Voltammetry in Studies on Drug and Alcohol Addictions

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Drug and alcohol addictions are chronic psychiatric conditions, which are characterized by uncontrolled substance seeking and taking behaviors, and long-lasting vulnerability to relapse. A wealth of evidence demonstrated that altered dopamine signaling is involved in all stages of this psychopathology. Due to a high temporal resolution and sufficient chemical specificity, fast-scan cyclic voltammetry was especially helpful in studying abnormalities in dopamine transmission in advanced animal models of addictions.

dopamine | neurotransmitter release | addiction

1. Introduction

Neuropsychiatric disorders such as drug or alcohol dependence, Parkinson's disease, and schizophrenia have undergone decades of research, but their prevalence has not decreased. Mechanisms contributing to these disorders have yet to be fully delineated and this is still an area of ongoing research. Despite constantly enhancing earlier diagnostics, modern health care is still experiencing a deficiency of effective pharmacotherapies. Undoubtedly, the success in developing effective treatments depends on detailed understanding of the neurobiological mechanisms that trigger and promote these pathological conditions. Since dopamine neurotransmission plays a pivotal role in pathogenesis of diseases such as Parkinson's, drug and alcohol addictions, remarkable progress has been made toward understanding how aberrations in dopaminergic transmission impact these pathologies.

In fact, development of pathology relevant animal models in parallel with the advance in monitoring of dynamic changes of neurotransmitters in the brain have provided researchers with a powerful toolbox for investigation in the neuroscience field. One of the most productive methodologies, which has been successfully used for many years, has become fast-scan cyclic voltammetry (FSCV). FSCV was developed and popularized as a revolutionary technique to measure rapid changes of neurotransmitters at a biological time scale by Wightman and colleagues in the 1980s as a logical continuation of the extraordinary efforts of the Adams' group, which pioneered the application of electrochemical methods to q*uantify in situ endogenous catecholamines* [1][2][3][4].

*The general principle of el*ectrochemical techniques, including FSCV, is based on oxidation and reduction of electroactive compounds when a certain potential is applied to the electrode, and measuring the resulting current. Differences in the ways in which the potential holds and generated current is measured provide benefits and limitations of certain electrochemical methods. The detailed comparison of technical aspects of FSCV with other

commonly used approaches such as amperometry, high-speed chronoamperometry, and microdialysis has been provided in previous reviews [5][6][7][8][9][10]. The features which make FSCV suitable and perhaps more prevalent than other techniques will be briefly highlighted here for the exploration of abnormalities associated with dopamine transmission.

FSCV and high-speed chronoamperometry apply waveforms, triangle and square, and sample with the resolutions of hundreds of milliseconds, while amperometry holds constant potential, measuring a current at least an order of magnitude faster. Therefore, amperometry offers much better temporal resolution than other real-time electrochemical approaches including FSCV. However, the resolution of FSCV is still sufficient for monitoring fast fluctuation in extracellular dopamine, including naturally-evoked phasic dopamine effluxes observed in different behavioral paradigms on freely moving animals [11][12][13][14][15][16][17][18][19][20][21].

Importantly, in contrast to FSCV and high-speed chronoamperometric measures, amperometry cannot provide information regarding the detecting analyte, since the current is measuring at fixed potential. The negative step in high-speed chronoamperometric measures allows this technique to establish a proportion between reductive and oxidative current that helps with analyte identification. FSCV shares with high-speed chronoamperometry this critical advantage in regard to a chemical resolution. Moreover, the use of background-subtracted voltammograms, which provide distinguishing current profiles within different potentials, affords FSCV an upgraded capability to reveal the identity of the detected substance. In contrast to amperometry, FSCV is sensitive to pH alterations, which are often associated with neuronal activation and therefore can contaminate the detecting signal. Nevertheless, based on the voltammogram, FSCV is capable to separate dopamine from pH changes. The special method was developed to statistically distinguish dopamine spikes using principal component regression [18]. This approach is especially valuable for revealing dopamine transients collected in freely moving animals, providing the exceptional opportunity to link the neurotransmitter release with behavior. Remarkably, a machine learning method was offered recently to uncover dopamine spikes in FSCV recordings performed in the human brain [22].

