CHAPTER FIFTEEN

Dehydroepiandrosterone and Addiction

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Abstract

Drug addiction has a great negative influence on society, both social and economic burden. It was widely thought that addicts could choose to stop using drugs if only they had some self-control and principles. Nowadays, science has changed this view, defining drug addiction as a complex brain disease that affects behavior in many ways, both biological and psychological. Currently there is no ground-breaking reliable treatment for drug addiction. For more than a decade we are researching an alternative approach for intervention with drug craving and relapse to its usage, using DHEA, a well-being

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and antiaging food supplement. In this chapter we navigate through the significant therapeutic effect of DHEA on the brain circuits that control addiction and on behavioral performance both in animal models and addicts. We suggest that an integrative program of add-on DHEA treatment may further enable to dynamically evaluate the progress of rehabilitation of an individual patient, in a comprehensive assessment. Such a program may boost and support the detoxification and rehabilitation process, and help patients regain a normal life in a shorter amount of time.

1. INTRODUCTION

Drug addiction has a great influence on society. In the United States alone, the annual societal cost of substance use disorders (SUDs) amounts to about $740 billion in medical care spending and productivity losses, and SUDs are listed among the top 10 nongenetic causes of death globally (McCollister et al., 2017). Drug addiction is also a growing social and psychological problem (Buchanan, 2006; Substance Abuse and Mental Health Services Administration (US) & Office of the Surgeon General (US), 2016). For many years, society considered drug addicts to be people with weak willpower. It was widely thought that addicts could choose to stop using drugs if only they had some self-control and principles. Nowadays, science has changed this view, defining drug addiction as a complex brain disease that affects behavior in many ways, both biological and environmental.

1.1 The Complexity of Drug Addiction

Drug addiction is a complex disease, involving mind and body as in other mental disorders. It is characterized by compulsive drug seeking and intense drug craving, against which the person cannot resist, even in the face of a dire outcome. Drug addiction is considered to be a "relapsing" disease, since an addict may return to drugs even after prolonged abstinence. Drug relapse indicates that it is difficult to treat drug addicts because of the many long-lasting and permanent changes that occur in the brain while using drugs. It seems that addiction is initially a dopamine (DA)-dependent disorder, in which the positive reward provided by the drug is mediated through activation of the mesolimbic DA system (Di Chiara, 1999). This system comprises DA neurons with cell bodies in the ventral tegmental area (VTA) of the midbrain and projection areas of these neurons in the limbic forebrain and in particular, the nucleus accumbens (NAc). This VTA–NAc circuit is a key detector of the reward stimulus; drug-induced changes in these regions may modulate sensitivity to the reward of drug exposure

(Self & Choi, 2004). In addition, other relevant brain regions have been studied, including the hippocampus, which is crucial for the memory of the context of drug exposure and withdrawal, and the hypothalamus, which is important in mediating effects of drugs on the body's physiological state. In addition, current studies indicate that the "cognitive arm" is weakened; this is crucial for drug relapse. The frontal regions of the cerebral cortex, which provide executive control over drug use, are often severely deregulated in addicts. Neurons in the striatum play a role in the expectation and detection of reward. These regions do not function separately, but are part of a complex and highly integrated circuit network that is profoundly altered as a result of chronic exposure to drugs (Chao & Nestler, 2004; Martin-Soelch et al., 2001; Nestler & Malenka, 2004). In recent years, researchers have looked for new mechanisms and factors that interfere with addiction. For example, microRNAs are epigenetic regulators of gene expressions that may play a role in reprogramming of the brain, which in turn leads to the motivational effects of addictive drugs (Kenny, 2014; Smith & Kenny, 2017). In addition, the β-endorphin and enkephalin systems are associated with cocaine-induced behavioral sensitization (Dikshtein et al., 2013; Mongi-Bragato et al., 2016). Even gut bacteria (microbiome) may be involved in drug addiction (Kiraly et al., 2016). Based on previous studies, there is strong evidence that bacteria may respond directly to stress-related host signals, vice versa (Lyte, Vulchanova, & Brown, 2011). Bercik showed that strain-specific anxiety-like behaviors could be transposed simply by transplanting the microbiome between strains of mice (Bercik et al., 2011). In addition, Burokas demonstrated that chronic prebiotic treatment exhibited both antidepressant and anxiolytic effects in stressed mice (Burokas et al., 2016). Moreover, it has been known for many years that stress and depression may be risk factors for the development of addiction. Both are often comorbid with addiction (Polter & Kauer, 2014). A piece of the puzzle that is currently garnering much attention and is shifting the research focus is reward-related learning, since memorizing substance-associated cues is the most powerful cause of relapse (Massart et al., 2015) (Fig. 1).

1.2 Addiction and Stress

All of the above presents a complex picture of "addiction disease" that is associated by response to stress. Consuming a substance of abuse is often a stressful event. Nonetheless, additional external stress can cause recurrence of drug usage. In other words, stress can be a meaningful moderator of the

Fig. 1 DHEA integration with the Addiction Puzzle.

addictive process (see "Stress psychobiology in the context of addiction medicine: from drugs of abuse to behavioral addictions," 2016). Koob et al. describe addiction as a three-stage cycle binge/intoxication, withdrawal/negative effect, and preoccupation/anticipation that worsens over time and involves allostatic changes in hedonic function via changes in the brain reward and stress systems (Kwako & Koob, 2017). They claim that the negative emotional state that drives negative reinforcement derives from dysregulation of key neurochemical elements involved in the brain stress systems within the frontal cortex, NAc, and extended amygdala (Koob et al., 2014). These brain elements include a variety of neurochemical factors: corticotropin-releasing factor, opioids, norepinephrine, vasopressin, hypocretin, and substance P. Thus, brain stress-response systems are hypothesized to be activated by acute excessive drug intake, sensitized during repeated withdrawal, and to persist into protracted abstinence, contributing to the development and persistence of addiction.

