g, 4 °C, 10 min) and filtration, 20 µl of the supernatant was injected into the HPLC-EC to assay DA. The HPLC system consisted of a PM-48 pump (Bioanalytical Systems, BAS) with a CMA/240 autoinjector (injection volume, 20 µl), a precolumn (15 × 3.2 mm, RP-18 Newguard, 7 µm), a column (100 × 4.6 mm, SPHERI-5, RP-18, 5 µm), and an amperometric detector (LC-4B, BAS, equipped with a Ag/AgCl reference electrode and a MF-2000 cell) operating at a potential of +0.85 V. The mobile phase, pH 2.69, consisted of K_2HPO_4 and citric acid buffer (pH 2.5), 10 % methanol, sodium octyl sulfate, 40 mg/l, and EDTA. The flow rate was 1 ml/min, and the temperature of the mobile phase was 35 °C.

4.1.5 BDNF Analysis

The methods and procedures described by Viberg et al. (2008) were maintained. Frontal cortex, parietal cortex, and hippocampus tissues from the mice in each group were sonicated in 20 volumes (w/v) of ice-cold lysis buffer (137 mM

NaCl; 20 mM Tris–HCl, pH 8.0; 1 mM phenylmethyl-sulfonyl fluoride; 10 lg/ml aprotinin; 1 lg/ml leupeptin). The homogenate was centrifuged for 20 min at 200,009 g at 4 °C, and the supernatant was acidified (pH 3) with HCl and neutralized back to pH 7.6 with NaOH. The Promega Emax TM ImmunoAssay System was used to determine the amount of BDNF in the samples according to the technical bulletin supplied by the distributor. Briefly, BDNF from each sample was captured with a monoclonal antibody (mAb) against BDNF; captured BDNF was then bound to a second specific polyclonal antibody (pAb) against BDNF. After washing, the amounts of specifically bound pAb were detected by using a specific anti-IgY antibody conjugated to horseradish peroxidase (HRP) as a tertiary reactant. Unbound conjugate was removed through washing, and after an incubation period with a chromogenic substrate, the color change was measured in a microplate reader at 450 nm. The amount of BDNF was proportional to the color change generated and compared with a standard curve. The cross-reactivity to other neurotrophic factors was less than 3 %, and the purity of the anti-BDNF antibodies was greater than 95 %.

4.2 Effects of Exercise-Milmed on MPTP-Induced Deficits

4.2.1 Spontaneous Motor Activity

Mice treated with MPTP showed a marked hypokinesic effect over all 14 Test days from Test day 2 onwards. Access to physical exercise (running wheel) retarded the onset of MPTP-induced hypokinesia until Test day 5 and then attenuated the hypokinesia throughout. Uncharged Milmed (Milm(0)) in combination with physical exercise also retarded and attenuated the hypokinesia induced by MPTP. Charged Milmed (Milm(1)) in combination with physical exercise abolished any sign of hypokinesia throughout. Split-plot ANOVA indicated a Treatment × Days interaction: ($F(52, 629) = 16.08$, $p < 0.0001$). Pairwise testing with Tukey's HSD indicated the following differences over all three motor activity parameters, locomotion, rearing, and total activity:

Vehicle, MPTP + Exer + Milm(1) > MPTP + Exer + Milm(0), MPTP + Exer > MPTP during Test days 2–14 (Fig. 14.1).

4.2.2 L-Dopa-Induced Activity

Mice treated with MPTP showed a marked hypokinesic effect over all five L-dopa-induced tests (Test days 6, 8, 10, 12, and 14). Both physical exercise, by itself, or combined with uncharged Milmed attenuated the loss of L-dopa-induced activity over Test days 6, 8, 10, and 12, but abolished this loss on Test day 14. Physical exercise combined with charged Milmed abolished MPTP-induced L-dopa activity deficits throughout. Split-plot ANOVA indicated a Treatment × Days interaction: $F(16, 224) = 9.65$, $p < 0.0001$. Pairwise testing with Tukey's HSD indicated the following differences over all three motor activity parameters, locomotion, rearing, and total activity:

Vehicle, MPTP + Exer + Milm(1) > MPTP + Exer + Milm(0), MPTP + Exer > MPTP during Test days 2–14 (Fig. 14.2).

