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Running is rewarding and antidepressive

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Abstract

Natural behaviors such as eating, drinking, reproduction and exercise activate brain reward pathways and consequently the individual engages in these behaviors to receive the reward. However, drugs of abuse are even more potent to activate the reward pathways. Rewarding behaviors and addictive drugs also affect other parts of the brain not directly involved in the mediation of reward. For instance, running increases neurogenesis in hippocampus and is beneficial as an antidepressant in a genetic animal model of depression and in depressed humans. Here we discuss and compare neurochemical and functional changes in the brain after addictive drugs and exercise with a focus on brain reward pathways and hippocampus.

Keywords

Addiction; Depression; Exercise; Neurogenesis; Hippocampus

1. Introduction

"The one and only" reward system is activated both by natural and drug-induced rewards

Desire to experience pleasure is the usual initial driving force to take drugs. Numerous studies have described acute effects of different rewarding drugs and the common denominator of their mode of action appears to be release of dopamine in nucleus accumbens [1]. Similarly, natural behaviors that are essential in daily life and reproduction also mediate release of dopamine in nucleus accumbens. Also other common behaviors such as playing computer games [2], listening to pleasant music [3], or watching attractive faces [4] mediate release of dopamine or increase energy consumption in nucleus accumbens. Non-drug associated behaviors can also develop into pathological behaviors such as anorexia nervosa, bulimia nervosa and pathological gambling or bulimia nervosa (see 307.1, 307.51 and 312.31, respectively in Diagnostic and Statistical Manual 4:th edition, (DSM IV)) [5]. Similarly, excessive physical training can result in fatigue and mood disturbances as has been reported in overstrained humans [6-8]. These symptoms are similar to hallmarks of withdrawal in substance abusers,

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mood disturbances such as depression and anxiety. Also, after withdrawal from an excessive natural rewarding behavior such as running or from addictive drugs the individual will show signs of depression and anxiety or other indications of negative affective states [9,10]. While the neurobiological origin of depression and anxiety in the withdrawal phase in drug addicts and in excessive runners and overtrained individuals could well be malfunction in the reward pathways, substantial evidence points to other parts of the brain such as amygdala, hippocampus and the cerebral cortex as giving rise to affective symptoms. It is not known why long-term use of rewarding drugs can lead from controlled recreational consumption to compulsive consumatory behavior. Such transition from controlled to compulsive reward seeking behavior is also seen with non-drug induced rewards. Neurochemically, several effects of long term use of addictive drugs have been reported and key molecules, e.g., ΔFosB, which is a component of the AP1 transcription factor, [11], and the opioid neuropeptide dynorphin [12,13] are increased in brain reward pathways. Interestingly, these molecules are increased in the same brain regions in rats that have had access to running wheels and that have developed a high level of daily running [12,14]. Following drug withdrawal, ΔFosB levels are relatively persistent, but do return to baseline with time [11]. As for the running-induced molecular alternations it is not known whether these changes return to baseline levels after cessation of running. However, even though the initial neurochemical changes such as the ΔFosB levels, returns to basal levels, the effects of the drugs are long-lasting, and can be life-long. For example, acute administration of drugs such as cocaine, amphetamine, morphine, or nicotine will mediate an increased motor response which can be detected using activity boxes. With daily repeated administration of the drug this effect gradually increases, a phenomenon termed behavioral sensitization [15,16]. This effect is long-lasting and can persist for more than a year in rodents [17], which is in contrast to the increased levels of ΔFosB that return to baseline earlier.

2. Genetics of drug consumption and other reward seeking behaviors

There are several ways in which to search for candidate genes that may influence addictive behaviors in animal models; a classical one is to use inbred animals. In rats, the Lewis strain is drug addiction-prone whereas the Fischer strain is not, although both were derived from the Sprague-Dawley strain [18,19]. Interestingly, the Lewis strain also develops a high running activity when given free access to running wheels and already after two weeks these rats can run as much as 10 km/day [20]. In contrast, rats of the non drug-preferring Fischer strain do not at all develop a high running activity; these rats run only approximately 2 km/day when given free access to running wheels [20]. In mice, the C57BL/6 and DBA inbred strains are often used in studies of addiction. Also, here the drug-preferring strain, C57BL/6, develops a high running activity whereas the DBA strain does not (Fig.1). The mice of the 129 mouse strain, which is the general source of embryonic stem cells needed for homologous recombination, do not develop preference for alcohol or other addictive drugs (data not shown), nor do they develop high activity running in the running wheels (Fig. 1). This would suggest that some rodent inbred strains that can develop high preference for addictive drugs will also develop a distinct preference for running in running wheels. However, there are also non-addiction-prone mouse strains such as Balb/c, C3H and CBA that develop high activity running in the wheels (Fig. 1) but do not develop preference for alcohol (data not shown). Thus, our data suggest that there is no absolute correlation between high running activity strains and strains with high preference to consume drugs such as alcohol. Future research will, hopefully, elucidate the impact of genetic background in inbred rodent strains on addiction to running and to addictive drugs.

