World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Published by Atom and Cell Publishers
Available online at: http://www.wjpsonline.org/
Editorial

A Healthy Body for a Healthy Mind

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Drug abuse and dependence are significant, yet preventable, public health concerns world-wide. There are few effective pharmacotherapies or treatment strategies available to help people struggling with drug addiction, especially with respect to psychostimulants like cocaine and methamphetamine. One of the greatest impediments to the treatment of psychostimulant addiction stems from the challenging development of pharmacotherapies, undermined in part by the lack of understanding of the genetic variability inherent to mechanisms of drug action within the brain and body. Although researchers have made strides in this regard over the last several decades, a complete picture of the complex interaction between individual differences in genetics and environment is just beginning to take shape. In 2008, the U.S. Department of Health and Human Services published *Physical Activity Guidelines for Americans*, a report detailing the vast and varying health benefits of physical exercise. The publication asserted that as little as two and a half hours of moderate exercise (e.g. riding a bike or brisk walking) each week can ameliorate and help prevent numerous chronic disease states including, but not limited to, heart disease, high blood pressure, colon and breast cancers, type-2 diabetes, and depression. Upon further examination of the connection between bodily health and exercise one might infer that what is good for the body might also be good for the mind. Where the approaches of a "magic-bullet" pill remedy for drug abuse and dependence have failed, an approach emerges where treating the body to good health in turn treats the mind to the same. A relatively unexplored avenue, ripe for research, is whether addiction – a widely accepted chronic disease state with roots in behavioral and biological causes – can be ameliorated or prevented by exercise, as numerous other chronic disease states have found to be. Preclinical evidence is accumulating that exercise (both voluntary and forced) may serve to protect an individual from the lure of stimulant drug abuse. Specifically, six weeks of exercise prior to initial amphetamine exposure induced conditioned place aversion to the drug-paired context in rats (Fontes-Ribeiro et al., 2011). These data suggest that exercise may increase one's sensitivity to amphetamine conferring an aversive state and may serve as a prophylactic against continued drug use following initial drug exposure. Not only might exercise deter the initiation of drug use behaviors, exercise increased dopamine signaling in the ventral tegmental area and produced conditioned place preference when paired with a unique context (Greenwood et al., 2011). These data suggest that exercise may be intrinsically or innately valued; with variable phenotypic expression within a given population. Exercise has also been demonstrated to attenuate the escalation of established drug-seeking behavior (Zlebnick et al., 2012), as well as substitute outright for intracranial self-stimulation (Morris et al., 2012); data that collectively propose a mechanism of generalized exercise-induced reduction of drug craving.

Although a clear beneficial role for exercise on drug use behaviors (i.e. acquisition, maintenance, extinction (abstinence), and reinstatement) has begun to emerge, most research has been limited to analysis of the environmental, or nurture, component of physical exercise in isolation. Equally central to the endeavor to understand the connection between bodily health and mental health (as it relates to addiction), is to identify if the genetic composition, or nature, drives the individual to engage or not in exercise and/or drug use. Interactions between these two biological predispositions (exercise and drug use) and environmental influences likely contribute to an individual's propensity for addiction. Recent work in our laboratory has seen the development of two lines of Wistar rats selectively-bred for high- and low-voluntary running (HVR/LVR). These lines of rats differ innately in terms of motivation to engage in wheel-running behavior, with HVRs running nightly distances 7-10 times those of the LVRs (Roberts et al., 2013), permitting an examination of the genetic and environmental origins of and interactions between physical activity and drug use.

Initial data from these divergent rat lines suggest that both male and female LVRs exhibit an enhanced response to acute cocaine-induced locomotor activity compared to their HVR counterparts, despite comparable dopamine transporter (DAT) mRNA levels between the lines (Brown, et. al., 2014). The nigrostriatal dopamine (motor) pathway underlies volitional motor movements and provides a convenient link between exercise and drug use behaviors. Once rewarding drugs like cocaine or methamphetamine enter the brain they increase activity at dopamine receptors system-wide; to include both the mesolimbocortical (reward) and nigrostriatal (motor) dopamine pathways. Following this logic one can infer that variables (e.g., genetics, drug treatment, physical exercise) affecting one pathway's dopamine activity likewise affect the other. In this regard, the use of genetic-variant animal models is a cost-effective, time-efficient, and informative approach to studying the exercise/addiction dynamic. As researchers continue to unravel the complex interaction between physical and mental health, the use of paradigms employing and analyzing combined genetic and environmental effects on behavior will become increasingly important. It is evident that further time and funding resources are necessary to promote the type and scale of data collection and analysis that is both required by and will result from this promising line of research.

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