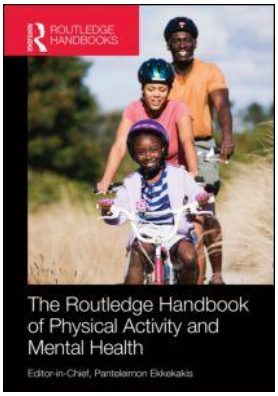

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THE NEUROBIOLOGY OF DEPRESSION AND PHYSICAL EXERCISE

Michael J. Chen

Chronic severe stress often culminates in major depression. Whereas stress/depression atrophies neurons and dendrites, enjoyable physical exercise restores them. Exercise, therefore, is conducive to neuronal survival and is considered antidepressant. Herein, I start with discussing neurotransmitters and gradually progress to how depression and exercise are involved in systemic diseases, such as metabolic disorders.

The monoamine hypothesis of depression and the neurotrophin hypothesis of depression

The earliest putative biological underpinnings regarding the etiology of depression were in a deficiency of monoaminergic neural transmission, historically giving rise to the monoamine hypothesis of depression (Chopra, Kumar, & Kuhad, 2011; Duman, Heninger, & Nestler, 1997; Krishnan & Nestler, 2008; Russo-Neustadt & Chen, 2005). With less norepinephrine and/or serotonin (5HT) to bind their respective postsynaptic receptors, the postsynaptic neuron is, in turn, stimulated less than normal. The overall result is a higher excitation threshold and, therefore, depressive symptoms. To reverse this trend, therefore, antidepressant drugs increase or restore the levels of synaptic monoamines either by preventing their metabolism or re-uptake into the presynaptic neuron. In depression, neurons will homeostatically respond to low synaptic levels of monoaminergic neurotransmitters by up-regulating postsynaptic receptors in an effort to compensate. This is in part supplemented by an antidepressant drug, which, likewise, prevents any further metabolism or re-uptake of any more neurotransmitter. In the event of chronic administration of antidepressant, and consequent higher levels of synaptic neurotransmitter, monoaminergic receptors begin to down-regulate or desensitize.

It soon became apparent, however, that major depression cannot be solely explained by a mere shortage of neurotransmitters in the synapse; other influences must be at work, such as increased hypothalamic-pituitary-adrenal (HPA) activity, and differential genetic (Chopra et al., 2011; Thakker-Varia & Alder, 2009) and epigenetic (Elsner et al., 2011; Gomez-Pinilla, Zhuang, Feng, Ying, & Fan, 2011) expression of receptors, transporters, and metabolic enzymes. Evidence implicating the role of these other variables contributing to the complex etiology of depression was accumulating, thereby underscoring the time-consuming plastic changes that might account for the long therapeutic lag consumed by antidepressant drugs.

Borne out of antidepressant-induced plasticity, was mounting evidence that neurotrophins, specifically brain-derived neurotrophic factor (BDNF) plays a central role in psychiatric disorders, learning, and development (Dwivedi, 2009; Greenwood & Fleshner, 2008; Russo-Neustadt & Chen, 2005; Zoladz & Pilc, 2010). According to the neurotrophin hypothesis (Chopra et al., 2011; Krishnan & Nestler, 2008; Russo-Neustadt & Chen, 2005), BDNF is a putative signaling molecule transcribed from its immediate early gene as a downstream result of monoaminergic receptor binding and which subsequently activates a wide variety of intracellular survival signaling pathways (Chen, Nguyen, Pike, & Russo-Neustadt, 2007; Stone, Quartermain, Yin, & Lehmann, 2007), resulting in gene expression-mediated synaptic plasticity.

Despite the oversimplification regarding the complex etiology of depression via the two aforementioned hypotheses (Russo-Neustadt & Chen, 2005; Krishnan & Nestler, 2008), there is much evidence that physical exercise is significantly linked to a reduction of depression and anxiety disorders (Greenwood & Fleshner, 2008; Ströhle, 2009; Young, 2007). Via increased HPA and sympathetic nervous system activity, exercise releases neurotransmitter into the blood (Eisenhofer, Kopin, & Goldstein, 2004) and increases the levels of circulating synaptic norepinephrine (Russo-Neusstadt & Chen, 2005) and 5HT (Chaouloff, 1997; Dishman, Renner, White-Welkley, Burke, & Bunnel, 2000; Meeusen & De Meirleer, 1995). Therefore, vesicle proteins, such as synapsin I (Ding, Vaynman, Akhavan, Ying, & Gomez-Pinilla, 2006), synaptophysin (Vaynman, Ying, Yin, & Gomez-Pinilla, 2006), and SNAP-25 (Hu, Ying, Gomez-Pinilla, & Frautschy, 2009) involved in presynaptic neurotransmitter release, would be induced by exercise and therefore, BDNF; conversely, TrkB with IgG prevents their increase (Vaynman et al., 2006).

