総　説

Trends of Analytical Research on Drug-drug Interaction

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薬物‒薬物相互作用の分析化学的研究に関する動向

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要　旨

　薬物‒薬物相互作用は薬物治療において非常に重要な事項である。薬物はそれ自身で副作用を生じうるが、複数の薬物を併用することで予期しない重篤な有害事象を引き起こすこともある。この意味で、薬物‒薬物相互作用に関する分析化学的な研究が非常に重要であり、薬物治療の手助けとなる。本総説では、薬物‒薬物相互作用の分析化学的研究の最近の動向について、特に微小透析技術に基づいた方法について記述する。

キーワード

　薬物‒薬物相互作用、微小透析法、分析法

Abstract

　　Drug-drug interaction is very important matter for the medicinal treatment of diseases.　Drugs can cause serious side effects by themselves, beside concomitant use of plural drugs sometimes causes unexpected serious adverse events.　In this sense, the analytical research for the drug-drug interaction is very important and helpful for medicinal treatment.　In this review, the recent trends of analytical research on drug-drug interaction, especially methods based on a microdialysis technique, were described.

Key words

　　drug-drug interaction, microdialysis technique, analytical methods

1.　Introduction

　　In these days, drug-drug interaction has been focused for the medicinal treatment, because concomitant use of drugs sometimes caused serious adverse reactions.　As well as side effects caused on a single use of drug, the complex adverse reactions give heavy damages to patients.　On the medicinal treatment, a single use of drugs is rare, because ordinary several kinds of drugs are used for the treatment of the same patient.

　　However, it is very difficult to predict

what adverse reactions may occur by the concomitant use of drugs. Therefore, we need clarify which concomitant use of drugs may cause adverse reaction case by case. Many studies on drug-drug interaction to elucidate its mechanism have been done using a variety of drugs. For this purpose, several analytical methods were utilized, i.e., high-performance affinity chromatography,[1] high-field solution nuclear magnetic resonance,[2] flow cytometry,[3] transient absorption spectrometry,[4] liquid chromatography -tandem mass spectrometry (LC−MS),[5, 6] and high-performance liquid chromatography (HPLC)−UV.[7] In these studies, many targets were utilized, e.g., human liver microsome,[8] rat,[5, 6, 9, 10, 11, 12, 13] mouse,[14] rabbit,[7] dog,[11] and human.[14, 15, 16, 17, 18, 19, 20, 21, 22]

Among the above recently proposed methods, in this review, we have aimed to summarize the analytical methods, especially these with microdialysis techniques.

2. Recently developed analytical methods for drug interaction

Recently, many kinds of remarkable analytical research on drug-drug or drug-peptide interactions have been accomplished, and clarified many queries on interactions. The effects of binding of drugs with serum proteins on their activity, distribution, rate of excretion, and toxicity in the body are reviewed by Hage et al. (2011).[1] The characterization of drug interaction with serum protein was studied using high-performance affinity chromatography, i.e., determining binding constants, characterizing binding sites, examining drug-drug interactions, and studying drug-protein dissociation.

Physiological processes are mainly con-trolled by intermolecular recognition mechanism involving protein-protein and protein-ligand interactions. Recently, the use of nuclear magnetic resonance (NMR) techniques has considerably increased for these studies. The NMR-based analysis of protein-ligand interactions was reviewed by Cala et al. (2013).[2]

In vitro study on assessment of affinity of drug candidate for multidrug resistance proteins is important to predict in vivo pharmacokinetics and drug-drug interactions. Strouse et al. (2013)[3] studied to identify and characterize of new substrates for ATP binding cassette (ABC) transmembrane efflux pumps such as P-glycoprotein (P-gp) using flow cytometry. Among 102 fluorescent probes, a total of 31 substrates with active efflux and practical fluorescence response ranges were identified and tested for interaction with eight known inhibitors and showed the method is an efficient tool for identification and characterization of new fluorescent substrates for ABC transporters.

A new direct and noninvasive methodology based on transient absorption spectroscopy was developed to probe the feasibility of drug-drug interactions within a common protein binding site by Nuin et al. (2013).[4] This is based on the result of triplet-triplet energy transfer from (S)-^{3}propanol* to (R)-cinacalcet, which suggest requirement of close contact between the two drugs within the same biological compartment. They concluded that the new methodology can, in principle, be extended to a variety of drug/drug/biomolecule combinations.

Simultaneous quantitation of IC 87114, roflumilast and its active metabolite roflumilast N-oxide in plasma was performed by a

high-performance liquid chromatography-tandem mass spectrometry（LC−MS/MS）using tolbutamide as an internal standard by Satheeshmanikadan et al.（2012）.[5] The developed method was successfully applied to simultaneous estimation of IC87114, roflumilast and roflumilast N-oxide in a pharmacokinetic drug-drug interaction study in Wistar rats.

