Substance Abuse: Research and Treatment

REVIEW

Elevated Norepinephrine may be a Unifying Etiological Factor in the Abuse of a Broad Range of Substances: Alcohol, Nicotine, Marijuana, Heroin, Cocaine, and Caffeine

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Abstract: A wide range of commonly abused drugs have effects on the noradrenergic neurotransmitter system, including alterations during acute intoxication and chronic use of these drugs. It is not established, however, that individual differences in noradrenergic signaling, which may be present prior to use of drugs, predispose certain persons to substance abuse. This paper puts forth the novel hypothesis that elevated noradrenergic signaling, which may be raised largely due to genetics but also due to environmental factors, is an etiological factor in the abuse of a wide range of substances, including alcohol, nicotine, marijuana, heroin, cocaine, and caffeine. Data are reviewed for each of these drugs comprising their interaction with norepinephrine during acute intoxication, long-term use, subsequent withdrawal, and stress-induced relapse. In general, the data suggest that these drugs acutely boost noradrenergic signaling, whereas long-term use also affects this neurotransmitter system, possibly suppressing it. During acute withdrawal after chronic drug use, noradrenergic signaling tends to be elevated, consistent with the observation that norepinephrine lowering drugs such as clonidine reduce withdrawal symptoms. Since psychological stress can promote relapse of drug seeking in susceptible individuals and stress produces elevated norepinephrine release, this suggests that these drugs may be suppressing noradrenergic signaling during chronic use or instead elevating it only in reward circuits of the brain. If elevated noradrenergic signaling is an etiological factor in the abuse of a broad range of substances, then chronic use of pharmacological agents that reduce noradrenergic signaling, such as clonidine, guanfacine, lofexidine, propranolol, or prazosin, may help prevent or treat drug abuse in general.

Keywords: clonidine, guanfacine, lofexidine, desipramine, yohimbine, hypertension, psychological stress

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Introduction

Norepinephrine (NE) is an important and widespread neurotransmitter system, present in most (if not all) circuits in the brain, as well as in the sympathetic nervous system, which innervates organs throughout the body. Evidence suggests that noradrenergic signaling is altered by a number of drugs of abuse during acute intoxication (eg, Ireland et al[1]), chronic use of these substances (eg, Yamanaka et al[2]), acute withdrawal after long-term use (eg, Hawley et al[3]), and stress-induced relapse or reinstatement of drug use (eg, Clarke et al[4]). However, it is not established that individual differences in noradrenergic signaling, which may be present prior to initiation of drug use, form an etiological (ie, causative) factor in substance abuse. If NE is involved in the rewarding or hedonic aspects of drug use,[5] genetically elevated signaling (which could also be modulated by lifetime experiences) may predispose certain individuals to drug abuse by rendering these substances more rewarding to them.

This paper puts forth the novel hypothesis that elevated noradrenergic signaling, largely as a result of genetics that may be exacerbated by significant exposure to psychological stress, is an etiological factor in the abuse of a broad range of substances, including alcohol, nicotine, marijuana, heroin, cocaine, and caffeine. Since abuse of multiple types of drugs is common in a given individual and may share underlying neural mechanisms,[6–8] this hypothesis is consistent with the notion that elevated NE is a shared factor in polydrug use. These 6 drugs were chosen as the focus of this paper because they represent a broad range of substances that are frequently abused, and, for each of these drugs, there is evidence for interaction with noradrenergic signaling. This paper is not suggesting that elevated noradrenergic signaling is the only etiological factor in substance abuse, just that it may be an important one in at least some cases.

This paper briefly reviews scientific literature relating NE with abuse of the 6 substances listed above. For each of these substances, the paper focuses on 4 aspects of drug use: (1) Is noradrenergic signaling increased or decreased during acute intoxication, which could be related to the rewarding effects of drugs? (2) Does chronic use alter noradrenergic signaling, which may promote dependence? (3) Does acute withdrawal after chronic drug use modulate noradrenergic signaling? (4) Does psychological stress interact with noradrenergic signaling to promote relapse or reinstatement of drug use in susceptible persons?

