

Review

Application of metabolomics to toxicology of drugs of abuse: A mini review of metabolomics approach to acute and chronic toxicity studies

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ABSTRACT

Metabolomics has been widely applied to toxicological fields, especially to elucidate the mechanism of action of toxicity. In this review, metabolomics application with focus on the studies of chronic and acute toxicities of drugs of abuse like stimulants, opioids and the recently-distributed designer drugs will be presented in addition to an outline of basic analytical techniques used in metabolomics. Limitation of metabolomics studies and future perspectives will be also provided.

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1. Introduction

Analytical techniques have recently improved dramatically, resulting in the development of comprehensive analysis of endogenous molecules, referred to as the omics sciences: transcriptomics, proteomics, lipidomics and metabolomics [1–5]. Metabolomics is one of the widely distributed omics-techniques and its application has been expanded to various scientific fields [6–10]. The metabolome includes low-molecular weight molecules like amino acids, organic acids, fatty acids, sugars and sugar phosphates, and is positioned at the bottom of “omics cascade” as shown in Fig. 1: the metabolome can be interpreted as one of the phenotypes derived from the results of protein activation. Metabolomics technique can be used for detecting “clues” for the cause of phenotype's variation and it leads to elucidate biological mechanisms of both endogenous pathological conditions and exogenous compounds-derived toxic effects. For such reason, application of metabolomics has also been extended to the field of toxicology [10–14]. In particular, metabolomics application to analyze the

mechanism of acute or chronic toxicities of drugs of abuse is keenly of interest [7,15].

Abuse of dependence-producing drugs continues to be a social problem worldwide, while some parts of the mechanism on drug dependence formation still remains veiled. This is because drug dependence is a “state” composed of rewarding effect, tolerance, withdrawal effect, craving and relapse to drug-seeking behavior, resulting in its complexity of mechanism of dependence formation (Fig. 2) [16,17]. Detailed toxicity information on newly-distributed designer drugs like synthetic cannabinoids and cathinone-derivatives are also generally unknown. In such situations, metabolomics can become an appropriate approach to investigate their toxicities. Thus, metabolomics has been widely used for investigations not only for key factors of drug dependence but also for acute effects of drugs of abuse on organisms. In this article, we will review the metabolomics application to acute and chronic toxic effects of drugs of abuse like stimulants, opioids and newly-distributed designer drugs as listed in Table 1, in addition to an outline of basic analytical techniques used in metabolomics.

2. Analytical techniques and experimental points to note in metabolomics

Although various kinds of analytical techniques can be used for metabolomics, nuclear magnetic resonance (NMR) spectroscopy

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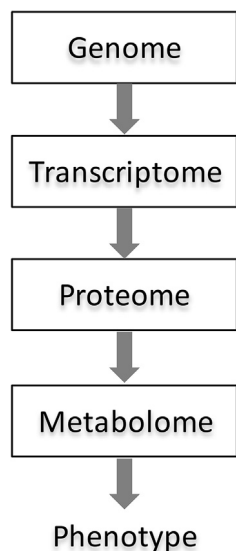


Fig. 1. The omics cascade. Metabolome is positioned at the bottom of the cascade, which is the closest link to phenotype.

and mass spectrometry (MS) are the most common techniques [4,8,9,18–24]. NMR-based technique has been used since the beginning of metabolomics history and has some merits: there is no need for sample pretreatment and it can analyze the intact metabolites even in crude solution. In addition, unknown metabolites can be identified when NMR-based technique is utilized in a non-targeted metabolomics approach [25,26]. However, relatively lower sensitivity of NMR spectrometry in comparison with that of MS and difficulty associated with results interpretation are generally problematic with NMR-based metabolomics.