Drug addiction is treatable but not fully curable (McLellan, Lewis, O'Brien, & Kleber, 2000). Scientists agree that the most effective treatment often combines medications with behavioral therapies. Treatment can manage withdrawal symptoms, prevent relapse, and treat cooccurring conditions. However, it is likely that reverting to drug use will be unavoidable. Hence, preclinical and clinical researchers should continue to develop new safe and effective treatments for SUD. In this chapter, we advocate DHEA as a conceivable novel treatment for drug abuse.

1.3 Addiction and DHEA

DHEA is a steroid produced in the gonads and in the adrenal gland. In addition it is produced in the brain and acts as a neurotransmitter, hence, it can be defined as a "neurosteroid" (Shah, Chin, Schmidt, & Soma, 2011). DHEA is currently used in Western countries as a food supplement. It has antiaging and antidepressant properties, and contributes to increasing motivation and a general well-being (Huerta-García, Montiél-Dávalos, Alfaro-Moreno, Gutiérrez-Iglesias, & López-Marure, 2013).

Studies indicate that DHEA administration improves memory and cognitive processing (Huerta-García et al., 2013), induces neurogenesis and neural survival, and attenuates levels of the stress hormone cortisol (Ulmann et al., 2009; Yadid, Sudai, Maayan, Gispan, & Weizman, 2010). In healthy men and women, DHEA has been shown to induce relaxation and a higher capability of handling stressful situations (Ulmann et al., 2009).

In a research monograph written by Wilkins et al. at the end of the previous millennium (1996), the authors suggested that plasma levels of DHEA sulfate (DHEAS) may be used to discriminate between treatment outcomes in groups of cocaine addicts (Wilkins et al., 2005). They found that those who had high basal levels of DHEAS remained abstinent following treatment for cocaine dependence/detoxification. Later, Buydens-Branchey et al. compared levels of cortisol and DHEA in cocaine addicts during abstinence (Buydens-Branchey, Branchey, Hudson, & Dorota Majewska, 2002). They demonstrated that levels of cortisol were highest on day 6 of abstinence and then subsequently decreased. DHEAS levels were low on day 6 and highest on day 18 of abstinence. Analyses revealed a significant effect of frequency of use of the drug. More sustained cocaine use was associated with higher cortisol levels and less pronounced cortisol decline after discontinuation of cocaine use, but drug intake variables had no influence on DHEAS levels. During cocaine abstinence, cortisol levels declined more noticeably, whereas DHEAS/cortisol ratios rose more dramatically in aggressive vs

nonaggressive addicts. Other studies (Wilkins et al., 2005) identified each of the patient outcome groups by levels of circulating DHEAS and distressed mood at treatment entry. Results showed that cocaine addicts with high circulatory DHEAS levels relapsed less to cocaine abuse after 3 weeks of nonpharmacological treatment, during a 6-month follow-up. The authors suggested that in abstaining patients, distressed mood during withdrawal may have been mitigated through antidepressant-like actions of enhanced endogenous DHEAS activity (Brzoza et al., 2008; Genud et al., 2009; Wolkowitz & Reus, 2003), thus contributing to continuing abstinence and treatment retention. Patients with high levels of distressed mood at treatment entry and low DHEAS levels may express higher susceptibility to leaving the rehabilitation or may more easily relapse. Hence, correlation between endogenous DHEA levels and treatment outcome of addicts suggests the possibility that patients may benefit from adjunctive pharmacotherapy with DHEA.

1.4 A New Horizon: Screening for Potential Treatments

1.4.1 An Immediate Need for Antiaddictive Treatment

Addiction to drugs is still unanswered by the pharmaceutical industry. Treatment of the urge to use drugs and relapse is considered extremely difficult, especially with regard to cocaine, which is a highly dangerous and aggressive drug of abuse. For over 30 years, no effective remedy has been found nor has any innovative treatment been offered to cocaine addicts. So far, the treatment offered is mainly psychological, provided in rehab villages. The only pharmacological treatment currently offered around the world in order to try and support addicts is the controlled, clinical administration of substitute drugs. In other words, the common therapeutic approach is detoxification followed by offering an alternative substance that replaces the addictive substance, such as Subutex and Adolan (Tomkins & Sellers, 2001). However, the addict may develop dependence to this replacement. A safer but longer rehabilitation program uses psychological and behavioral treatment in an enriched environment, such as that provided in rehab centers (McLellan & Weisner, 1996).

1.4.2 Use of Animal Models for Testing New Medications

Two main animal models are used for studying addiction. The first model is conditioned place preference (CPP), in which substance injections are paired with sensorially distinguished compartments of an apparatus, so that the animal can associate the drug-induced changes it experiences with environmental cues provided by the apparatus (Aguilar, Rodríguez-Arias, & Miñarro, 2009; Mucha, Van Der Kooy, O'Shaughnessy, & Bucenieks,

1982). Another animal model is self-administration, in which animals are trained to press a lever, thereby self-administering substances of abuse. Animals thus become substance-dependent, developing behavioral, and neurological changes that simulate human addiction (for review, see Haney, 2009; Panlilio & Goldberg, 2007). Clinical and laboratory observations suggest that addiction represents the pathological usurpation of neural processes that normally serve reward-related learning. This process results in brain plasticity that is hypothesized to be driven by the emotional stress-inducing capacity of the drug.

2. DHEA TREATMENT FOR SUBSTANCES OF ABUSE

For over a decade, treatment of drug addiction with DHEA has been examined, with ground-breaking insights. This ongoing research, although reaching the clinic, is based on work with animal models. The effect of DHEA has been examined in terms of behavior in the various stages of addiction: acquisition (initiation), maintenance, extinction, and reinstatement (relapse). The added value of animal studies is the finding of biological and structural effects of DHEA treatment.

2.1 Effect of DHEA Treatment on Acquisition of Substance Dependence

In a study investigating the influence of high levels of brain DHEA on the acquisition of cocaine intake in rats, the authors showed that DHEA pretreatment and with the concomitant use cocaine, attenuated cocaine-seeking behavior, and elevated the levels of dopamine and serotonin in several brain regions relevant to cocaine addiction (Maayan et al., 2006).