Monoaminergic receptors and projections in depression and exercise

Besides monoamines themselves, receptors may also play pivotal roles in mediating the effects of exercise on depression. The effects of depression and exercise on beta-adrenergic receptors (βAR), alpha-adrenergic receptors (αAR), and 5HT receptors across studies are not consistent. Generally, however, depression increases, while antidepressant drugs decrease βAR binding and/or number; like antidepressant drugs, exercise also decreases βAR number (reviewed by Russo-Neustadt & Chen, 2005; Stanford, 2001). Antidepressant drugs increase α_1ARs (Stone et al., 2007) and decrease α_2ARs (Lucki & O'Leary, 2004; Russo-Neustadt & Chen, 2005; Stanford, 2001). Stress increases corticosterone levels, which decreases norepinephrine release from the locus coeruleus and leads to α_1AR desensitization and/or decreased activation, which, in turn, lead to depression (Ressler & Nemeroff, 1999; Stone & Quartermain, 1999). While Morishima et al. (2006) found that high-intensity running down-regulated α_2AR, Greenwood and Fleshner (2008) reviewed no significant differences in α_2AR mRNA between sedentary and exercising rats. And finally, depression increases $5HT_{1A}$ and $5HT_{2A}$ receptor numbers, whereas antidepressants decrease them (Carr & Lucki, 2011). In exercise-primed experienced rats, however, compared to those in sedentary controls, $5HT_{1A}$ mRNA increased (Greenwood & Fleshner, 2008) in the dorsal raphé, while also decreasing stress-induced activation of norepinephrine from the locus coeruleus. Exercise also decreases $5HT_{2C}$ receptor subtype (Broocks, Ahrendt, & Sommer, 2007), thereby augmenting norepinephrine and dopamine release from limbic areas (Pytliak, Vargová, Mechírová, & Felsöci, 2011) and increasing monoaminergic synaptic activity and counteracting the stress-to-depression response.

Gross morphological changes associated with depression and exercise

Numerous studies have indicated that in depressed humans, overall decreased brain volumes reflect severe neuronal and glial cell loss (Manji et al., 2003). Specifically, the hippocampal formation is one of several brain structures directly impacted by stress and depression. In patients suffering from major depression or post-traumatic stress disorder, a significant decrease in hippocampal volume (Bremner et al., 2000; Gerritsen et al., 2011; MacQueen et al., 2003; Stockmeier et al., 2004) or change in shape (Tae et al., 2011) has been reported, although it may not be necessarily due to neuronal loss per se, as interventions that ameliorate stress, allowing animals to recover, have been shown to restore such volume changes (Lucassen et al., 2010). Such volume changes may result from factors other than that of cell death, such as mere somatodendritic atrophy (which can be reversed) (Xiao, Feng, & Chen, 2010) or changes in glia or extracellular fluid volume (Lucassen et al., 2010). Thus, the decreased hippocampal volume was asymmetric and only transient (Ahdidan et al., 2011). However, whether volumetric reductions in motor and limbic structures in humans are strictly due to depression is unknown (Canbeyli, 2010).