4.2.3 Neurochemical Analysis

Mice treated with MPTP showed a marked loss of DA in the striatum (17 % of control values). This effect was attenuated strongly by physical exercise by itself (MPTP + Exercise = 64 % of control values) or combined with uncharged Milmed (MPTP + Exercise + Milmed[yeast](0) = 65 % of control values). The combination of physical exercise with charged Milmed (MPTP + Exercise + Milmed[yeast](1)) abolished completely any loss of DA (101 % of control values). One-way ANOVA indicated a significant group effect: $F(4, 30) = 47.27$, $p < 0.0001$. Tukey testing indicated the following differences:

MPTP + Exercise + Milmed[yeast](1), Vehicle > MPTP + Exercise + Milmed[yeast](0), MPTP + Exercise > MPTP (Fig. 14.3).

4.2.4 BDNF Analysis

Mice treated with MPTP showed a marked elevation of BDNF in the parietal cortex (including motor cortex) of the MPTP group (431 % compared with control values) compared with the

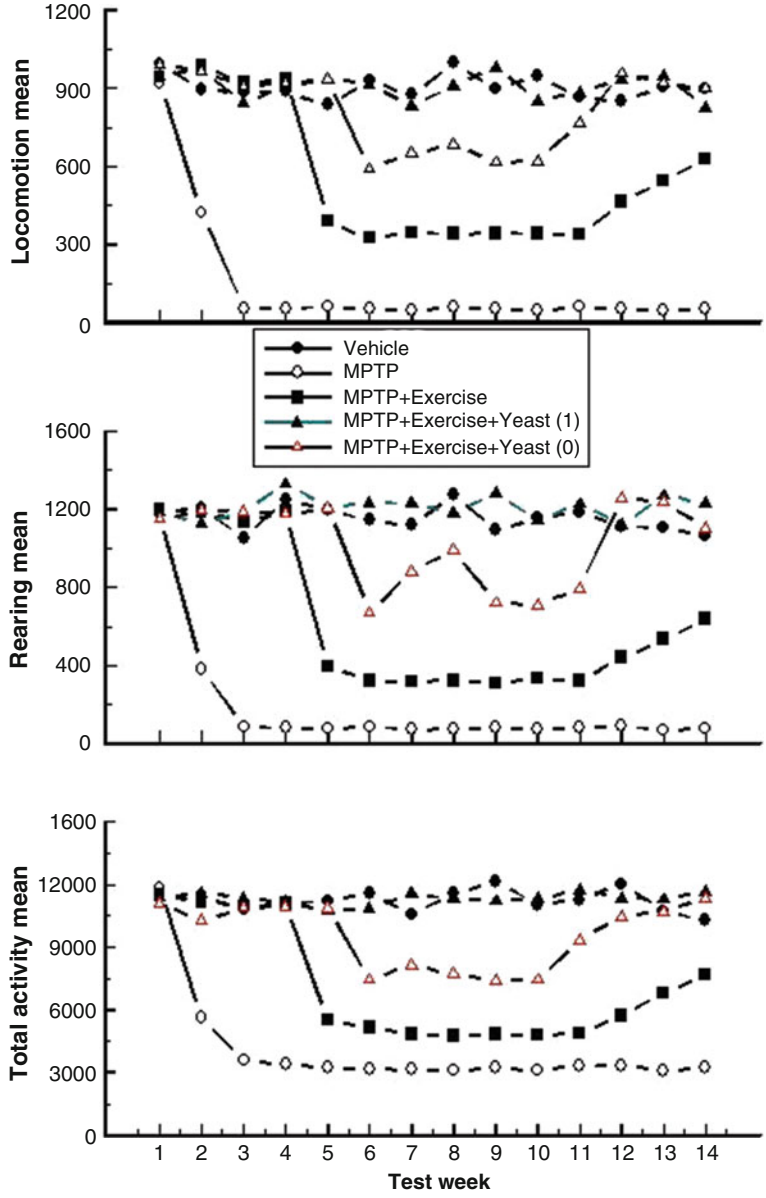

Fig. 14.1 Mean locomotion, rearing, and total activity during the spontaneous motor activity by Vehicle, MPTP, MPTP + Exercise, MPTP + Exercise + Milmed [yeast](1), and MPTP + Exercise + Milmed [yeast](0) over Test days 1–14

vehicle group. This elevation of BDNF was increased by both physical activity itself (528 % of control values) and in combination with uncharged Milmed (MPTP + Exercise + Milmed [yeast](0) = 534 % of control values). BDNF elevation was greatest in the case of the charged Milmed (MPTP + Exercise + Milmed[yeast](1)) group (853 % of controls). One-way ANOVA indicated a significant group effect: $F(4, 30) = 18.27$, $p < 0.0001$. Tukey testing indicated the following differences:

MPTP + Exercise + Milmed[yeast](1) > MPTP + Exercise + Milmed[yeast](0), MPTP + Exercise > MPTP > Vehicle (Fig. 14.4).