Chronic cocaine self-administration induced elevations in brain DHEA, its sulfate ester, DHEAS, and pregnenolone. The increased brain DHEA following cocaine self-administration may serve as a compensatory protective mechanism geared to attenuating the craving for cocaine. Such anticraving activity is further enhanced by DHEA treatment before and during cocaine self-administration, accompanied by normalization of DHEA levels in the brain (Maayan et al., 2006).

DHEA may be involved in one or more of these phases by affecting different neural mechanisms such as the hypothalamic–pituitary–adrenal axis, the activity of glutamate receptors (Glu-R; both NMDA and non-NMDA as AMPA/kainate), nicotinic receptor, sigma-1 receptor (σ1R), in addition to the enhancement of DA release.

Cocaine simultaneously affects mood and the neuroendocrine hormones such as adrenocorticotropic hormone (ACTH) and corticosterone (CORT) (Levy et al., 1991; Mendelson et al., 2002; Moldow & Fischman, 1987; Saphier, Welch, Farrar, & Goeders, 1993). Goeders (1997) claimed that CORT is necessary during acquisition, and that substance self-administration does not occur unless this stress-related hormone is increased above the threshold critical for reward. Drugs blocking central corticotropin-releasing hormone (CRH) receptors or decreasing ACTH and CORT can attenuate self-administration (Goeders, 1997, 2002a, 2002b). In addition, other clinical and preclinical studies link stress to drug dependence since stress is accompanied by the release of neuroactive hormones which activate brain circuitries similar to psychostimulants such as cocaine (Majewska, 2002). Studies using several strains of rats showed that stress and elevated glucocorticoid increased acquisition and maintenance of psychostimulant use (Goeders, 1997; Piazza & Le Moal, 1998; Piazza et al., 1991). It was also reported that extrahypothalamic brain CRH systems may be involved in behavioral and physiological manifestations of drug-seeking behavior induced by environmental stressors (Sarnyai, Shaham, & Heinrichs, 2001). DHEA treatment caused a decrease in both CORT and ACTH levels at similar doses (Maayan et al., 2006, 2005). Such a decrease may explain, at least in part, the attenuation in cocaine-seeking behavior.

However, new findings indicate that the CORT level is directly related to DHEA attenuation of drug-seeking behavior, and that other mechanisms may exist. In addition, recent work (Guerin, Schmoutz, & Goeders, 2014) showed that adrenalectomy did not significantly affect the maintenance phase of cocaine self-administration. Since an earlier study found that adrenalectomy blunted the acquisition of cocaine self-administration (Goeders & Guerin, 1996), CORT levels may exert greater influence on drug self-administration during the acquisition phase than during the maintenance phase.

An additional mechanism to explain DHEA effect on substance-seeking behavior is the interrelationship of σ1R, DHEA, and reward. σ1R is localized in the endoplasmic reticulum and is used as a chaperone for diverse proteins including IP3R, BiP, K+ channel subunit, and RAC1 (Aydar, Palmer, Klyachko, & Jackson, 2002; Hayashi & Su, 2001). Direct interaction between σ1R and other proteins is important for σ1R cell function (Hayashi & Su, 2007). Studies found that cocaine binds to σ1R receptors with high affinity (Chen, Hajipour, Sievert, Arbabian, & Ruoho, 2007); hence, the σ1R receptor may be essential to substance addiction treatment (Miyatake, Furukawa, Matsushita, Higuchi, & Suwaki, 2004; Stefanski et al., 2004; Ujike, Kanzaki, Okumura, Akiyama, & Otsuki, 1992;

Ujike, Kuroda, & Otsuki, 1996). σ1R selective antagonists, when given simultaneously with cocaine, decrease the effect of locomotion caused by cocaine and can prevent cocaine addiction (Ujike et al., 1996). On the other hand, treatment with dehydroepiandrosterone (DHEA), a σ1R receptor agonist, albeit chronically, attenuates cocaine self-administration and relapse to cocaine-seeking behavior in rats (Doron, Fridman, Gispan-Herman, et al., 2006). Additionally, σ1R agonists protect from nerve damage (Nguyen et al., 2015). It remains to be determined whether agonists or antagonists are the better choice for treatment. Exposure to cocaine causes σ1R gene expression changes in the nucleus accumbens (NAc), a region associated with reward and addictive disorders (Liu & Matsumoto, 2008). The above evidence suggests the σ1R receptor as a target for treating cocaine addiction (Matsumoto, Liu, Lerner, Howard, & Brackett, 2003; Maurice et al., 2002).

Although it was originally thought that the sigma receptor was a subtype of the opioid receptor, it is now clear that both σ1R and σ2R are unique brain proteins. σ1R regulates glutamate NMDAR function and the release of neurotransmitters such as DA, and thus may be involved in neuropsychiatric disorders and reward (Hayashi & Su, 2003; Su & Hayashi, 2003). σ1R is critically involved in the rewarding effect of cocaine as measured in the CPP procedure in mice (Romieu, Martin-Fardon, Bowen, & Maurice, 2003), and σ1R agonist pretreatment facilitated cocaine self-administration (Hiranita, Soto, Tanda, & Katz, 2010). Sutton et al. found that rats repeatedly exposed to cocaine develop glutamate deficits in the NAc (Sutton et al., 2003). DHEAS, which promotes presynaptic glutamate release in the prelimbic cortex via activation of σ1R (Dong et al., 2007), may alleviate drug-seeking behavior.

Short- and long-term memory should be considered as another process involved in drug-seeking behavior beyond reward and stress. An alternative neuronal system affected by DHEA is the NMDA- and AMPA-glutaminergic system—which is involved in learning and memory.