Exercise increases neurogenesis and dendritic complexity

The gross morphological changes resulting from stress/depression or age on one hand and the ameliorative reversal, or at least, maintenance effects, of exercise on the other, can be partly attributed to altered levels and/or patterns of neurogenesis. Physical exercise has been shown to increase neurogenesis in the hippocampus (Bjφnebekk, Mathé, & Brené, 2005; Ernst, Olson, Pinel, Lam, & Christie, 2006; Kitamura, Mishina, & Sugiyama, 2003) and dentate gyrus (Åberg, Perlman, Olson, & Brené, 2008; Fuss et al., 2010; Kitamura & Sugiyama, 2006; Pereira et al., 2007; Redila & Christie, 2006; Snyder, Glover, Sanzone, Kamhi, & Cameron, 2009). In addition, exercise increases mossy fiber density (da Silva et al., 2012), both hippocampal and entorhinal cortical dendritic spines (Stranahan, Khalil, & Gould, 2007) and synaptic transmission (Kobayashi, Ikeda, & Suzuki, 2006). Consequently, exercise can increase, or at least maintain, hippocampal volume in older adults (Erickson et al., 2009, 2011). Highly correlated with neurogenesis is BDNF, which is up-regulated in the well-known environmental enrichment protocols (Russo-Neustadt & Chen, 2005) in which running, dietary restriction (Kitamura, Mishina, & Sugiyama, 2006), and possibly the other varied stimuli increase hippocampal angiogenesis (Ekstrand, Hellsten, & Tingström, 2008) and neurogenesis (Kitamura et al., 2006), dendritic length and arborization complexity of parietal cortical pyramidal neurons (Leggio et al., 2005), and hippocampal mossy fibers (Toscano-Silva et al., 2010), compared to those in rats housed in standard conditions. Conversely, in trkB knock-out mice, exercise resulted in no neurogenesis of hippocampal neuroprogenitor cells (Li, Jarvis, Alvarez-Borda, Lim, & Nottebohm 2000; Li et al., 2008).

Antidepressant medications and physical exercise engage the same neuroprotective, prosurvival pathways

According to the neurotrophin hypothesis, plastic changes, resulting from antidepressant drug treatment and/or exercise, begin with enhanced synaptic monoamine concentrations allowing for increased norepinephrine and/or 5HT binding (above) to their respective G-protein coupled receptors, which activate adenylate cyclase to produce cAMP, which activates protein kinase A. A major target of the cAMP cascade is the cAMP response element binding (CREB) protein, a

transcription factor that regulates gene expression by binding to cAMP response element (CRE)—a cis-acting enhancer element in the regulatory region of various genes (Meyer and Habener, 1993; Montminy, Gonzalez, & Yamamoto, 1990). The increase in phosphorylated CREB up-regulates BDNF, which activates neuronal survival signaling pathways (Chen et al., 2007; Chen & Russo-Neustadt, 2005; Russo-Neustadt & Chen, 2005) against various forms of stress, such as trauma, ischemia, and diabetes mellitus (Dishman et al., 2006; Greenwood & Fleshner, 2008; Kazanis, Giannakopoulou, Philippidis, & Stylianopoulou, 2004; Matsuzaki, Namikawa, Kiyama, Mori, & Sato, 2004; Schabitz, Schwab, Spranger, & Hacke, 1997; Schabitz et al., 2000; Yamashita, Wiessner, Lindholm, Thoenen, & Hossmann, 1997; Zhang & Pardridge, 2001).

Stress, physical exercise, and BDNF

The hippocampus is particularly vulnerable to cortisol (Lee, Ogle, & Sapolsky, 2002), which is increased during times of prolonged unremitting stress (Lee et al., 2002; Uno, Ross, Else, Suleman, & Sapolsky, 1989). Conversely, an antidepressant regimen, which includes exercise, ameliorates stress and/or depression via BDNF (da Silva et al., 2012; Duman & Monteggia, 2006; Dwivedi, 2009; Marais, Stein, & Daniels, 2009; Mata, Thompson, & Gotlib, 2010; Sartori et al., 2011; Siefert et al., 2010; Zheng et al., 2006) and TrkB (da Silva et al., 2012; Widenfalk, Olson, & Thorén, 1999) expression and subsequent intracellular signaling-mediated plasticity (Vaynman et al., 2006) and therefore, cell survival (Chen & Russo-Neustadt, 2007; Li, Jarvis, Alvarez-Borda, Lim, & Nottebolm, 2000). And when running stops, both BDNF and TrkB mRNAs down-regulate (Widenfalk et al., 1999).