FSCV coupled to electrical stimulation is one of the few approaches comprehensively used to evaluate functional uptake of endogenous dopamine in brain slices and anesthetized preparations [5][23][24][25][26][27][28][29][30][31]. Since the method measures extracellular dopamine concentrations at a subsecond time scale inducing minimal tissue damage due to the micrometer dimension of electrodes, changes in dopamine uptake can be sensibly determined in small brain subregions. The signal can be analyzed by Michaelis–Menten model, providing information on dopamine concentration released per stimulation pulse and separating changes in V_{max} and K_m parameters, which characterized different aspects of dopamine uptake kinetics. This was particularly beneficial to explore neuroadaptations in dopamine transmission in models of drug addiction [23][24][25][26][27][28] and Parkinson's disease [32].

2. Drug and Alcohol Addictions

Drug and alcohol addictions, also called substance use disorders (SUDs), are chronic psychiatric conditions involving complex interactions between brain neurotransmitter systems, genetics, and environment. SUDs are

characterized by uncontrolled substance seeking and taking behaviors, and long-lasting vulnerability to relapse. The key features of these neuropsychiatric pathologies can be reproduced in animal models including different paradigms of substance self-administration in rodents. Such models are widely used for the exploration of the neurobiological mechanisms underlying the development and escalation of addictions. A wealth of evidence demonstrated that altered dopamine signaling is involved in all stages of addiction, from initiation and maintenance to escalation and relapse [33]. Due to a high temporal resolution and sufficient chemical specificity, FCSV was especially helpful in evaluating the details of fast dopamine transmission changes in different experimental paradigms.

Several critical factors were implicated for the development, shaping, and escalation of addictive behaviors. The first of them is a prominent brain response triggered by stimuli, which were previously associated with the exposure to abused substances. This response can be tightly linked with a desire and motivation to obtain a drug, while a learning function was equally proposed as well. The discovery that projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) release dopamine at subsecond time scale during the presentation of cocaine-related cues in rats trained to self-administer the drug was made with the use of FSCV [11]. Moreover, rapid changes in extracellular dopamine concentrations were detected in the NAc of rats before lever presses for cocaine in coincidence with the initiation of drug-seeking behaviors. A subsequent study revealed that extinction of cocaine self-administration resulted in functionally and temporally distinct dopamine signals in the same brain region [12]. Specifically, phasic dopamine release that occurs following a lever-press for cocaine gradually diminishes during extinction, but the signal that arises before the pressing episode appears persistent to extinction. Moreover, drug-seeking behaviors could be reproduced by evoking accumbal dopamine release by electrical stimulation of the VTA [11]. These findings suggest that subsecond dopamine efflux (phasic) may promote drug seeking if, indeed, a cause-and-effect relationship between the neurochemical changes and induced behavior exists. However, since the consequence of electrical VTA stimulation can be the release of various neurotransmitters in different brain areas, including dopamine [34], a causal role of the release of this neurotransmitter in the nucleus accumbens in the triggering or enhancing of drug-seeking (motivational) behavior can be questioned.

Other support for a possible role of phasic dopamine in promoting motivated behavior comes from voltammetric studies demonstrating that repeated cocaine exposure may increase cue-evoked motivation via augmented phasic dopamine release [13]. Furthermore, phasic dopamine changes were positively correlated with lever pressing for reward, while slow alterations in dopamine concentration (tonic) were not linked to this activity [14]. Although these studies advocate for the role of accumbal dopamine in reward-seeking behaviors, this evidence remains correlative in nature.

An alternative hypothesis postulates that phasic dopamine signaling may serve a teaching function, encoding the association between cues that predicted reward events and report errors in reward prediction. In fact, these postulates are based on compelling data [15][16][17][35][36] including the proof of the causal link between dopamine and learning from optogenetic studies [37]. Perhaps these two hypotheses can coexist without opposing each other, since the learning component is causally involved in cue-elicited reward-seeking through a phasic dopamine

signaling [37]. Nevertheless, there is the need for additional studies, which should combine optogenetic approaches and FSCV recordings in a cocaine self-administration paradigm, in order to prove the causality between phasic dopamine release and triggering drug-seeking behaviors independent from the learning.