A literature search of the PubMed database was performed as recently as September 21, 2013. Search terms included: (1) norepinephrine + ethanol/alcohol + acute/consumption/intake/tolerance/(withdrawal clonidine)/(stress relapse); (2) norepinephrine + nicotine + acute/(cerebrospinal fluid)/prefrontal/tolerance/withdrawal/(stress relapse); (3) norepinephrine + marijuana/THC; (4) norepinephrine + heroin; (5) norepinephrine + cocaine + acute/chronic/withdrawal/stress; (6) norepinephrine + caffeine + acute/chronic/withdrawal/stress. Less specific search terms were used for marijuana and heroin because there were fewer studies on these drugs related to norepinephrine. This is not meant to be an exhaustive review of the literature relating NE with substance abuse, but rather to present some representative studies.

Alcohol

While acute intake of alcohol has been linked with action at inhibitory gamma-aminobutyric acid (GABA) receptors and the glutamatergic N-methyl-D-aspartate (NMDA) receptor, a number of studies indicate that acute alcohol intake also affects measures of NE, which may play a role in acute intoxication produced by this drug. A study of healthy persons found that drinking alcohol caused plasma NE to rise 30 minutes later, which lasted about 4 hours and also caused an increase in erect and supine blood pressure just before the rise in NE.[9] Acute alcohol intake in persons produced an increase in plasma epinephrine and a delayed increase in NE and also increased systolic blood pressure and heart rate.[1] In contrast, a study of healthy subjects found that alcohol ingestion produced no significant changes in plasma NE 1 or 8 hours later.[10] Changes in blood pressure produced by alcohol or other drugs are relevant to our discussion because NE plays a role in regulating blood pressure.

When alcohol was acutely administered to rats, it decreased brain NE levels, and withdrawal also produced decreases in brain NE.[11] In another rat study, acute alcohol intoxication did not affect brain levels of NE, whereas continuous intoxication reduced brain NE and decreased the activity of the NE synthesizing

enzyme, dopamine beta-hydroxylase, in the hippocampus.[2] Acute administration of alcohol to mice increased plasma NE, whereas chronic drinking of alcohol over 14 days resulted in NE returning to its baseline level, and acute withdrawal produced a significant increase in plasma NE.[12] Systemic or localized administration of alcohol to the rat locus coeruleus, a major noradrenergic cell nucleus in the brainstem, produced suppression in the firing rate of cells there, which could decrease release of NE.[13]

Chronic exposure of rodents to alcohol may also have effects on the endogenous NE system, and manipulating noradrenergic signaling with pharmacological agents may affect behavioral responses to alcohol. In alcohol-dependent rats, acute treatment with alcohol increased the brain concentration of the NE metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG), and this metabolite continued to be elevated during acute withdrawal.[14] Disruption of brain catecholamine systems, which include NE, with drugs such as 6-hydroxydopamine and alpha-methyl-para-tyrosine, slowed the rate of mice developing tolerance to the hypnotic effect of alcohol.[15] Chronic alcohol administration to rats produced tolerance to the hypothermic effect of subsequent test doses of alcohol, while also modulating activity of the Na+ -K+ ATPase enzyme, which is thought to be regulated by NE.[16]

Acute withdrawal from alcohol, after chronic use or administration of this drug, may be associated with increased noradrenergic signaling. This may be ameliorated by the NE release lowering drug, clonidine. A recent review of the alcohol withdrawal literature found there is sympathetic overdrive during withdrawal, which may play a role in symptomatology. Alpha2 agonist drugs (such as clonidine) that lower noradrenergic signaling may safely and effectively reduce these symptoms.[17] In alcohol-dependent persons undergoing acute withdrawal, clonidine suppressed symptoms of withdrawal and reduced plasma catecholamines, blood pressure, and pulse rate.[18] In persons undergoing acute alcohol withdrawal versus those who had recovered, cerebrospinal fluid NE was higher during withdrawal than recovery.[3] In another study of persons undergoing acute alcohol withdrawal, the NE metabolite MHPG in cerebrospinal fluid declined in the days that followed, and early withdrawal was associated with a positive correlation between cerebrospinal fluid NE and corticotropin-releasing factor.[19] In general, chronic alcohol exposure and withdrawal is associated with changes in corticotropin-releasing factor in the hypothalamic-pituitary-adrenal (HPA) axis and other brain sites, as well as alteration in noradrenergic signaling.[20] In rats that had alcohol dependence induced by repeated intragastric administration, clonidine suppressed withdrawal symptoms, whereas the NE level increasing drug yohimbine exacerbated withdrawal.[21]