DHEA is a positive modulator of the NMDA-R (Dubrovsky, 2005; Mellon & Griffin, 2002a, 2002b; Rupprecht & Holsboer, 1999) and may attenuate cocaine-induced effects by enhancing glutamate activity. A decrease in brain extracellular glutamate was obtained during the extinction from drug usage and was suggested to contribute to the susceptibility to relapse (Baker et al., 2003). DHEA may enable acquisition of new memories dissociating drug from the cue. Glutamatergic activity is connected to decision-making and working memory processes (Finn, 2002). Hence, DHEA may produce an inhibitory cognitive control in present of incentives and attenuate relapse to drug usage.

In addition, AMPA-R antagonists attenuate behavioral sensitization and self-administration in mice (Jackson, Mead, Rocha, & Stephens, 1998; Reeves, Thiruchelvam, & Cory-Slechta, 2004), and PREG sulfate acts as an AMPA-R negative modulator (Dubrovsky, 2005). Therefore, one may assume that DHEAS (partially converted from DHEA) acts similarly. This is supported by Kimonides et al. (1998), who found that DHEAS attenuates AMPA and kainate neurotoxicity in hippocampal neurons (Kimonides, Khatibi, Svendsen, Sofroniew, & Herbert, 1998). It is possible that as an antagonist of the AMPA-R, DHEAS may also attenuate cocaine self-administration and contribute to the glutamate homeostasis suggested by Kalivas (2009).

The rewarding effect of cocaine which promotes its reinforcement is mediated by the blockade of the presynaptic DA transporter, thus increasing transient DA activity in the mesolimbic or mesocortical DA reward system. DHEA caused an increase in the content of DA and 5-HT and their metabolites in the VTA and NAc following chronic cocaine intake. It is possible that such an increase in DA homeostasis may attenuate the need for cocaine intake and cocaine seeking-behavior (Maayan et al., 2006).

In one study (Maayan et al., 2006), rats initiated cocaine self-administration already with high basal levels of both peripheral and brain DHEA, which was achieved by pretreatment followed by continuous concomitant treatment with DHEA. This prevented drug consumption and drug seeking (see Fig. 2). Thus, it can be assumed that timing is a crucial factor in the anticraving effect of DHEA. Subjects with high basal DHEA may be less prone to developed drug addiction. This observation is supported by Reddy and Kulkarni (1997a, 1997b) who showed that DHEA treatment prevented the development of tolerance to benzodiazepines (BZ) in mice. In addition, DHEAS treatment prevents the development of morphine tolerance and attenuates abstinent behavior in mice (Reddy & Kulkarni, 1997a, 1997b; Ren, Noda, Mamiya, Nagai, & Nabeshima, 2004). Assuming that overlapping mechanisms are involved in brain response to different substances of abuse, these studies may support each other, since DHEA is converted partially to DHEAS both peripherally and in the brain by sulfatransferase (Maayan et al., 2006, 2005). The authors emphasize that control and DHEA-treated rats displayed similar levels of lever-pressing for water reinforcement during the maintenance phase of water self-administration, verifying that DHEA treatment specifically disrupted lever-pressing for cocaine reinforcement and not by impairment of physical performance.

Rats showed no interest in pressing the active lever even when the dose of infused cocaine was nullified; supporting the assumption that DHEA

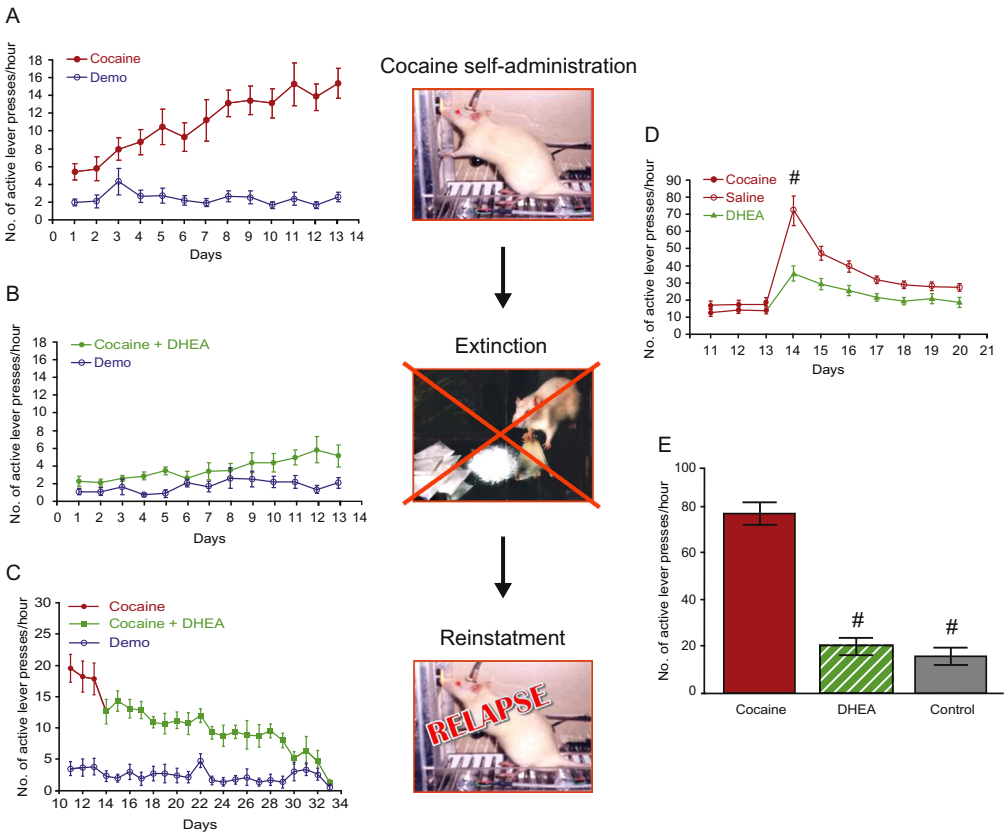

Fig. 2 See legend on next page.

probably has an anticraving effect and not a potentiating one. One cannot exclude the possibility that DHEA on its own may be a substitute to cocaine though no such effect has been found in the CPP model (Romieu et al., 2003). Consequently, this attenuation in cocaine-seeking behavior by DHEA may be explained either by it having an anticraving effect (the rats show no interest in cocaine) or by it potentiating the effect of cocaine (need for lower doses of cocaine in order to get the same reinforcement). However, a descending phase of the dose response proved that DHEA treatment did not overpotentiate activation of lever presses when cocaine infusion was decreased or withheld (Maayan et al., 2006).