Recombinant inbred rodent strains have been developed using selected cross breeding of defined inbred rodent strains such as the C57BL/6 and DBA mouse strains leading to over 20 different recombinant BXD strains. These strains have been analyzed for ethanol preference

and several loci been detected. One of the strongest loci for ethanol preference in the BXD strains is on mouse chromosome 2 [21], a region in which the Nurr1 gene is localized. Using QTL-analysis in rat strains with high and low preference for ethanol a strong QTL is found on rat chromosome 4 [22,23], a region in which the NPY gene is localized. To the best of our knowledge, there are no QTL reports on the genetics of running.

The function of different putative candidate genes controlling activity of the brain reward pathways has been evaluated in both transgenic and null-mutated mice. One example of a molecule that is upregulated in the reward pathways after both addictive drugs and voluntary wheel running is ΔFosB. To further understand the function of ΔFosB, Nestler and coworkers developed transgenic mice with tetracycline-inducible overexpression of ΔFosB in striatum and accumbens [24]. These mice have increased sensitivity and preference for cocaine [24]. Following cocaine administration these animals show increased locomotor activity [24]. The same strain of mice also has an increased preference to run (Table 1) [14].

In another line of experiments, mice that were heterozygous for a Nurr1 deletion were analyzed both for ethanol preference and preference to run in running wheels [25]. The rationale behind analyzing the Nurr1 heterozygous mice was that Nurr1 is located within a QTL for alcohol preference on mouse chromosome 2 and is necessary for development of dopamine neurons [26]. Nurr1 knock out animals lack dopamine neurons and die shortly after birth, presumably due to of respiratory problems [27]. Heterozygous Nurr1 mice are viable and have no gross abnormalities. However, they show increased novelty-induced locomotor response, which suggests they do not have any gross motor deficits. The Nurr1 heterozygous mice show decreased activity in the running wheels and they also show a decreased preference to consume ethanol (Table 1) [25].

In summary, we have provided two examples of genetically modified mice that have similar responses to seeking reward from an addictive drug (alcohol) and a naturally rewarding behavior (wheel running). Thus it is possible that the same genes that control preference for addictive drugs also control the preference for naturally rewarding behaviors.

3. Behavioral interaction between running and alcohol consumption

A common feature of addictive drugs is that they increase dopamine levels in nucleus accumbens and this mechanism could account for the cross-sensitization phenomenon, i.e., that one drug may potentiate or sensitize the locomotor activating effect of another drug. Few studies have tested if there is behavioral cross-sensitization between a naturally rewarding behavior and drug-induced behavior. Wheel running is a rewarding behavior that shares many features with those of addictive drugs. For instance, rodents that run have increased levels of dopamine in nucleus accumbens and can be trained to lever press for access to running wheels [28]. They also develop conditioned preference to an environment that is associated with after-effects of running in running wheels [29].

To test whether there is a behavioral interaction between running in running wheels and preference for addictive drugs [30] we gave Lewis rats access to 10% ethanol in the two-bottle free-choice model for ethanol consumption during a 4 weeks period. The rats developed a 50-60% preference for ethanol. We then removed ethanol during 1-4 weeks. During this period half of the animals had access to running wheels. This was followed by a last phase of the experiment in which we analyzed how much ethanol the mice consumed in the two-bottle free-choice model for ethanol consumption during 1 week. The results showed that runners had increased ethanol-intake and -preference during the last week of the experiment [30]. Thus we exemplify a behavioral interaction between a non-drug induced and a drug induced reward-seeking behavior.

The duration of access to the rewarding stimulus is an important factor for the transition from a low to a high consumption pattern. In one study [31], rats were given access to cocaine one or six hours/day in a self-administration paradigm. The animals with the longer daily access to cocaine dramatically increased their daily administration over a period of one month. In contrast, rats that only had the possibility to self-administer the drug during one hour every day did not increase their drug intake [31]. A similar design of limited access time to the rewarding stimuli has been performed for running wheel activity [32]. Also in this experiment the group that had longer access to running wheels shifted from low to high activity in the running wheels, while rats with shorter daily running wheel access did not increase their daily running [32]. This example of transition from moderate to high reward consumption that is similar for addictive drugs and for wheel running raises the possibility that there is a common mechanism for the development of compulsive drug intake and excessive running in humans.