Alcohol administration may interact with psychological stress to attenuate NE release. In rats, alcohol administered 15 minutes before immobilization stress reduced increases in plasma and brain NE that resulted from this stressor, whereas alcohol given without this stressor also reduced brain NE levels.[22] Systemic administration of alcohol to rats attenuated stress-induced increases in MHPG (a metabolite of NE) in the amygdala and locus coeruleus, which could be related to anxiolytic properties of alcohol.[23]

Three other studies suggest a relationship between the NE system and alcohol use. A genetic study in alcohol-dependent adults and controls found that 2 noradrenergic genes, SLC6A2 and ADRA2A, are associated with alcoholism.[4] This suggests that environmental factors alone do not fully explain the potential relationship between alcohol abuse and the NE system. Another study suggests that noradrenergic signaling may play a critical role in the rewarding effects of alcohol intake. In that mouse study, when NE was selectively depleted in medial prefrontal cortex, the animals no longer exhibited alcohol-induced conditioned place preference.[24] Male mice with constitutive deletion of dopamine beta-hydroxylase, the enzyme necessary for NE biosynthesis, have reduced ethanol preference in a 2-bottle choice paradigm. Taste aversion data from this study also suggest that these mice may drink less alcohol because they find its effects more aversive.[25]

In summary, the above alcohol studies suggest that acute alcohol intake in humans tends to boost measures of NE, although this is less clear in rodents. Chronic alcohol administration to rodents affects NE-related measures, but it is unclear if such intake is enhancing or suppressing noradrenergic signaling. In humans as well as in rats, acute alcohol withdrawal after chronic use tends to enhance noradrenergic signaling, and the NE lowering drug clonidine tends to

suppress withdrawal symptoms. This observation is consistent with the hypothesis that chronic alcohol use suppresses noradrenergic signaling, and that there is rebound of the system during acute withdrawal, resulting in increased NE release. Acute alcohol administration to rats may oppose the effects of psychological stress by suppressing noradrenergic signaling.

Nicotine

Nicotine is most closely associated with activation of nicotinic acetylcholine receptors. However, acute administration of nicotine to humans or animals also appears to affect NE measures, suggesting that this drug may in part produce its psychological effects by altering noradrenergic signaling. Acute infusion of nicotine, a potent stimulant of the central nervous system, in humans increased mean arterial pressure, heart rate, and plasma NE, although chronic smoking did not produce hypertension.[26] In dogs, acute nicotine increased blood pressure and heart rate, whereas chronic nicotine tended to decrease blood pressure.[27]

Acute nicotine also affects NE-related measures in rats. Nicotine produced little effect on plasma NE release when given intraventricularly, whereas systemic administration increased plasma NE.[28] Acute nicotine tended to increase brain release and turnover of NE as indicated by increases in metabolites.[29] In a microdialysis study, acute nicotine increased NE levels in medial prefrontal cortex and nucleus accumbens shell and core.[30] A microdialysis study in freely moving rats found that nicotinic agonists, which activated various receptor subtypes differentially, increased NE release in frontal cortex and hippocampus.[31] Subcutaneous in vivo administration of nicotine increased NE levels in the cortex.[32] Another study found that exposure of the spinal cord to nicotine induced release of NE in spinal microdialysates.[33]

Infusion of nicotine into localized brain regions also affects NE measures. A microdialysis study in rats found that injection of nicotine or a nicotine agonist (cytosine) into the fourth ventricle produced dose-dependent increases in NE release in the paraventricular nucleus of the hypothalamus.[34] In awake rats, nicotine antagonists microinjected or microdialyzed into the hippocampus blocked NE release in this brain structure that was produced by intravenously administered nicotine.[35] Low-dose nicotine infused into local regions of the rat brain increased NE in dorsal hippocampus and decreased it in ventral hippocampus, increased NE in cortex and amygdala, and decreased NE in the ventral tegmental area.[36]

In vitro studies also suggest that acute nicotine or nicotinic agonists modulate NE measures. In rat hippocampal slices, the alpha7 nicotinic agonist, anatoxin-a, evoked phasic release of NE.[37] A study of rat prefrontal cortex slices found that application of nicotine produced increases in NE release.[38] In the rat brain, microiontophoretic application of nicotine to the noradrenergic locus coeruleus brain region produced a dose-dependent increase in firing of these cells,[39] which is consistent with increased acute release of NE.