Depression, metabolism, and exercise

There is ample evidence that major depressive disorder and obesity are linked (Anderson, Cohen, Naumova, Jacques, & Must, 2007; Dong, Sanchez, & Price, 2004; Herva et al., 2006; Roberts, Deleger, Strawbridge, & Kaplan, 2003). In fact, many diseases for which overeating is a risk factor (e.g., cardiovascular disease, diabetes mellitus, cancer) tend to cluster with neurodegenerative and psychiatric diseases (Mattson, 2005; Pedersen et al., 2009). Conversely, regular exercise and/or dietary restriction can regulate neuronal plasticity through the expression and activation of BDNF and release of 5HT (Mattson, Maudsley, & Martin, 2004). Indeed, BDNF levels are relatively low in those with metabolic diseases (Pederson et al., 2009). Further, the link between depression and obesity may reside with the hormone leptin, to which many obese people may be resistant (Klok, Jakobsdottir, & Drent, 2007). Thus, leptin may be antidepressant, as leptin increases hippocampal BDNF in diet-control mice, but not in diet-induced obese mice (Yamada et al., 2011) in which obesity could be directly attributed to decreased leptin (Mainardi et al., 2010). Similarly, the antidepressant effects of leptin were abolished by the presence of a TrkB inhibitor; therefore, leptin activity in the hippocampus may at least partly explain the depression–obesity connection (Yamada et al., 2011).

The benefits derived from physical exercise (Dishman et al., 2006) and dietary restriction (Mattson, 2000) have revealed that both increase resistance to oxidative stress involving ROS-mediated damage to proteins, lipids, and nucleic acids. With dietary restriction, nutrient metabolism is more efficiently utilized, thereby promoting neuronal mitochondrial function (Mattson, Gleichmann, & Cheng, 2008), activating and deactivating cell survival and apoptotic cascades, respectively (Mattson, 2000; Mattson, Duan, & Gao, 2003). Chronic mild stress, however, has been shown to inhibit respiration rates and dissipate the membrane potential of hippocampal mitochondria in mice (Gong, Chai, Ding, Sun, & Hu, 2011).

The opposite of dietary restriction is overeating, which, as mentioned above, clusters with depression (Pederson et al., 2009). Following a carbohydrate-rich meal and release of insulin, there is a decrease in both glucose and amino acids in the blood. However, blood tryptophan levels remain steady, because branched-chain amino acids (BCAAs) prevent tryptophan from being taken up into the brain, which drastically decreases the ability of this organ to synthesize 5HT. The resultant lower brain 5HT levels then can lead to or contribute to depression (Wurtman, 1993). Depressive symptoms can then, in turn, lead to over-eating, completing the vicious cycle. Such a cycle, over a span of decades, would eventually lead to insulin resistance. To break this cycle, therefore, (more) 5HT must be able to enter the brain and/or the brain must be able to synthesize it *de novo*. Thus, 5HT-selective re-uptake inhibitors (SSRI)s have been shown to increase insulin sensitivity; specifically, citalopram leads to increased glucose tolerance and a decrease in cardiovascular response to stress and attendant decrease in hyperglycemia (Mattson, 2005). Therefore, medications often used to treat obesity target the same neurotransmitter system (5HT) as those used to treat depression (Bello & Liang, 2011). Thus, because there is initially a deficiency in 5HT (say, before SSRI administration and as a result of carbohydrate indulging), there is a defect in the ability of 5HT to regulate hypothalamic function, which may underlie the inability of patients with insulin resistance to effectively cope with stress/depression. On the other hand, dietary restriction increases 5HT hypothalamic signaling, which may decrease oxidative stress and enhance mood (Mattson, 2005). Moreover, exercise has been shown to reverse many of the aforementioned trends. During exercise, there is an increase in plasma BCAAs, which are taken up by muscle, thereby nullifying their inhibitory effect of tryptophan (which is also increased by exercise) uptake into various brain regions (Fernstrom & Fernstrom, 2006; Newsholme & Blomsbrand, 2006). As a result, central 5HT synthesis and release are increased (Fernstrom & Fernstrom, 2006).