On the other hand, some progress was made in the understanding of the causative relationship between dopamine release and alcohol-seeking behavior. Using FSCV recordings coupled with the selective optogenetic activation of dopamine VTA-nucleus accumbens circuitry, it was confirmed that high and low frequencies may generate phasic and tonic increases in dopamine release, respectively [38][39], which were previously detected in behaving animals [11][12][13][40]. This allowed Budygin's group to explore the relationship between dopamine transmission patterns and alcohol self-administration [41]. It has been revealed that phasic pattern of accumbal dopamine transmission within mesolimbic circuitry enhanced alcohol seeking, whereas tonic pattern inhibited alcohol-seeking and taking behaviors [39][42]. The fact that these two patterns had opposite effects on alcohol-seeking behavior emphasizes the importance of temporal dopamine dynamics in controlling motivated behaviors. Thus, sustained tonic stimulation of accumbal dopamine may decrease alcohol seeking by preventing dopamine terminals from engaging in phasic signaling patterns that promote alcohol-seeking behavior under normal circumstances. Together, these results implicate dopamine release in the ventral striatum as a critical neurochemical substrate, controlling behaviors directed to obtain abused substance and emphasize the role of discrete patterns of the neurotransmission for the initiation and inhibition of this action.

A second factor that may play a key role in the escalation of addiction as well as in relapse is the neuroadaptation induced by chronic use of a drug. One of the important consequences of repeated increases in extracellular dopamine concentrations following prolonged exposure of addictive substances, including cocaine and alcohol, is an altered reuptake rate. FSCV coupled with electrical stimulation offers some advantages for the evaluation of these changes. Since the technique detects dopamine changes with subsecond resolution at micrometer-dimension probe, endogenous reuptake can be measured in real time with minimal tissue damage. Moreover, FSCV is able to resolve changes in dopamine uptake kinetically, separating changes in maximal uptake rate (V_{max}) and affinity (K_m) parameters. The measurements can be performed in vitro, using brain slice preparations, and in vivo on anesthetized and freely moving animals.

Due to the above-mentioned advantages of FSCV, the consequences of escalated cocaine self-administration (0.75 mg/kg, fixed-ratio, 6 h session for 14 days) on dopamine uptake in rat nucleus accumbens were revealed. First of all, it was found that cocaine-induced dopamine uptake inhibition (changes in K_m) reached a proportionally higher level during the loading phase of cocaine self-administration [23]. Correspondingly, the dopamine uptake inhibition thresholds associated with the maintenance of responding were rising with new compressed intervals between self-injections. These changes were consistent with an escalation of cocaine-taking behaviors. Examination of dopamine uptake rate parameters revealed that Vmax is significantly increased following long-access escalation training, while no changes in the affinity of cocaine for the dopamine transporter were observed [23]. Using a self-administration paradigm that did not result to escalated intake of cocaine, no alterations in either uptake parameter were found in another in vivo voltammetry study [24]. However, in rats self-injecting the combination of cocaine and heroin (speedball), there was a significant increase in the V_{max}. The combined effect of

cocaine and opiates on dopamine transmission is of special interest when considering the unique neurochemical profiles reported with speedball that are thought to contribute to the increased abuse potential. Microdialysis studies have shown that speedball induces a synergistic elevation in extracellular dopamine concentrations in the nucleus accumbens compared to cocaine or heroin alone [43]. Therefore, the enhanced rate of dopamine uptake (V_{max}) is likely the result of an upregulation in functional dopamine transporter efficiency in response to the increased dopamine level.

In parallel with in vivo findings, the rate of accumbal dopamine uptake measured with FSCV in brain slice preparation *ex vivo* was significantly increased following a 10-day binge of cocaine self-administration (1.5 mg/kg, fixed-ratio for 24 h) [25]. However, a 5-day cocaine self-administration paradigm (1.5 mg/kg, 40 injection per day) was not sufficient to induce V_{max} adaptation in another *ex vivo* voltammetry study [26]. Therefore, this presynaptic neuroadaptation may occur following relatively prolonged cocaine exposure, probably as a compensatory response of the system to persistently elevated extrasynaptic dopamine concentration.

Ex vivo FSCV was used to explore the consequences of chronic alcohol exposure on dopamine transporter-mediated uptake parameters. Thus, the acceleration in striatal dopamine uptake (V_{max}) was observed in brain slices obtained from monkeys that were taking alcohol over a year [27], and in rats [28][29] and mice [30] chronically exposed to ethanol vapor or solution. It has been shown that chronic ethanol treatment leads to an increase in dopamine transporter (DAT) levels [44]. Consequently, an enhanced reuptake can be involved in the decrease of extracellular dopamine concentrations following chronic ethanol exposure.