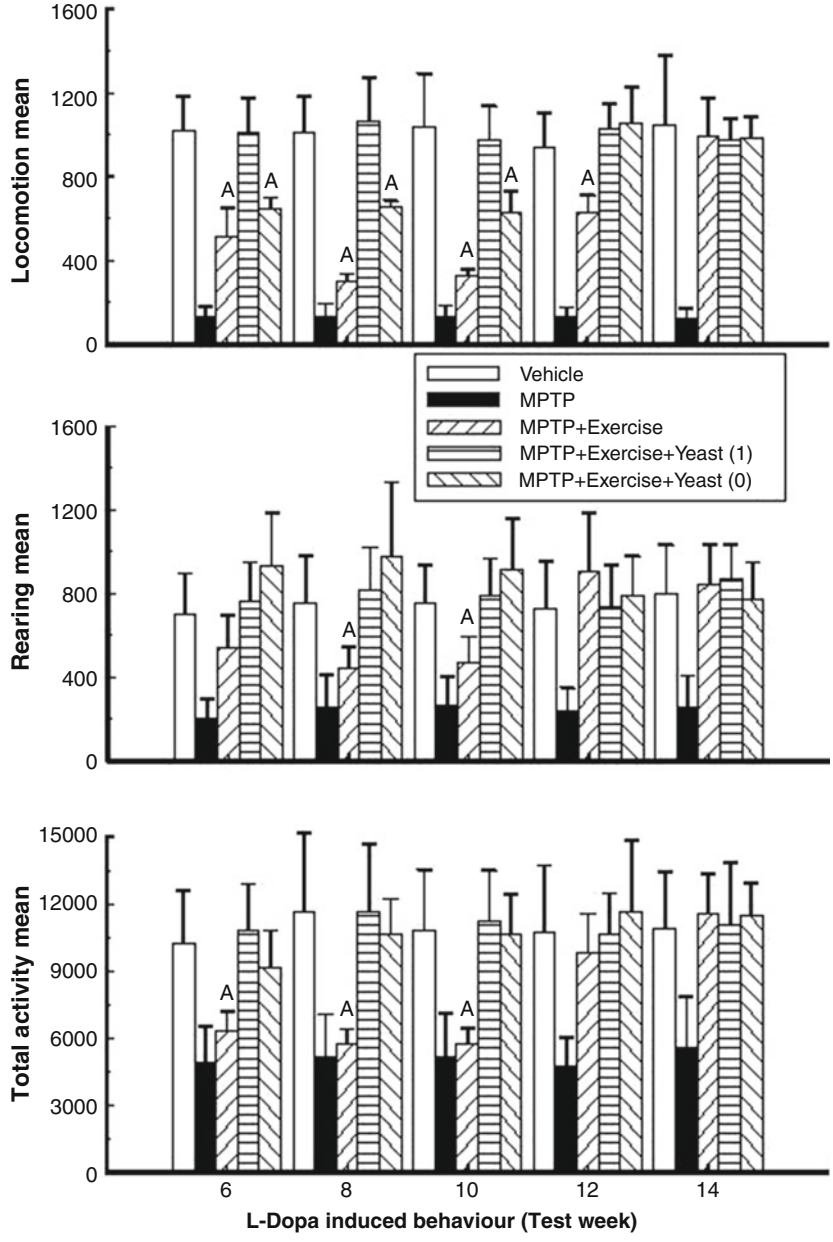

Fig. 14.2 Mean locomotion, rearing, and total activity during the L-dopa-induced motor activity by Vehicle, MPTP,MPTP + Exercise,MPTP + Exercise + Milmed[yeast] (1), and MPTP + Exercise + Milmed[yeast](0) groups on Tests 1–5 over Test days 6, 8, 10, 12–14

4.3 Milmed-Exercise Synergism Abolishes MPTP-Induced Deficits

Physical exercise alleviates both the symptoms and the biomarkers (e.g., DA loss) of PD in the laboratory and in the clinical setting (Archer and Fredriksson 