Chronic exposure to nicotine may also modulate NE-related measures. Chronic exposure of rats to unfiltered cigarette smoke resulted in a 10% increase in catecholamine levels in the hypothalamus.[40] Adrenal chromaffin cells release catecholamines such as NE upon exposure to nicotine, and, with repeated exposure, this response exhibits nicotine tolerance.[41] After chronic self-administration of nicotine in rats, this drug reduced paraventricular nucleus hypothalamic NE release induced by footshock stress, which could modulate corticotropin-releasing factor neurons in this nucleus and lead to sensitization to stress during chronic nicotine use.[42]

Acute withdrawal after chronic use of nicotine may be characterized by changes in endogenous noradrenergic signaling. Kappa-opioid receptor agonists attenuate nicotine withdrawal symptomatology and may do so by inhibiting calcium channels, thereby inhibiting release of NE.[43] Nicotine withdrawal is characterized by depression-like symptomatology, and chronic administration of the NE boosting antidepressant desipramine to rats rescued reward threshold elevations and decreased somatic signs of distress during nicotine withdrawal.[44]

Exposure to psychological stress can promote relapse of nicotine use, possibly through changes in stress hormone signaling such as NE. A recent review suggested that psychological stress facilitates the initiation of smoking, decreases motivation to quit, and increases risk for relapse.[45] When cigarette smokers try to quit their habit, psychological stress can undermine abstinence, and the NE (and dopamine) boosting antidepressant, bupropion, may help maintain

physiological measures of stress during nicotine withdrawal.[46] Individuals who are strongly reactive to psychological stress are also strongly reactive to nicotine; high anxiety levels are a strong predictor of desire to smoke and of withdrawal.[47] Smokers exhibited blunted increases in cortisol and more prolonged subjective agitation after exposure to the Trier Social Stress Test.[48] Data in rats suggest that clonidine decreases stress-induced reinstatement of nicotine-seeking behavior, supporting the hypothesis corticotropin-releasing factor and NE mediate this behavior.[49]

Nicotine may in turn suppress the effects of psychological stress. In mice, pretreatment with nicotine suppressed sympathetic activity induced by immobilization stress.[50] However, in a rabbit study, acute nicotine enhanced restraint stress-induced increases in plasma corticosterone and epinephrine, suggesting that the stress relieving effects of cigarette smoking are not mediated by reduction in peripheral sympathetic nervous system signaling.[51]

In summary, the above nicotine studies suggest that acute nicotine intake in humans and (with more evidence) in rats tends to boost measures of NE. Chronic nicotine administration to rodents affects NE-related measures, but it is unclear if it is enhancing or suppressing noradrenergic signaling. Acute nicotine withdrawal may be associated with changes in noradrenergic signaling, and its symptomatology is reduced by kappa-opioid receptor agonists and desipramine. Psychological stress can induce relapse to nicotine use and is opposed by clonidine, but there are mixed data in animals as to whether nicotine suppresses noradrenergic signaling during acute stress.

Marijuana

Marijuana may produce its "high" through action at endocannabinoid receptors, such as the CB1 receptor. Acute presentation of delta(9)-tetrahydrocannabinol (THC), the main psychoactive ingredient in marijuana, also alters NE measures in rodents. Administration of THC to mice decreased brain NE at low doses, and increased it at high ones.[52] In another study, administration of THC to mice produced hypothermia and increased brain catecholamine synthesis.[53] In the mouse, THC and morphine both produced antinociception and hypothermia after systemic injection, and THC produced greater increases in NE synthesis.[54] Also in the mouse, THC dose-dependently increased brain NE synthesis.[55] A rat study found that THC activated NE turnover in prefrontal cortex after systemic administration.[56]

Pharmaceutical agents that act upon the endocannabinoid CB1 receptor may also modulate NE release. THC may produce its psychoactive response by acting on this receptor. A rat study found that systemic administration of the CB1 agonist, WIN 55,212-2, dose-dependently increased NE release in frontal cortex.[57] Recordings from the locus coeruleus in the anesthetized rat found that systemic administration of WIN 55,212-2 or THC dose-dependently increased the firing rate of these neurons, which could increase release of NE.[58] In awake rabbits, WIN 55,212-2 and the THC analog CP55940 dose-dependently increased renal sympathetic nerve activity and plasma NE, while also lowering heart rate.[59]