Compared to NMR-based metabolomics, MS-based metabolomics is superior in terms of having higher sensitivity, higher operability of instruments and separation ability of metabolites in combination with chromatography. Thus, MS-based metabolomics has become widely used, especially in biological fields. Mass

spectrometers have also improved more rapidly than ever, resulting in the generation of high-spec instruments achieving high speed data acquisition and/or high mass resolution like quite-high sensitive tandem mass spectrometers or quadrupole-time of flight hybrid mass spectrometers (Q-TOFMS). Targeted metabolomics is generally executed using gas chromatograph (GC)–mass spectrometer (GC–MS), GC-tandem mass spectrometer (GC–MS/MS), liquid chromatograph–mass spectrometer (LC–MS/MS) and capillary electrophoresis (CE)/MS/MS, while non-targeted metabolomics is carried out by using Q-TOFMS or other high resolution instruments like Fourier transform mass spectrometers [27,28]. For non-targeted metabolomics, varieties of informatics tools to efficiently analyze metabolome data have been also developed [29–31].

In metabolomics, the number of the detected metabolites ranges from at least hundreds to thousands, and thus, multivariate statistical analysis like principal component analysis (PCA) and projection to latent structures-discriminant analysis (PLS-DA) is mandatory to overlook the metabolome disruption and interpret metabolome data [32]. In addition, to evaluate metabolome variation, there is a need to apply appropriate significance tests to the results in consideration to multiple comparisons problem.

To execute a metabolomics study, strict control of experimental conditions is crucial because the metabolome is easily affected by external stimulations like diet and circadian rhythms [4,33,34]. In general, however, foreseeable difficulties exist in controlling experimental conditions of humans including drug history and diet for metabolomics study. Therefore, studies using animal models are equally important to investigate metabolome profiles. Although it is difficult to extrapolate the results obtained from animal models to humans completely, metabolomics is superior to other omics sciences in that the metabolome is common between species.

3. Application to toxic studies on drugs of abuse

3.1. Stimulants

Stimulants like cocaine and methamphetamine are most investigated by metabolomics approach and thus there are

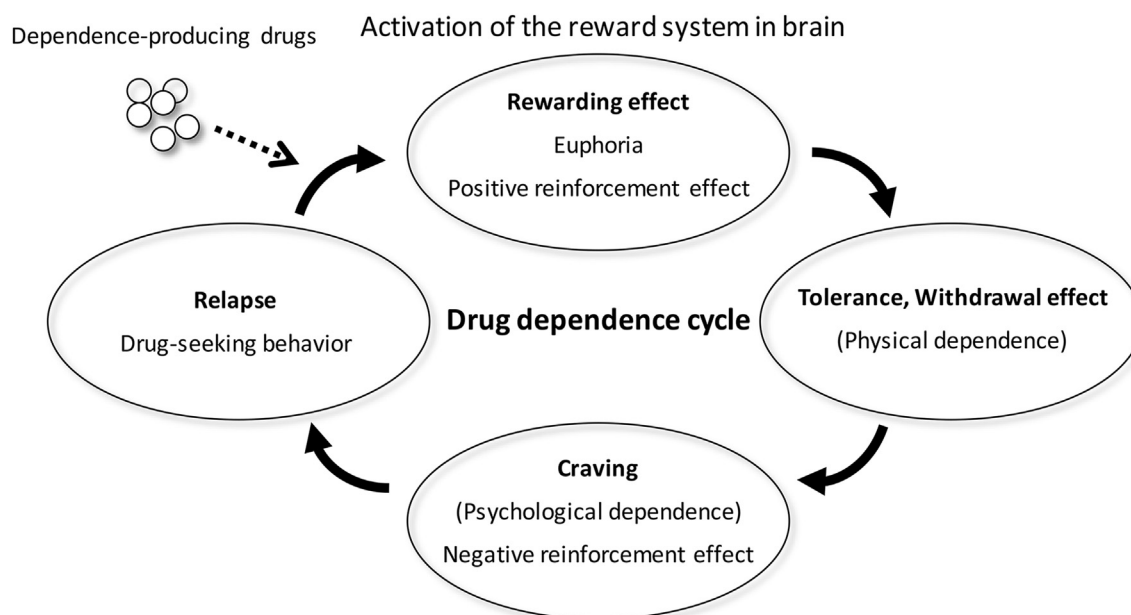


Fig. 2. Drug dependence cycle and each stage. Intake of dependence-producing drugs initially cause rewarding effect, but tolerance and withdrawal effect come to occur after repeated use of the drugs. To escape these effects, craving to the drug intake arises, leading to relapse of drug-seeking behavior.

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