Fig. 2 Effect of DHEA on cocaine-seeking behavior and relapse-preclinical experiments. Rats were operated and implanted with i.v. catheters. After 10 days of rehabilitation they were trained to self-administer cocaine (1 mg/kg) in a FR-1 paradigm. (A) An animal model for drug addiction: A typical progress of drug self-administration progress is depicted, from acquisition to maintenance, which is fully controlled by the animal. (B) Effect of DHEA on cocaine acquisition. DHEA (2 mg/kg, B) was administrated prior consecutively 5 days before training and during training, 90 min before entering the rat into the self-administration chamber. Presses on the active-, nonactive levers (demo) were recorded. A marked effect of DHEA pretreatment on drug-seeking behavior was noticed. (C) Effect of DHEA on cocaine maintenance. After rats reached stable maintenance (the figure indicate the three last days of maintenance before treatment; *red symbols*) and during DHEA (2 mg/kg) administration consecutively during maintenance (access to the drug intake was available), 90 min before entering the rat into the self-administration chamber. Presses on the active-, nonactive (demo) levers were recorded. A longitudinal decrease in cocaine self-administration is depicted. (D) Effect of DHEA on cocaine during drug extinction (washout). After rats maintained 10 days of stable drug self-administration (the figure indicate the three last days of maintenance before treatment; *red symbols*), cocaine was extinct and DHEA (2 mg/kg) was injected, 90 min before entering the rat into the self-administration chamber. Presses on the active-, nonactive (demo) levers were recorded. An immediate significant ($^{\#}P < 0.01$) decrease in cocaine craving is depicted. (E) Effect of DHEA on cocaine priming-induced reinstatement. Rats were treated with DHEA (2 mg/kg) or saline consecutively during maintenance 90 min before entering the into the self-administration chamber, when the drug was available. After reaching the abstinence criterion (pressing <10% of maintenance), rats were reinstated with 10 mg cocaine i.v. and entered the chamber without accesses to cocaine. Craving was evaluated by measuring their presses on the active lever. As shown, relapse was abolished ($^{\#}P < 0.01$) by DHEA treatment. *Panel (B) modified from Maayan, R., Lotan, S., Doron, R., Shabat-Simon, M., Gispan-Herman, I., Weizman, A., et al. (2006). Dehydroepiandrosterone (DHEA) attenuates cocaine-seeking behavior in the self-administration model in rats.* European Neuropsychopharmacology, 16*(5), 329–339. https://doi.org/10.1016/j.euroneuro.2005.10.002. Panel (C) modified from Doron, R., Fridman, L., Gispan-Herman, I., Maayan, R., Weizman, A., & Yadid, G. (2006). DHEA, a neurosteroid, decreases cocaine self-administration and reinstatement of cocaine-seeking behavior in rats.* Neuropsychopharmacology, 31*(10), 2231–6. https://doi.org/10.1038/sj.npp.1301013.*

2.2 Effect of DHEA Treatment on Maintenance of Drug-Seeking Behaviors

It has been successfully shown that chronic exposure to exogenous DHEA (2 mg/kg) attenuated cocaine self-administration and decreased the cocaine-seeking behavior of the rats to <20% of their maintenance levels (Doron, Fridman, Gispan-Herman, et al., 2006; see Fig. 2).

No surge in active lever response accompanied initiation of DHEA treatment, which would have been expected if DHEA blocked the reward effect of cocaine. This result is interesting, since most difficulties of addicts to stay on an antidrug program occur during the first weeks, when expectation for reward is highest (Self & Choi, 2004). Indeed, when higher doses of DHEA (10–20 mg/kg) were coadministered with cocaine for a short period of time (4 days), a markedly increased cocaine-induced CPP was reported (Romieu et al., 2003). Extinction of responding maintained by appetitive reward has been suggested to induce multiple stress events including activation of the hypothalamus–pituitary–adrenal axis, glucocorticoid secretion, and central β-endorphin release (Shaham, Shalev, Lu, De Wit, & Stewart, 2003; Vescovi, Coiro, Volpi, & Passeri, 1992). Hence, it was previously suggested that alleviation of distress associated with cocaine withdrawal may facilitate achieving abstinence (Self & Choi, 2004; Wilkins et al., 2005). Furthermore, during withdrawal, cocaine addicts have high plasma cortisol levels, which peak 6 days after initiation of the withdrawal and then gradually decrease (Buydens-Branchey et al., 2002). As the levels of plasma cortisol decrease, the levels of DHEAS gradually increase.

Only patients in which a spontaneous increase in DHEAS levels was observed were identified as being successful at abstaining from cocaine usage over time (Wilkins et al., 2005). Although a connection between DHEA/DHEAS, low distressed mood levels, and changes in CNS salience during withdrawal was suggested (Wilkins et al., 2005), it seems that appropriate DHEA dose is critical for relapse prevention (Shoptaw et al., 2004). The effect of exogenously applied DHEA (2 mg/kg) on cocaine-seeking behavior may be due to its conversion to DHEAS in the serum and brain (Maayan et al., 2006, 2005), in addition to increases of other bioactive neurosteroids (Dubrovsky, 2005). These neurosteroids may interact with various neurosystems involved in mood and drug-seeking behaviors, such as glutamatergic, GABAergic, and dopaminergic systems. Since DHEA can function as an antidepressant in both animals and humans (Maayan et al., 2006, 2005; Wolkowitz et al., 1997), it may lower the depression/distress involved with

cocaine withdrawal (Self & Choi, 2004), similar to the β-endorphin-induced lowering of frustration during extinction (Roth-Deri et al., 2004, 2003).