2010, 2012; Archer et al. 2011a, b; Fredriksson et al. 2011). The combination physical exercise and Milmed abolished MPTP-induced parkinsonism in the laboratory both functionally and neurochemically such that the antiparkinsonian effects were in excess of the summation of exercise and Milmed effects by

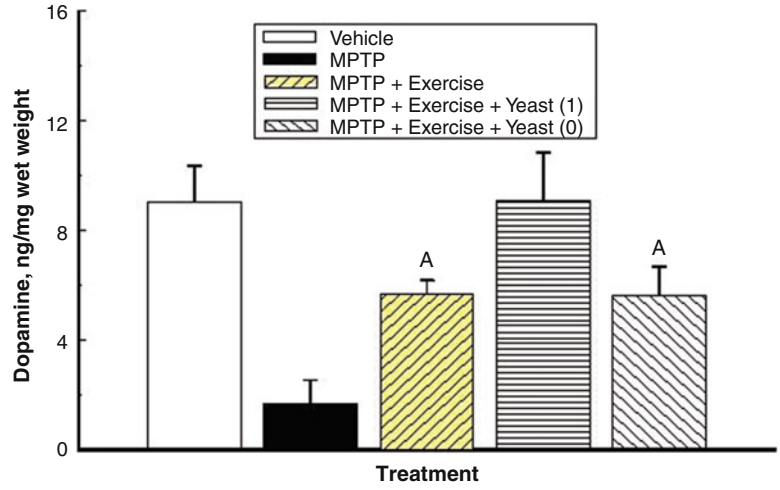

Fig. 14.3 Mean striatal dopamine concentrations in the Vehicle, MPTP, MPTP + Exercise, MPTP + Exercise + Milmed[yeast](1), and MPTP + Exercise + Milmed[yeast](0) groups