In vitro studies also suggest that CB1 agonists modulate NE release. In rats, WIN 55,212-2 inhibited electrical stimulation-evoked release of NE in prefrontal cortex slices.[60] In contrast, another rat study found that direct application of WIN 55,212-2 into the frontal cortex produced a significant increase in NE release.[61] WIN 55,212-2 reduced electrically-evoked NE outflow in guinea pig hippocampal slices and also reduced calcium-evoked NE release in guinea pig and human hippocampal slices.[62]

Chronic administration of THC or WIN 55,212-2 to rats may also modulate NE measures. Rats were injected chronically with THC and appeared to develop a tolerance to both the excitatory and depressant effects of this drug, although the brain level of NE did not change markedly.[63] Two studies of chronic administration of THC to rats found reduction in preoptic area and medial basal hypothalamic NE while also reducing plasma NE.[64,65] A high dose of WIN 55,212-2 administered chronically to adolescent rats increased in vivo activity of noradrenergic neurons.[66]

Psychological stress may interact with cannabinoid agents to modulate NE metabolism. In rats housed under normal conditions, delta8-THC increased brain NE synthesis, whereas housing under stressful conditions for 24 hours eliminated the effect of this drug on NE metabolism.[67] Exposure to psychological stress may also be associated with increased craving and use of marijuana in persons.[68]

In summary, many of the above rodent studies suggest that acute marijuana/THC administration increases measures of NE, although some of the CB1 agonist data for the drug WIN 55,212-2 suggest decreases in noradrenergic signaling, as did a study by Holtzman and colleagues (1969)[52] of low doses of THC. Chronic administration of THC or WIN 55,212-2 can have effects on noradrenergic measures, although the nature of these changes is unclear. There appear to be limited data relating marijuana with noradrenergic measures during withdrawal or stress-induced relapse, although stress can enhance craving in users of this drug.[68]

Heroin

The intoxicating effects of heroin are most closely associated with action at opioid receptors. However, acute exposure to heroin or other opiates may also modulate NE-related measures. In drug-free human subjects, exposure to heroin increased urinary catecholamines, and NE remained increased during 10 days of administration of this drug.[69,70] In rat cortical slices, opiates induced inhibition of potassium-stimulated release of NE.[71] Also in rats, depletion of central and peripheral NE by the lesioning drug 6-hydroxydopamine had no significant effect on the ability of heroin to produce conditioned place preference, suggesting this drug may not achieve its rewarding effects by boosting NE.[72]

Chronic use of heroin by persons may modulate plasma NE or brain adrenoceptors. In persons addicted to heroin versus healthy controls, neuroendocrine testing with clonidine suggested that continuous opiate use does not lead to the development of hypersensitive alpha2 adrenergic receptors.[73] In persons addicted to heroin, NE plasma levels were lower in those who had been using this drug for fewer than 6 years, versus longer-term users.[74] Administration of clonidine may have a therapeutic role in persons addicted to heroin by improving impulsive decision making.[75]

Human data may also link noradrenergic genes with heroin use. Polymorphisms of the NE transporter gene may be associated with development of heroin dependence in Han Chinese individuals, suggesting that NE plays a role in the motivation-reward system of such drug dependence.[76] Polymorphisms in the dopamine beta-hydroxylase gene, which regulates endogenous synthesis of NE, have been associated with longer heroin addiction time and higher dosage of self-administration of this drug.[77]

NE measures may be elevated during acute withdrawal from chronic heroin use. Clonidine (and the related drug, lofexidine) can reverse symptoms of opiate withdrawal in humans, consistent with noradrenergic hyperactivity during this period of drug abstinence.[78,79] In rats, corticotropin-releasing factor (CRF)1 receptors and noradrenergic alpha2 receptors may play a key role in the elevated anxiety-like behavior found during acute heroin withdrawal, possibly by CRF inducing the release of NE in stress-related brain regions.[80]

Psychological stressors may promote relapse of heroin use both in humans and in animal models, possibly through noradrenergic mechanisms. Exposure to stressful life events, such as recent loss or depression, in recovering heroin users is associated with recurrence of use.[81] In rats, the NE boosting "pharmacological stressor" drug yohimbine enhanced cue-induced reinstatement of heroin seeking.[82] Systemic clonidine blocked stress-induced reinstatement of heroin seeking in rats, although it did not do so when injected directly into the locus coeruleus.[83] Rats trained to self-administer heroin showed decreased cue-controlled heroin seeking after being treated with the NE boosting drug, atomoxetine.[84]

In summary, there appear to be limited data, shown above, on the acute effects of heroin on noradrenergic signaling. And while chronic use of heroin appears to affect measures of noradrenergic signaling, it is unclear if chronic use is suppressing or enhancing this signaling. Clonidine can reduce withdrawal-related symptomatology in heroin users, consistent with NE overdrive in stress-related circuits of the brain during acute withdrawal. Psychological stress is also associated with relapse of use in humans and in animal studies and is antagonized by clonidine.