An additional possible mechanism for the DHEA-induced attenuation of the maintenance of cocaine-seeking behavior suggests the involvement of σ1R. Based on data indicating that DHEA acts as an agonist of these receptors (Maurice et al., 1999), it is possible that long administration of cocaine downregulates σ1R and DHEA acts in a compensatory neuroadaptation mechanism that leads to attenuation of cocaine-seeking behavior (Ben-Ami, Kinor, Perelman, & Yadid, 2006).

2.3 Effect of DHEA on Extinction of Drug-Seeking Behaviors

In order to learn more about the effect of DHEA on the extinction phase after cocaine self-administration, an experiment was conducted in which two groups of rats were trained to self-administer cocaine until stable maintenance levels were attained. On the following days, rats were exposed to cocaine extinction in order to assess their craving to the drug. The conditions during the extinction phase were the same as during training with the exception that the cocaine syringes were removed, and that rats were injected either with DHEA (2 mg/kg i.p.) or with saline as a vehicle (same volume) 90 min prior to placement in the operant chambers.

Results showed (Fig. 2) that saline-treated rats pressed on the active lever significantly more on the first day of extinction. Moreover, the rate of return to baseline (maintenance) during the extinction period was different. DHEA-treated rats returned to baseline from day 2 forward, whereas saline-treated rats never returned to baseline behavior.

The most significant and important effect of DHEA treatment during drug washout was in the long term. After a total of 34 days since last exposure to cocaine (27 days from the end of treatment), rats received a priming injection of cocaine before being placed in the self-administration chambers. Active lever responses, reinforcements, and inactive lever responses were recorded. In the relapse test, number of active lever responses was significantly lower in the DHEA-treated group compared to saline-treated group (Fig. 2).

Since the influence of DHEA treatment is much longer than just the short term immediately after treatment (Doron, Fridman, Gispan-Herman, et al., 2006), the authors tested its influence on the dentate gyrus in the hippocampus.

A main factor in brain plasticity is neurogenesis. Neurogenesis is the process by which new neurons are created from progenitor cells. Adult neurogenesis is restricted mainly to two areas of the central nervous system: the subventricular zone and the subgranular zone of the dentate gyrus in the hippocampus.

High-dose cocaine intake (1.5 mg/kg) significantly reduces proliferation and neurogenesis levels (Sudai et al., 2011), in the hippocampus of adult rat. Significantly more newly formed cells (BrdU+) were found 24 h after the end of treatment in the dentate gyrus of cocaine self-administrated rats treated with DHEA than in cocaine self-administrated rats treated with saline (data not published).

A month later, the number of new cells that eventually survived and became adult neurons was assessed and proved that DHEA repaired the decrease in neurogenesis as a result of cocaine consumption.

Not all of the new cells observed during proliferation eventually turn into neurons. Significant numbers of the new progenitor cells in the dentate gyrus turn into glia cells. The possible involvement of astrogliosis in addiction is intriguing and has been suggested in some other neurodegenerative diseases (Colangelo, Alberghina, & Papa, 2014).

Regarding stress, circulating CORT secretion is increased during cocaine withdrawal (Erb, Shaham, & Stewart, 1998; Goeders & Clampitt, 2002; Mantsch et al., 2008; Shalev, Marinelli, Baumann, Piazza, & Shaham, 2003). DHEA given only throughout extinction, although having no effect on CORT levels, significantly attenuated cocaine-seeking behavior.

2.4 Effect of DHEA Treatment on Reinstatement to Drug-Seeking Behaviors

There is very little literature on neuroactive steroids and drug reinstatement. Nie and Janak (2003) trained rats to press levers for 0.1 mL of 10% ethanol or 5% sucrose solutions. Response was then extinguished, and subjects were tested for reinstatement of lever-press response (Nie & Janak, 2003). Allopregnanolone promoted response for ethanol, but not sucrose, following a period of abstinence, suggesting that GABA-A receptor modulation may contribute to processes involved in reinstatement of ethanol-seeking behavior. Another study reported that progesterone, and to a greater extent allopregnanolone, decreased cocaine-primed reinstatement in females, while having no effect on cocaine-primed reinstatement in males (Anker, Holtz, Zlebnik, & Carroll, 2009).

The effect of DHEA on cocaine-induced reinstatement of drug seeking in rats exposed to withdrawal conditions was also examined. Rats receiving DHEA (2 mg/kg) daily showed a minimal response to acute priming with cocaine. This may suggest that DHEA can protect against relapse to cocaine usage following reexposure to the drug (Doron, Fridman, Gispan-Herman, et al., 2006).

Substance dependence is accompanied by usurpation of natural memory mechanisms resulting in long-lasting memories of the drug experience (Geier & Luna, 2009; Kauer & Malenka, 2007; Koob, 2009; Peters, Kalivas, & Quirk, 2009; Wang, 2008). Elevating endogenous glutamate or glutamate receptors reduces the propensity for relapse (Baker et al., 2003; Sutton et al., 2003). Therefore, the consequence of increasing glutamate activity may be eradication of memories associated with substance reward-related learning and gaining of new memories linked to drug extinction. If glutamate activity is increased by DHEA in the addicted brain, it may help drug extinction and attenuate relapse and may be in accordance with the glutamate homeostasis suggested by Kalivas (2009).

In addition, Sutton et al. (2003) found that increasing the GluR1 subunit of AMPA receptors in the NAc may promote extinction of cocaine seeking (Sutton et al., 2003). AMPA-R antagonists attenuate behavioral sensitization and self-administration in mice (Jackson et al., 1998; Reeves et al., 2004). The neurosteroid sulfate, PREG-S, acts as an AMPA-R negative modulator (Dubrovsky, 2005). Therefore, one may assume that DHEAS acts similarly. For reinstatement, it was found that CORT plays a role in stress-induced, cue-induced, environmental cue-induced, and food deprivation-induced reinstatement, whereas it has only a partial role in cocaine-induced reinstatement (Erb et al., 1998; Goeders & Clampitt, 2002; Mantsch et al., 2008; Shalev et al., 2003).