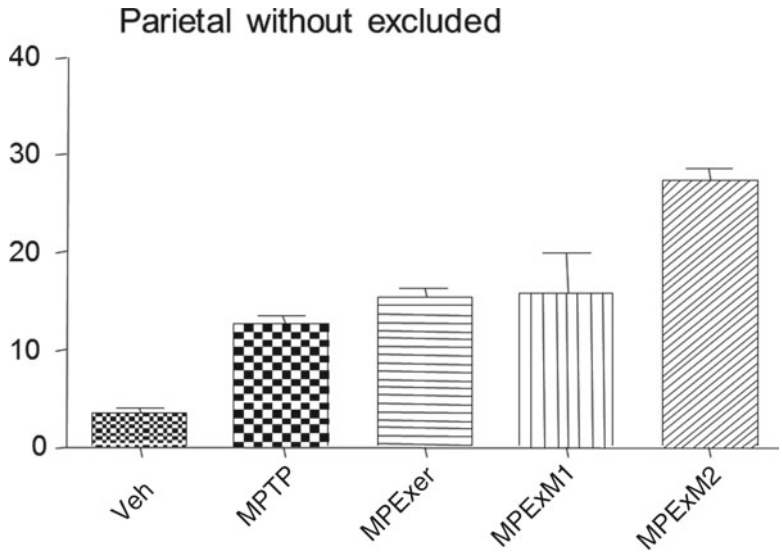

Fig. 14.4 Mean parietal cortex (including motor cortex) BDNF concentrations in the Vehicle, MPTP, MPTP + Exercise, MPTP + Exercise + Milmed[yeast](1), and MPTP + Exercise + Milmed[yeast](0) groups

themselves; in the absence of exercise, Milmed does not affect MPTP-induced hypokinesia or DA loss at all (Archer and Fredriksson, unpublished results). The notion that exercise-induced elevations in BDNF may be of significance for the treatment of aging disorders is not novel, since memantine, a medium-affinity uncompetitive *N*-methyl-D-aspartate receptor antagonist applied clinically as a neuroprotective agent to treat AD and PDs, increased BDNF mRNA levels markedly in the limbic cortex at clinically relevant doses (Marvanová et al. 2001). The present findings that (a) MPTP treatment induced a marked increase in parietal BDNF and (b) exercise over 14 weeks further increased levels of BDNF in the parietal cortex appear to lend credence for the involvement of BDNF in the exercise-induced recovery of function and DA

innervation following repeated doses of MPTP. The lack of exercise-induced changes in hippocampal BDNF suggests that the level of running-wheel exercise per day and week under present conditions was insufficient. It appears that parietal cortex BDNF may exert an important mediatory role, hitherto unobserved, upon functional and biomarker recovery in experimental parkinsonism. The manifest benefits of physical exercise on neurodegenerative states are dependent on a variety of parameters that determine prognosis, intervention, and outcome, not least pertaining to the particular disorder under consideration (Archer 2011; Archer et al. 2011a, b).

5 Conclusions

Clinicogenetic trials have demonstrated that therapeutic drug efficacy or toxicity or susceptibility for adverse effects presents disorder-intervention features increasingly found to be governed by genetic and epigenetic principles (Kalinderi et al. 2011). In a large multicentered study to ascertain the frequency and pathogenicity of reported VPS35 variants worldwide, Sharma et al. (2012) sought to identify a mutation (p.Asp620Asn) in the vacuolar protein sorting 35 (VPS35) gene as possible cause for autosomal dominant form of PD. The identified pathogenic variant p. Asp620Asn was identified in 8 cases and 1 control from Italy, US, Poland, and Australia; three sites (Poland, Ireland, and US) detected p.Leu774Met variant in 6 cases and 4 controls; and one site (Norway) detects p.Gly1Ser variant in 3 cases and 1 control with two reported variants (p.Arg524Trp and p.Ile241Met) monomorphic. The overall analysis described an increased risk for PD for p.Asp620Asn and p.Leu774Met variants, respectively, in their cohort, thereby highlighting the role of rare variants in the complex PD condition. Current levels of information pertaining to notions of pharmacogenomics, epigenetics, and biomarkers that are modulated by interindividual variability affect the diagnosis, intervention, and prognosis of both PD disorder expression and therapeutic strategies. Symptom profiles and course of disease, etiopathological heterogeneity, and etiopathogenesis may be elucidated through recourse to a dimensional approach to pathophysiology through the distinguished endophenotypes and biomarkers of disorder progression (Archer et al. 2010). Much increasing evidence suggests that epigenetic mechanisms, such as DNA methylation, histone modifications, and small RNA-mediated mechanisms, may regulate the expression of PD-related genes (Coppedè 2012). Finally, the coadministration of exercise regimes with agents (like Milmed) offering potential neuroreparative/neurogenesis agency may present useful ingredients for personalized medicine.

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