Cocaine

It is well-established that cocaine acts on the NE transporter to modulate acute release of NE. Cocaine is a reuptake inhibitor of NE, serotonin, and dopamine,[85–87] and these pharmacological actions may in turn produce its euphoric effects. Mice on a mixed 129S1/SvImJ × C57BL/6J genetic background that had a cocaine-insensitive dopamine transporter, exhibited

conditioned place aversion to cocaine, which may mean that cocaine's NE or serotonin boosting properties (as opposed to its dopamine boosting effects) are aversive in these mice.[87] In other words, boosting of synaptic NE by cocaine may not produce the rewarding effect of this drug and may even be unpleasant to experience.

Chronic exposure to cocaine in animals appears to affect the endogenous NE system. Repeated cocaine administration to rats decreased peripheral NE release, although celiac ganglion NE showed a tendency towards being increased.[88] Repeated cocaine administration to rats also increased hypothalamic NE an hour after the last treatment, but this chronic treatment regimen otherwise did not change the amount of NE or its metabolite MHPG in frontal cortex, septum, striatum, or nucleus accumbens.[89] In rats injected with cocaine for up to 21 days, cortical and striatal NE was unchanged aside from a transient increase in cortical MHPG on day 3.[90] In rats given chronic cocaine in their drinking water, binding to the NE transporter by the drug nisoxetine (which can provide a measure of the abundance of NE transporters, which pump NE back into the neurons that released it) tended to be reduced in multiple brain areas while still on drug, whereas 4 days of withdrawal tended to reverse these effects.[91] Rats exposed to 7 days of daily cocaine injections exhibited blunted growth hormone responses to clonidine challenge, suggesting alterations in alpha2 receptor sensitivity after cocaine administration.[92] Monkeys exhibited greater nisoxetine binding in the A1 noradrenergic cell group after both 5 and 100 days of cocaine self-administration; at this latter time point nisoxetine binding also differed in diverse forebrain regions.[93]

In humans or animals that were chronically exposed to cocaine, NE release lowering drugs may reduce withdrawal symptomatology, whereas the NE release enhancing drug yohimbine may exacerbate withdrawal. Cocaine-dependent persons rated themselves more nervous during yohimbine administration in early compared with late withdrawal, which was mirrored by changes in MHPG response to yohimbine.[94] Persons acutely withdrawing from cocaine exhibited impairment in cognitive flexibility tasks, which the authors suggested may be due to transiently increased noradrenergic activation.[95] In persons recovering from cocaine dependence, the alpha2 agonist (and NE lowering drug) guanfacine was associated with lowered cue-induced cocaine craving, anxiety, and arousal.[96] Rats undergoing cocaine withdrawal exhibited increased anxiety-like behavior in the defensive burying task, which was reversed by guanfacine. In addition, yohimbine facilitated reinstatement of cocaine seeking during early withdrawal, whereas guanfacine antagonized this effect.[97]

Exposure to psychological stress may enhance cocaine-seeking behavior in persons or animals chronically abusing this drug, and NE transmission reducing drugs may block stress-induced reinstatement of use. In persons addicted to cocaine, early withdrawal is associated with heightened anxiety states and low levels of craving, although craving tends to increase over time and can be worsened by psychological stress.[98] Disulfiram, a drug that blocks NE synthesis, increased the number of cocaine-negative urine samples in 5 randomized clinical trials.[99] In rats, the pharmacological stress-inducing drug yohimbine, which increases NE release, was associated with potentiation of cue-induced reinstatement of cocaine seeking.[100] Furthermore, the bed nucleus of the stria terminalis may interact with yohimbine to modulate cocaine-seeking behavior in rats.[101] In rats, the dopamine beta-hydroxylase inhibitor nepicastat, which reduces NE synthesis, lowered the breakpoint in cocaine-seeking behavior and also attenuated cue-, footshock-, and yohimbine-induced reinstatement.[102] In rats trained to perform cocaine self-administration, clonidine and lofexidine attenuated footshock- but not cocaine-induced reinstatement of cocaine-seeking behavior.[103] In another rat study, reinstatement of cocaine seeking was prevented by the NE reuptake inhibiting drug atomoxetine, which is known to decrease impulsivity.[104]