Because exercise is antidepressant, it might confer the same antioxidant neuroprotective effects that treatment with SSRIs and antioxidants produced. Regular exercise in both young and middle-aged rats led to decreased accumulation of oxidatively damaged proteins (protein carbonyls) (Radak et al., 2001). And by increasing BDNF, exercise reverses the deleterious effects of a high-fat diet, such as increases in reactive oxygen species (ROSs). On its own, without exercise, BDNF injected chronically into the paraventricular nucleus of the hypothalamus reverses obesity brought about by a high-fat diet (Wang, Godar, Billington, & Kotz, 2010). Conversely, deletion of the *bdnf* gene in the ventral medial hypothalamus (VMH) results in hyperphagia and obesity (Unger, Calderon, Bradley, Sena-Esteves, & Rios, 2007), which, in turn, decreases hippocampal BDNF (Park et al., 2010; Wu, Molteni, Ying, & Gomez-Pinilla, 2003), and impairs neurogenesis. Both effects are associated with increased lipid peroxidation (Park et al., 2010), thereby compromising these plastic changes.

The antidepressant effects of exercise, namely increased BDNF release, combined with dietary restriction, can suppress feeding (Klok et al., 2007; Lebrun, Bariohay, Moyse, & Jean, 2006), thereby increasing glucose metabolism and energy expenditure (Pederson et al., 2009). Intracerebroventricular infusion of BDNF has led to increased peripheral insulin sensitivity in normal rodents, a reduction in diabetes in mice (Mattson, 2005), decreased leptin resistance, and decreased obesity (Kernie, Liebl, & Parada, 2000). Without BDNF (or exercise), there is increased sensitivity to stress, increased plasma glucose (Pederson et al., 2009) and insulin (Maniam & Morris, 2010) levels, and obesity (Kernie et al., 2000). Exercise plus dietary restriction, therefore, will lead to increased BDNF signaling, which, in turn, may stimulate signaling pathways that increase glucose metabolism and cellular resistance, leading to protection against stress-associated diseases such as cardiovascular disease, diabetes mellitus, and obesity.

Normally, glucose is a satiety signal, inducing BDNF and TrkB in the VMH (Unger et al., 2007). Below a certain brain glucose level, however, leptin is released from adipose stores

and then acts on neuropeptide Y (NPY) receptors in the VMH, culminating in decreased leptin binding to leptin receptors. NPY receptor activation increases feeding and body weight and decreases resting metabolic rate, all of which then increase adipose tissue mass. Increased adipose then absorbs more glucose, again depriving the brain of glucose, and thereby completing the cycle (Noble, Billington, Kotz, & Wang, 2011; Peters et al., 2004). On the other hand, physical exercise increases adipose tissue metabolism, thereby releasing higher amounts of leptin into the circulation (higher than that released during severe depression, above). Leptin then binds its receptors residing on neurons in the arcuate nucleus and VMH. In the latter, α-melanocyte-stimulating hormone (α-MSH) increases leptin binding to leptin receptors. Alpha-MSH then binds to MC4 receptors, which increases BDNF binding to TrkB (Xu et al., 2003). Increased BDNF activity then suppresses feeding and decreases hyperglycemia, hyperinsulinemia, hyperlipidemia, and GABA receptor binding; this last effect then increases excitation, which then increases physical exercise, thereby completing the cycle (Mainardi et al., 2010; Noble et al., 2011).

Oxidative damage and exercise

It has been suggested that exercise can ameliorate the effects of stress-induced ROS production (Mattson, 2000), perhaps by maintaining a redox homeostasis conducive to brain function. However, exercise itself is a stressor. The type of exercise (running vs swimming), protocol intensity, length of running (acute vs chronic), voluntary vs forced, species, brain region, and physiological status (age, gender, overweight, diabetic) of the animal all interact in determining whether exercise is beneficial (enjoyable) or stressful (aversive). Thus, one must consider the activity of various antioxidant enzymes, as well as the oxidative damage to lipids, proteins, and DNA, which occur as by-products of routine cellular metabolism. These free radicals are extremely reactive and have been implicated in various neurodegenerative disorders (Chrissobolis, Miller, Drummond, Kemp-Harper, & Sobey, 2011; Genovese et al., 2011; Hegde, Hegde, Rao, & Mitra, 2011). Generally, exercise was shown to decrease such damage (Radak, Kumagai, Taylor, Naito, & Goto, 2007). More recently, Radak, Chung, and Goto (2008) found that as a result of an acute, stressful bout of forced exercise, there is increased production of free radicals, oxidative damage, antioxidant enzyme activity, and decreased resistance to oxidative stress and declining physiological function. Chronic exercise, on the other hand, generally results in decreased levels of these measures, except for antioxidant enzyme activity and oxidative damage, which both acute and chronic exercise increase (Radak et al., 2008). The central player in exercise-mediated amelioration of brain health during depression is BDNF. Earlier studies from our lab have shown that nitric oxide production (Boveris & Navarro, 2008) is related to exercise-induced and norepinephrine-induced increases in BDNF expression *in vivo* (Chen, Ivy, & Russo-Neustadt., 2006) and *in vitro* (Chen & Russo-Neustadt, 2007).