2.5 DHEA Affects Addiction Beyond Attenuating Stress

It was demonstrated above that DHEA treatment attenuates cocaine acquisition, extinction, and reinstatement (Doron, Fridman, Gispan-Herman, et al., 2006; Maayan et al., 2006; Yadid, Redlus, Barnea, & Doron, 2012). But the question is whether this effect is caused indirectly, through decreasing CORT levels (Maayan et al., 2005), or by DHEA itself.

Research has shown that rats treated with DHEA or simultaneous DHEA and CORT showed a significantly lower response to cocaine compared to control rats throughout all phases of the study: acquisition,

maintenance, extinction, and reinstatement. However, the plasma level of CORT in DHEA-treated rats was low, whereas its level in DHEA- and CORT-treated rats was maintained at control levels. It was previously shown that a persistent decrease in brain DHEA levels may be associated with the decreased ability to cope with mood fluctuations and stress that accompany heightened drug craving (Yadid et al., 2012; Yadid, Sudai, Maayan, Gispan, & Weizman, 2010). DHEA may lower the distress associated with cocaine withdrawal (Self & Choi, 2004), similar to the β-endorphin-induced decrease in frustration during extinction (Roth-Deri et al., 2004, 2003). Thus, exogenous, long-term administration of DHEA may also have a beneficial effect on stress and anxiety, which increase particularly during heightened drug craving at extinction and reinstatement (Yadid et al., 2012, 2010). This may contribute to the attenuating effect of DHEA on cocaine-seeking behavior.

DHEA treatment attenuated cocaine self-administration and cocaine seeking even when CORT levels were constantly maintained in the normal range. Therefore, the effect of DHEA on cocaine intake and seeking is likely independent of fluctuations in CORT levels. Moreover, DHEA attenuated self-administration when given as pretreatment, at extinction or at reinstatement, emphasizing its potential as an effective anticraving agent.

3. DHEA IN CLINICAL TRIALS

3.1 DHEA as a Treatment for Mental Disorders

There are many manuscripts on psychiatric disorders, such as depression and anxiety that are comorbid with addiction. DHEA and its sulfated metabolite generated curiosity among researchers of psychiatry disorders as early as the 1990s. Wolkowitz and colleagues reported that DHEA may have antidepressant and promemory effects after they delivered it to six elderly patients with major depression (Wolkowitz et al., 1997). They also initiated a double-blind placebo study to test the efficacy of DHEA (Wolkowitz et al., 1999). They found that half of the DHEA-treated patients showed a 50% decrease in depressive symptoms. Most of them were resistant to treatment with traditional antidepressant medication alone. In 2006, a randomized, double-blind controlled study evaluated the effect of DHEA (200 mg/day) on schizophrenia symptoms (Ritsner, Gibel, Ratner, Tsinovoy, & Strous, 2006). The results showed no significant improvement in clinical symptoms. There was, however, an improvement in positive and negative symptom scale ratings compared with baseline

and in cognitive functions of visual sustained attention and visual and movement skills compared with placebo conditions. In another study, 100 mg/day DHEA were sufficient to improve extrapyramidal symptoms in patients with schizophrenia (Nachshoni et al., 2005). DHEA was also tested in Alzheimer disease (Wolkowitz et al., 2003). Although it did not significantly improve cognitive performance, the authors suggested that the study was underpowered and DHEA should be tested in larger-scale and longer-term studies. The common denominator of most of these cases is that the levels of DHEA and DHEAS decrease over time in these diseases. Additionally, in human drug addicts, levels of these hormones were found to decrease during abstinence. These findings suggest that increased circulating DHEAS levels may be of benefit in these diseases, as well as in drug addiction.

3.2 Using DHEA as a Treatment for Detoxification of Polydrug Users

There are many clinical studies that assess the involvement of DHEA and its sulfate form (DHEAS) in SUD (see Section 1.3). However, only a few of them examine the effect of DHEA as a treatment for SUD. In a double-blind controlled study Maayan et al. (2008) reported that providing DHEA to heroin addicts as an add-on compound to their routine medication protocol was mostly effective (60% of treated subjects) in patients who had not previously used either cocaine or BZ and who had experienced only a few withdrawal programs (Maayan et al., 2008; see Fig. 3). In another placebo-controlled pilot, Shoptaw et al. (2004) suggested that DHEA treatment resulted in worse treatment outcome in cocaine addicts (Shoptaw et al., 2004). Therefore, more clinical trials should be carried out to test the efficacy of DHEA as a treatment for addiction detoxification.

3.3 Effect of DHEA Add-on Therapy on Rehabilitation of Polydrug Users

In view of these previous clinical and preclinical findings, whether DHEA will prove to have efficacy as an adjunctive treatment in drug users must be further examined. Consequently, Yadid's laboratory proposed a double-blind, placebo-controlled study to test the long-term effect of DHEA on addiction indices that succeeded to improve decision-making and lower relapse rates significantly (Ohana et al., 2016; see also Fig. 3). As mentioned in Section 1.3, levels of DHEA and DHEAS were found to decrease during abstinence in human drug addicts (Buydens-Branchey et al., 2002; Wilkins et al., 2005), and this decrease was found to predict later drug reuse