Considering DAT as the initial target, which is responsible for cocaine's reinforcing action, the most intriguing results obtained with FSCV regarding neuroadaptations of presynaptic dopamine function are findings that DAT becomes less sensitive to cocaine inhibition following binge-like self-administration procedure [25][31]. Analysis of dopamine kinetics in brain slices revealed that cocaine was markedly less effective in inhibiting the DAT apparent K_m [25]. Noticeably, there were similar changes in K_m in rats at 1 and 7 days of cocaine deprivation. This is in sharp contrast to behavioral experiments, which have shown that the reinforcing effects of the drug are significantly augmented after 7 days of deprivation [25][45]. Therefore, adaptive alterations due to changes of the cocaine efficacy cannot account for distinct behavioral consequences following a binge/deprivation history of self-administration. However, these changes may be involved in a key mechanism underlying self-reports of lessened euphoria or tolerance produced by psychostimulants in addicts [26]. Therefore, decreased sensitivity of the DAT to cocaine could be associated with development of the tolerance.

Due to its excellent spatial resolution (~6 µm × 100 µm), FSCV is capable of accurate monitoring of dopamine release changes in distinct brain subregions of freely moving animals. This advantage allowed Phillips' group to discover hierarchical recruitment of phasic dopamine signaling in the striatum during the progression of cocaine self-administration. They carried out longitudinal subsecond dopamine detections simultaneously in the ventromedial striatum (VMS) and dorsolateral striatum (DLS) during the establishment of drug taking in rats [19]. They detected dopamine releases in both the VMS and DLS following the operant response for cocaine during the course of self-administration, in which the VMS signal declined and the DLS signal emerged during the progression

of drug taking. The finding of these neuroadaptations within limbic and sensorimotor striatal projections provides insight into neurobiological processes that establish drug-taking habits. Therefore, the progression of drug taking beyond recreational use might indeed reflect the engagement of dopamine signaling in distinct areas of striatum [46][47], with an emphasis of shift from the VMS to DLS during the development of established drug-seeking behavior [46][48].

The consequent question answered by the same researchers [20] was whether drug-directed behaviors are encoded by phasic dopamine release as drug taking escalates. By combining FSCV with self-administration regimen that is capable of producing escalated and compulsive drug seeking, they explored the regional dynamics of dopamine signaling following long access to cocaine. Remarkably, it was found that phasic dopamine decreased in both VMS and DLS regions as the rate of cocaine intake increased; with the reduction in neurotransmitter in the VMS significantly correlated with rate of escalation [20]. Furthermore, L-DOPA at a dose that refilled dopamine release reversed escalation, thus demonstrating the causal relationship between decreased dopamine transmission in the VMS and escalated cocaine self-administration [20]. Results from this voltammetric study provided mechanistic insights into excessive drug-taking behavior.

Stress is the third factor with a well-established role in escalation and relapse of drug- seeking and -taking behaviors in SUDs that can be reproduced in the animal models. However, dopaminergic mechanisms by which stress impacts addictive behaviors are still unclear. The evolutionary significance of the brain response to stress is to orchestrate adaptations, which have been influenced by natural selection to mobilize the individual bodily abilities to optimally deal with situations that needs escaping action or defense (flight or fight). The increase in phasic dopamine detected with FSCV in the NAc of intruder rat during social defeat episodes [21] is perhaps a part of this response. Consequent voltammetric studies in vitro revealed that stress-induced dopamine release is triggered by corticotropin-releasing factor (CRF) [49][50][51] that orchestrates brain responsiveness to stress exposure. One remarkable finding is that CRF loses the ability to increase mesolimbic dopamine release [49][50][51] and produces an aversive behavioral response [49]. It should be highlighted that experience-dependent dysregulation of the CRF system has been considered as a main contributor to vulnerability for stress hyperresponsivity as well as addictive behaviors. Collectively, these voltammetric findings pointed in a promising direction for the identification of neurochemical mechanisms underlying stress-promoted (associated) development and escalation of addictive behaviors, that is, the CRF-dopamine release interaction in the nucleus accumbens.

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