Glutamate

One of the ways by which exercise can rapidly and robustly increase BDNF is via glutamatergic activation (Castrén, Berninger, Leingärtner, & Lindholm, 1998) and nitric oxide signaling (Chen et al., 2006; Chen & Russo-Neustadt, 2007). General physical activity not only increases release of norepinephrine (above), but also glutamate (Richter-Levine, Canevari, & Bliss, 1998). While antidepressant drugs and exercise activate intrasynaptic norepinephrine and/or 5HT-induced increased CREB-mediated BDNF transcription (Russo-Neustadt & Chen, 2005), increased glutamate release (Lonart & Johnson, 1995) activates nitric oxide synthesis (Fedele, Marchi, &

Raiteri, 2001), which, in turn, may lead to more norepinephrine release (Lonart, Wang, & Johnson, 1992; Stout & Woodward, 1994) and up-regulated NMDAR1 mRNA (Dietrich et al., 2005; Lou, Liu, Chang, & Chen, 2008), NMDAR2B (Dietrich et al., 2005; Farmer et al., 2004; Hu et al., 2009), glutamate receptors GluR1, GluR2/3 (Dietrich et al., 2005), and GluR5 (Farmer et al., 2004), and AMPA receptors (Real, Ferreira, Hernandez, Britto, & Pires, 2010). This would result in a rapid positive feedback and potentiation of the norepinephrine-to-BDNF signal (Chen et al., 2007; Mattson, 2008), perhaps by induction of PSD-95 (Hu et al., 2009). In addition, nitric oxide activates the PI-3K pathway directly via ras (Deora, Win, Vanhaesebroeck, & Lander, 1998) and the subsequent transcription of many pro-survival genes involved in neurite outgrowth and synaptogenesis (Mattson, 2008).

Research concerns in depression/exercise experimentation

Methodological issues of research of the neurobiological mechanisms of exercise and depression were addressed earlier by Dishman et al. (2006). One of the most disconcerting issues facing the practice of using animal models of human depression is its content validity. Because we are assuming that the various behavioral tests and therefore biochemical measures we use (e.g., forced swim, tail suspension) are indeed valid models of depression, it is difficult to imagine that a full understanding of the complex mechanisms involved in the etiology of this disorder will ever be achieved. Such behavioral tests fail to take into account the emotional contribution of the animal to the observed results. Additionally, there may be simpler interpretations, such as lack of motivation or simple fatigue resulting from so much struggling (tail suspension test). Assuming that a lack of struggling is not due to fatigue or lack of motivation, how long must a rat *not* struggle before it is considered a valid model of human depression, which can last for years, long-term? Because it is neither practical nor ethical to effect a proportional length of time a rat must struggle to mirror a human depressive episode, there is a paucity of human studies demonstrating whether such long-term changes in synaptic efficacy induced by stress/depression can be partially reversed by antidepressant treatment/exercise (Popoli, Gennarelli, & Racagni, 2002). Further, there are often distinct differences between voluntary exercise (enjoyable) vs that which is forced (aversive and stressful). Just as it does in humans, exercise in other animals, therefore, may carry an emotional component with it.

Is depression anatomically localized?

Most of the neurobiological research of depression and exercise has examined the hippocampus and cortex, where most of the brain BDNF is expressed. Much of the pathophysiology of depression, however, also occurs in the ventral tegmental area-nucleus accumbens (Nestler & Carlezon, 2006); anhedonia indicates problems with this mesolimbic reward pathway, where disturbances may also cause decreased BDNF (Angelucci, Brenè, & Matheé, 2005).