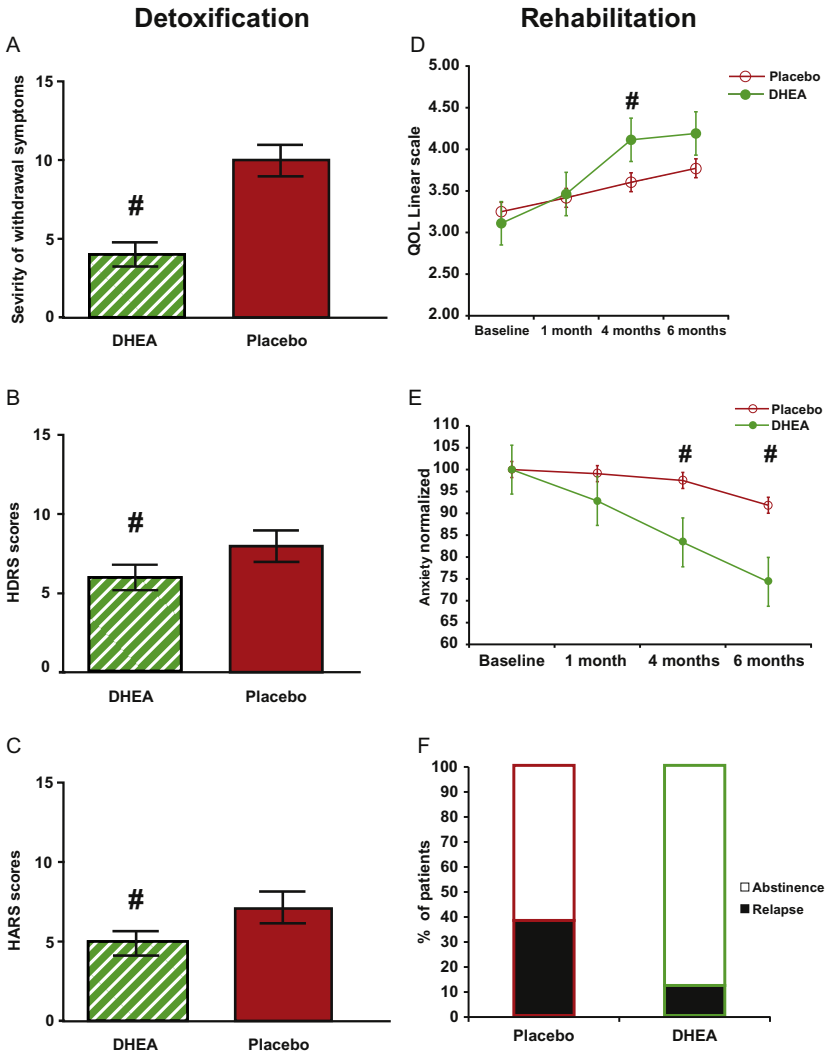

Fig. 3 Effect of DHEA on cocaine-seeking behavior and relapse-clinical trials. Treatment in a Detoxification center: DHEA effect as a complementary treatment was evaluated in opiate addicts undergoing detoxification. DHEA (100 mg/day) or placebo was added as a to the routine medication protocol in a randomized, double-blind controlled study. Severity of withdrawal symptoms (A), depression (B), and anxiety (C) scores were measured as a follow-up for 12 months. $^{\#}P < 0.05$ indicate statistically significant. *HARS*, Hamilton anxiety scores; *HDRS*, Hamilton depression scores. Treatment in a rehabilitation center: A double-blind, placebo-controlled study examined the effect of DHEA in adult polydrug users taking part in a detoxification program enriched with intensive

(Continued)

(Wilkins et al., 2005). This has led to the suggestion that increased circulating DHEAS levels may enhance brain resiliency during withdrawal by lowering the distressed mood levels of addicts (Doron, Fridman, Gispan-Herman, et al., 2006; Doron, Fridman, & Yadid, 2006; Wilkins et al., 2005). In research conducted by Ohana et al., participants (79% males, mean age 28) consumed DHEA (100 mg/day) or placebo daily for at least 30 days during their routine treatment. Of the 121 initial volunteers, 64 participated (34 placebo, 30 DHEA) for at least 1 month. The initial evaluation meeting with the participants consisted of two sessions in which they provided demographic details, performed psychological tests, and gave blood samples. In addition, further assessments involving psychological testing and blood samples were collected after 1, 4.5, and 6 months (study termination). They found that DHEA treatment resulted in an increase in DHEAS 1 month following treatment, and the level of DHEAS predicted relapse in the follow-up assessment. Additionally, based on the PANAS scale, DHEA seemed to decrease negative effect during treatment. Importantly, in a 16-month follow-up, the reuse rates in the DHEA condition were about a third compared with placebo. It seems that these results highlight the potential relevance of findings in animal studies of DHEA to recovery following addiction of human addicts. The current findings offer early confirmation of the potential long-term effect of DHEA on drug reuse.

4. EPILOG

The essence of this chapter is to suggest the use of dehydroepiandrosterone (DHEA), a natural neurosteroid shown to prevent relapse to drug use. *DHEA add-on treatment* is an innovative and highly effective intervention, which increases the percentage of rehabilitated addicts, more rapidly and for prolonged periods of time. Hence, we propose that *DHEA add-on treatment*

Fig. 3—Cont'd psychosocial interventions and aftercare. During treatment, participants consumed DHEA (100 mg/day) or placebo daily for at least 30 days. While in treatment, DHEA significantly improved quality of life (QOL; D), anxiety (E), and release rates in a 16-month follow-up about a third compared to placebo (F). $^{\#}P < 0.01$ indicate significance between treatment groups. *Modified from Maayan, R., Touati-Werner, D., Shamir, D., Yadid, G., Friedman, A., Eisner, D., et al. (2008). The effect of DHEA complementary treatment on heroin addicts participating in a rehabilitation program: A preliminary study.* European Neuropsychopharmacology, 18*(6), 406–413.* https://doi.org/10.1016/j.euroneuro.2007.12.003.

may be seamlessly incorporated into existing rehabilitation programs, complementing, and enriching the various therapies in each center.

Drug abuse and addiction have negative consequences for individuals as well as for society as a whole. Addiction is a complex disease with high relapse rates and no reliable treatment. DHEA, together with a unique software and novel algorithms that can integrate many output parameters from the patient dynamically, may enable to evaluate the progress of rehabilitation of an individual patient, in a comprehensive assessment. Such a program may boost and support the detoxification and rehabilitation process, and help patients regain a normal life in a shorter amount of time.

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