4. Running, alcohol and neurogenesis

Running can be addictive and reinforcing, and it also has an antidepressant effect in humans. There are two major sites in the brain for adult neurogenesis, the sub-granular zone of the dentate gyrus and the sub-ventricular zone. New cells formed in the sub-ventricular zone migrate along the rostral migratory stream to the olfactory bulb whereas those formed in the sub-granular zone remain within the dentate gyrus. All commonly used antidepressive treatments such as ECT, tricyclics and SSRI increase neurogenesis [33] (Table 2). Moreover, running also increases hippocampal neurogenesis [34]. To investigate whether running is antidepressant in experimental animals a genetic model of depression, the Flinders Sensitive Line (FSL) [35], were given access to running wheels during a month. Interestingly, cell proliferation was lower in the depressed FSL rats compared to the non-depressed Flinders resistant line rats (FRL) in the sub-granular zone of the dentate gyrus, Moreover, running was antidepressant in FSL rats and was also associated with increased cell proliferation in the sub-granular zone of the dentate gyrus and increased levels of NPY mRNA in the dentate gyrus (Table 2). None of these effects were seen in the non-depressed FRL rats [36]. Thus running as well as all antidepressants used in treatments of depressed humans, seems to increase cell proliferation in the sub-granular zone [33] and NPY in dentate gyrus [36] (Table 2) [35,37]. In contrast, running had no effect on cell proliferation in the non-depressed FRL strain that served as a control [38].

In a recent study [39], female spontaneous hypertensive rats with free access to running wheels for 24 days inhibited proliferation of hippocampal progenitor cells by approximately 50 %, whereas a shorter time, 9 days of running with free access to the running wheels resulted in a 5-fold increase in proliferation. Also, with the long-term free access to running wheels, animals run approximately 20 km/day and had increased levels of plasma corticosterone, weight of the adrenal glands and the thymus. When distance allowed to run in the running wheels during 24 days was restricted to 6 km/day, animals did not develop this response [39]. These results indicate that different doses of running can cause dynamic regulation of hippocampal cell proliferation together with an altered hormonal balance in hypertensive rats. Whether these effects can be repeated in non-hypertensive rats or if they in any way could mirror a development of an overtraining syndrome in humans remains to be shown.

There are several reports that repeated administration of addictive drugs has neurotoxic effects in the adult mammalian brain. For example, met-amphetamine has damaging effects on particularly the 5-HT [40] and dopamine terminals [41]. Phencyclidine is another drug that has long-lasting toxic effects on the brain [42] possibly remaining for the rest of an individual's life. Long term administration of morphine and heroin self-administration decreases neurogenesis in hippocampus [43]. Also, alcohol has neurotoxic effects in parts of the cerebral cortex [44] after long term use. In many rodent studies, very high and toxic doses of ethanol,

which rarely are reached in human consumers, have been given. This has generated reports of neurodegenerative effects of ethanol in hippocampus. In contrast, in humans, when using stereological analysis methods the number of nerve cells in hippocampus is unchanged even after very long time of alcohol abuse. Instead, a decrease in the size of hippocampus, caused by a reduction of white matter and astrocytes has been reported [45,46]. As with other drugs the effects of alcohol can persist for the rest of an individual's life. It has been suggested that even after long periods without alcohol intake the brain remains reprogrammed; a drug-paired alcohol memory has been formed, and thus the risk to relapse persists.

We recently reported that single housed female C57BL/6 mice that voluntarily consumed moderate levels of alcohol during 2 months in fact have increased cell proliferation and neurogenesis in the dentate gyrus and that there were no overt neurotoxic effects (Table 2) [47]. The reason for these results seemingly opposite effects of ethanol compared to certain other studies could be that our mice at the time of sacrifice had a blood alcohol level of 0.24% thou and most likely never reached neurotoxic concentrations. The mice in our experiment thus consumed ethanol in amounts that what would correspond to levels seen in recreational consumers rather than heavy drinkers. Since the mice in our study were single-housed it is conceivable that they developed a degree of stress and anxiety and consequently that the alcohol intake had anxiolytic effects. It can be hypothesized that cells born in hippocampus under the influence of ethanol will differentiate to neurons and become integrated into functional neuronal networks that carry alcohol-paired memories. Although speculative, this possibility should be viewed against the background of paucity of neurobiological mechanisms that have been put forward to explain the long-term functional adaptations caused by alcohol and other drugs of addiction. It is not understood why detoxified addicts remain at high risk of relapsing. One hypothesis is that a stable drug-paired memory with a high emotional impact is formed following reinforcing or rewarding experiences of alcohol or other drugs and stored by as yet unknown mechanisms. Hypothetically, this drug-paired memory can be activated by drug-paired cues and craving for the drug develops.