In summary, it is well established that cocaine is acutely a reuptake inhibitor of NE but also boosts dopamine and serotonin. Chronic use of cocaine appears to affect measures of noradrenergic signaling, although it is unclear if chronic use is suppressing or enhancing this signaling. Acute withdrawal appears to produce noradrenergic overdrive, which may be reduced by the alpha2 agonist drug guanfacine. Psychological stress can promote craving in persons addicted to cocaine and clonidine and lofexidine attenuated stress-induced reinstatement in rats.

Caffeine

Some studies suggest that acute intake of caffeine modulates noradrenergic measures in human subjects, although the stimulant properties of this drug are more closely related to effects at adenosine receptors. Acute caffeine intake increased plasma NE, but long-term use and subsequent withdrawal did not have any effects on blood pressure, heart rate, or plasma or urinary catecholamines.[105] In persons with recent myocardial infarction, caffeine increased mean blood pressure and plasma epinephrine but not plasma NE.[106] Caffeine, which inhibits adenosine receptors in vitro, increased blood pressure and plasma epinephrine levels in humans.[107] Acute administration of caffeine increased blood pressure both in users and nonusers, but the effect appeared unrelated to plasma NE, which did not change.[108] In human subjects, caffeinated coffee drinking is associated with a dose-dependent increase in urinary NE.[109]

Animal data also suggest changes in noradrenergic signaling after short-term intake of caffeine. In rats, subchronic treatment with caffeine enhanced reduction in forebrain NE levels produced by the drug alpha-methyl-para-tyrosine and also reduced the apparent number of beta adrenoceptors in forebrain.[110] In rabbits, administration of caffeine increased blood levels of NE and epinephrine.[111]

Chronic intake of caffeine may also affect noradrenergic measures. In young persons who consumed caffeine frequently, administration of this drug lowered plasma insulin and NE.[112] In habitual coffee drinkers, caffeine administration boosted urinary epinephrine but not NE during the workday.[113] Also in habitual coffee drinkers, caffeine enhanced the increases in blood pressure and heart rate associated with higher levels of self-reported stress during the workday.[114]

Data on chronic exposure to caffeine in rats shows potential enhancement or suppression of NE measures, depending on the study. In rats, long-term caffeine intake decreased circulating catecholamines in animals fed high fat and high sucrose diets, leading to decreased insulin resistance and lowered blood pressure.[115] Caffeine was chronically administered to rats for 30 days, which increased frontal cortex NE and cerebellar MHPG.[116] In ZSF1 rats, an animal model of obesity, hypertension, and metabolic syndrome, chronic caffeine consumption showed a trend toward increasing plasma NE levels.[117]

In human subjects, clonidine reduced alertness, impaired cognitive performance, and slowed saccadic eye movements; caffeine antagonized these impairments and opposed the blood pressure lowering effect of clonidine.[118] One interpretation of this study is that caffeine boosts noradrenergic signaling. Exposure to psychological stress, which is thought to boost NE outflow, may interact with caffeine intake. In healthy subjects exposed to a stressful laboratory task, caffeine increased blood pressure and plasma NE at rest, which added significantly to the physiological effects of stress.[119] On the other hand, a recent study has shown that caffeine is a noncompetitive inhibitor of the acetylcholinesterase enzyme and could, thereby, boost synaptic acetylcholine, a molecule that is functionally opposed to NE in the autonomic nervous system.[120]

In summary, it is unclear if acute intake of caffeine boosts NE in humans or animals, although several studies suggest that it does. There are also mixed data on how chronic caffeine intake may affect NE measures in humans or animals. It is not established as to whether acute withdrawal from chronic caffeine intake alters noradrenergic signaling. It is also unclear if caffeine antagonizes the effects of psychological stress through noradrenergic mechanisms or otherwise.

Conclusions

The data reviewed above on the 6 drugs certainly suggest that these substances have effects on noradrenergic signaling. It is possible that they all produce their rewarding effects, at least in part, by boosting noradrenergic signaling, although this topic requires further investigation. Marijuana, for example, may actually acutely reduce noradrenergic signaling, at least at lower doses.[52] It is not clear whether chronic use of these drugs in human subjects or animals suppresses or enhances noradrenergic signaling, although the fact that the NE transmission reducing drugs clonidine and guanfacine treat withdrawal symptomatology for many of these drugs (ie, alcohol, heroin, cocaine) may suggest that chronic use suppresses noradrenergic signaling and that there is noradrenergic rebound when the user stops taking the drug. The effects of many of these drugs on blood pressure and heart rate may also suggest that they affect noradrenergic signaling.