Genetic models of depression

Other animal models of depression may provide new information and warrant further consideration. For example, the Flinders sensitive/resistant line has exhibited increased BDNF. This could mean that there is a compensatory increased BDNF expression in response to down-regulated TrkB signaling (Angelucci et al., 2005); it could also mean a decreased BDNF turnover with a higher pool of BDNF in the tissue that is not released (Angelucci et al., 2005). Such a pool of BDNF could be released as a result of exercise-induced increases in monoaminergic

activation (Chen et al., 2007) and could shorten the length of time required for plastic changes to occur and therefore, therapeutic efficacy would be reached sooner.

Sedentary lifestyle is not normal

Standard laboratory conditions of sedentary lifestyles are those of deprivation and lack of stimulation (Gould, Tanapat, Rydel, & Hastings, 2000; Würbel, 2001). Sedentary rodents may not be the most valid models of human disease. It has been noted, therefore, that rodents should perhaps have access to a running wheel in their cages (Van Praag, Barlow, & Gage, 2001), thereby simulating as closely as possible what their lives would be outside captivity. Because runners are often compared to their sedentary controls, the baseline of various molecules, such as that of BDNF, is already rather low. Therefore, it often does not take much running stimulation to increase this already very low amount of BDNF. The vast majority of studies use young adult rodents starting at 2–3 months of age. Voluntary running usually entails a running wheel accessible 24 hr/day for the pre-specified length of the study, the objectives of which will determine the exercise protocol. Exercise durations, therefore, vary widely and can range from only an acute bout of running for, say, 6 hours (Chen & Russo-Neustadt, 2009) to as long as 28 or even 90 days (Berchtold et al., 2005). Between these extremes, access to running wheels, depending on the objectives of the study, typically lasts 1, 2, 3, or 4 weeks (Russo-Neustadt & Chen, 2005). In addition, it is common practice to initially allow the rodents a brief period of 3–5 days of voluntary running, followed by a period of 7–10 days of wheel removal from their cages, followed by the beginning of the running protocol itself. This brief priming or training period allows the rodents to gain dexterity while also decreasing the effects of novelty and learning during the actual treatment period (Russo-Neustadt, Ha, Ramirez, & Kesslak, 2001; Berchtold, Kesslak, & Cotman, 2002; Vaynman et al., 2006). Running distances and speeds are computer-monitored and calculated as meters run per night, typically 2–6 km/night, although these distances also vary widely across labs, strains, and species (mice vs rats). Other investigators have used forced running, in which rodents are placed on a treadmill for, say, 7 sessions/10 days at 30 min/session/day and in which the speed of the treadmill gradually increased (Soya et al., 2007).

Interpretive hurdles

Applying the observation that exercise increases neurogenesis in rodents to human major depressive disorder is, at best, suggestive. Whether exercise-induced increases in neurogenesis in humans are actually therapeutic for major depression remains to be seen. Establishing a direct connection between exercise and neurogenesis in humans would be difficult, unless BDNF activity could somehow be tracked in a way similar to that of glucose in fMRI.

Future research directions

Because of the potential validity issues facing the use of animal models for studying mood disorders (above), a major challenge for future research would be to conduct more human studies, addressing the genetics of major depressive disorder, such as polymorphisms of the genes of the 5HT receptor subtypes, BDNF, and other monoaminergic receptors and transporters.

In addition, exercise should be prescribed in doses, gradually increasing over time. Such a practice might serve to overcome the inertia that depressed individuals often find daunting in starting an exercise regimen; treating exercise and diet the same as one would any other drug provides a systematic and predictable outcome measure – whether or not mood improves.

Moreover, researchers and clinicians should both recognize that emotions play a significant role. The critical difference seems to lie in whether the activity is enjoyable. Physical activity can be aversive and exercise can be enjoyable. Often, it is the "intent" of the activity that distinguishes these two. Physical activity relates more strongly to daily movements, and exercise more to structured, purposeful, or planned activity with the aim of increasing strength, cardiovascular fitness, etc. Just as it has been observed that an increase in BDNF and neurogenesis is associated with voluntary running (enjoyable, exercise), these biological measures are not increased with treadmill (stressful, forced) running. Although these interventions increase central expression of BDNF, it is possible that intense exercise raises body temperature enough to allow BDNF to exchange between the CNS and the periphery (Goekint, Roelands, Heyman, Njemini, & Meeusen, 2011).

Finally, specific human characteristics, such as age, gender, health/disease state, etc. should be considered when evaluating the effects of leisure-time physical exercise on depression.

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