While formation of new neurons is one possible effect of drug intake, other structural rearrangements that have been reported include decreased complexity of dendritic branching and spine numbers on medium spiny neurons in nucleus accumbens after chronic morphine [48]. Chronic morphine treatment also decreases the size of the dopamine cells in the ventral tegmental area [49]. In contrast, repeated administration of psychostimulants increases the number of dendritic branching points and spines in nucleus accumbens and prefrontal cortex [50,51]. Thus, examples of structural rearrangement that involves, dendritic branching, and fluctuations in the size of the nerve cells hippocampus, accumbens, prefrontal cortex and the ventral tegmental area [47-51] both after administration of addictive drugs and antidepressant treatments, including running, have been documented and are likely of importance to understanding of the neurobiological basis of addiction and antidepressant treatments. Since antidepressant treatments, addictive drugs and naturally rewarding behaviors, such as running, affect the levels of transcription factors, growth and trophic factors it is reasonable to assume that these proteins may have a role in mediating the structural rearrangement processes in the brain.

5. Concluding remarks

Running can be rewarding, antidepressive and can increase neurogenesis/cell proliferation in hippocampus in rodents. In this paper we have reviewed work on adaptive effects of running and compared it to the effects of addictive drugs and antidepressant treatments. In animal studies running causes neurochemical and morphological adaptations in brain reward pathways and hippocampus that also are shared by addictive drugs. As running has beneficial effects in treatment of depression a better understanding of its neurochemical and morphological effects

in the brain could constitute a basis for developing novel treatments for depression and drug addiction.

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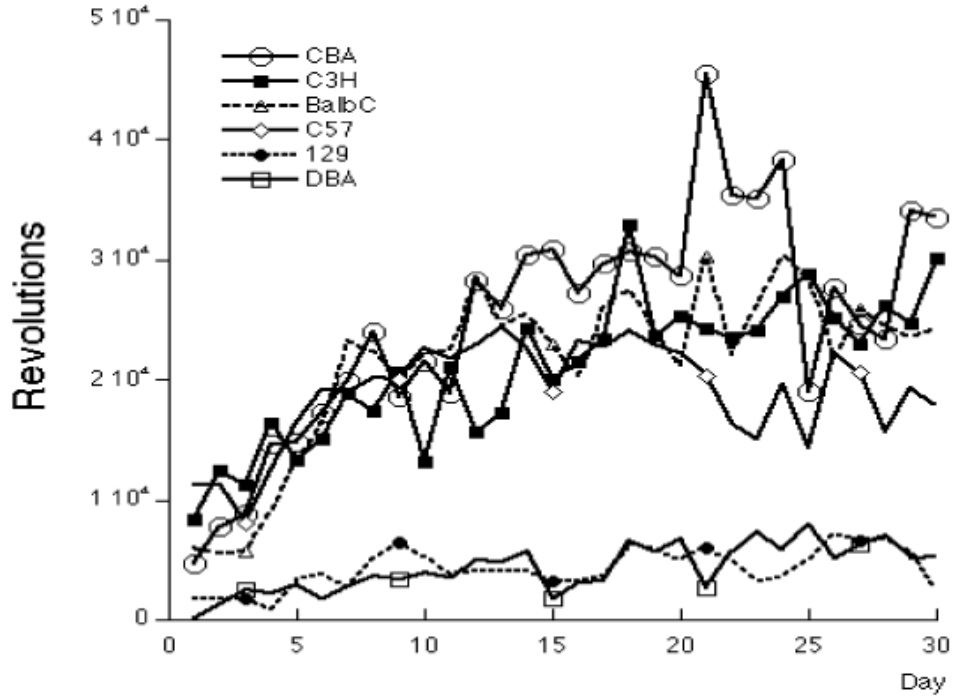

Fig 1.

Wheel running in six inbred mouse strains. The mice were single housed in cages containing a running wheel with a diameter of 12,4 cm. Note the gradual increase in daily running activity in the CBA, C3H/He, Balb/c, C57BL/6 strains that stabilized on a high level around day 15 and the lower running in the DBA/2 and 129/SV strains.

Table 1

Behavioral phenotypes in genetically modified animals

	Wheel running	**Drug self administration**
Overexpression of □FosB in dynorphin cells in striatum/accumbens	Increase	Increase
Nurr1 heterozygous animals	Decrease	Decrease

Table 2

Treatment effects on cellproliferation/neurogenesis and NPY levels in hippocampus

	Voluntary running	Moderate ethanol consumption	Antidepressant treatment
Neurogenesis/cellproliferation	Increase	Increase	Increase
NPY	Increase		Increase