It is interesting to note that macaque monkeys will intravenously self-administer the NE lowering drug

clonidine, suggesting it has rewarding properties.[121,122] In contrast, many of the data from the 6 drugs suggest boosting noradrenergic signaling is rewarding in humans and in animals.[5] One possibility is that changes induced in noradrenergic signaling by certain drugs, whether increasing or decreasing such transmission, can be rewarding, and the direction of this effect (ie, whether increasing or decreasing noradrenergic signaling) may be dose-dependent.[52] Another possibility is that boosting noradrenergic signaling in reward-related circuits, as opposed to stress-related ones, is rewarding. By extension, lowering noradrenergic signaling in stress-related circuits may also be rewarding. One possibility is that noradrenergic signaling helps mediate opponent motivational processes in drug addiction by contributing to the rewarding properties of drugs in certain brain circuits while also helping mediate dysphoric effects (particularly in withdrawal) perhaps by acting on stress-related circuits in conjunction with corticotropin-releasing factor.[123]

Polydrug use and overlapping risk factors for relapse (such as psychological stress) among different drugs of abuse suggest that there may be similar underlying brain mechanisms at work in these disorders,[6–8,124,125] such as alterations in noradrenergic signaling.

Since psychological stress is a risk factor for development of drug addiction and relapse,[126] perhaps elevated endogenous noradrenergic signaling helps promote habit formation in such individuals by deactivating prefrontal cortical goal-directed behaviors and activating subcortical, striatal-based habit circuits.[127] A related point is that acute boosting of NE by drugs such as nicotine may help produce an anxiolytic effect by deactivating prefrontal cortical signaling.[127]

Regarding alcohol abuse in particular, this drug appears to regulate the endogenous synthesis of NE, including through interaction with its biosynthetic enzyme, dopamine beta-hydroxylase, contributing to the complexity of alcohol's relationship with addiction.[128] Another point is that substance abuse in general may affect subjective mood in humans, and possibly in animals, through its interaction with noradrenergic signaling, as this transmitter has long been linked with major depression and bipolar disorder.[129]

Another issue to consider in a noradrenergic theory of substance abuse is tonic versus phasic output of the system, where tonic is the more steady synaptic signaling and phasic refers to transient changes in signaling.[130] Perhaps phasic output is more important in the rewarding properties of NE, whereas tonic output plays a greater role in dependence and withdrawal.

One of the main points of this paper, that elevated (largely genetic) endogenous noradrenergic signaling is an etiological factor in substance abuse, is difficult to address directly with the existing, largely associative data. The studies described above do strongly suggest that noradrenergic signaling is modulated by acute intake of the 6 drugs, may also be affected by chronic use, can rebound during acute withdrawal, and may also be modulated by psychological stress. While the NE system is clearly affected by drug abuse, its baseline state, prior to drug use, is not well understood and remains a subject for future studies. The above studies are consistent with the hypothesis that some individuals have elevated or dysregulated endogenous noradrenergic signaling prior to substance abuse, possibly contributing to its etiology. Several genetic studies mentioned above suggest that differences in the endogenous NE system may affect the propensity for substance abuse in a given individual,[4,76,77] consistent with the hypothesis that there are baseline individual differences in noradrenergic signaling that contribute to the etiology of substance abuse. Future genetic studies of the NE system would further test this hypothesis, which is not established at this point.

If elevated endogenous noradrenergic signaling is indeed an etiological factor in the abuse of a broad range of substances, then chronic use of pharmacological agents that reduce NE transmission—such as clonidine, guanfacine, lofexidine, propranolol, or prazosin—may help prevent or treat these disorders. Randomized, prospective studies aimed at testing the effects of these pharmacological agents on substance abuse, including polydrug use, would provide critical information on their effectiveness for this indication, while also testing whether NE contributes to substance abuse.

Author Contributions

Conceived the concept: PJF. Analyzed the data: PJF. Wrote the first draft of the manuscript: PJF. Made critical revisions: PJF. The author reviewed and approved of the final manuscript.

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Disclosures and Ethics
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