Warfarin is often used with etravirine, an anti-HIV drug to prevent HIV-related thromboembolic events. As both warfarin and etravirine bind to plasma proteins and are metabolized by hepatic cytochrome P450s, they are likely to interact. John et al.（2013）[6] studied the effect of etravirine on the pharmacokinetics and blood clotting time of racemic warfarin in rats by using LC−MS/MS. They concluded that their data obtained suggest that etravirine may potentiate the anticoagulant effect of warfarin and this could have clinical significance.

Nishimura et al.（2013）[23] studied drug-drug interaction using chimeric mice with humanized livers which can produce known human metabolites for test substrates. The interaction study was performed between clemizole and a CYP3A4 inhibitor, and could correctly predict a drug-drug interaction in chimeric mice. A LC−MS/MS method was used for the quantitation analysis of clemizole and its metabolite. As a conclusion, they obtained the useful results that using chimeric mice can improve the quality of preclinical drug assessment.

3. Drug-drug interaction studies on medicinal drugs

Many kinds of medicinal drugs have been elucidated to cause a drug-drug interaction.

Shirasaka et al.（2013）[8] evaluated the contribution of metabolites to drug-drug interactions using the inhibition of CYP2C19 and CYP3A4 by omeprazole, a proton pump inhibitor, and its metabolites as a model. Omeprazole, which is metabolized by CYP2C19 and CYP3A4 is also an in vivo inhibitor of these two enzymes. They elucidated that all of the metabolites inhibited these enzymes reversibly, in addition omeprazole, omeprazole sulfone and 5'-O-desmethylomeprazole were mechanism-based inhibitors of CYP2C19 while omeprazole and 5'-O-desmethylomeprazole were mechanism-based inhibitors of CYP3-A4. The obtained data was used to assess the relative importance in in vivo drug-drug interactions and their risk assessment.

Holmstock et al.（2013）[24] tested the hypothesis that transgenic mouse model, expressing both human pregnane X receptor （PXR）and CYP3A4 can predict PXR-mediated induction of intestinal P-gp in humans. By using the in situ intestinal perfusion technique with mesenteric blood sampling, the effect of oral rifampicin treatment on intestinal permeability for the HIV protease inhibitor darunavir, a dual CYP3A4/P-gp substrate, was investigated. Rifampicin treatment lowered the intestinal permeability for darunavir by 50% compared to that in nontreated mice. The P-gp inhibitor GF120918 increased the permeability for darunavir by 400% in rifampicin-treated mice, whereas this was only 56% in mice that were not treated, thus indicating P-gp induction by rifampicin. Quantitative Western blot analysis of the intestinal tissue showed that rifampicin treatment induced intestinal P-gp levels 4-fold, while CYP3A4 levels remained unchanged. Oral co-administration of rifam-

picin with the phytochemical sulforaphane for 3 days increased the permeability for darunavir by 50% compared to that with rifampicin treatment alone. These data show that PXR/CYP3A4-humanized mice can be used to study the inducing effects of xenobiotics on intestinal P-gp.

A risk of interaction of sunitinib with clarithromycine or azithromycine was investigated by Szatek et al. (2012).[7] Sunitinib and its active N-desmethyl metabolite are oral multikinase inhibitor, and is approved for the treatment of advanced renal cell carcinoma, imanitib-refractory gastrointestinal stromal tumor, and advanced pancreatic neuroendocrine tumors. However no significant effect of the co-administration of clarithromycine or azithromycine on the pharmacokinetics of sunitinib in rabbits was found.

4. Determination and evaluation of drug-drug interaction using microdialysis

1）Microdialysis

Microdialysis is an excellent sampling technique for monitoring the unbound concentrations of drugs or endogenous compounds in extracellular fluid in experimental animal and human.[25] It has been used for pharmacokinetic studies such as tissue penetration of drugs in various tissues and drug-drug interaction. Microdialysis is based on sampling of analytes from outside of the microdialysis probe consisted of a semipermeable membrane by passive diffusion. A tentative diagram of microdialysis probe and process are shown in Fig. 1. Briefly, for example, perfusate (●) is pumped up into the inner tube of the probe and pass through the semipermeable membrane to the interstitial space of the vein, and at the same time drugs in interstitial space come into probe as the components of dialysate (○). The probe is very small of 2-mm diameter made from several kinds of polymers. By a passive diffusion, drugs or biomaterials in the tissue are collected in a dialysate. The compounds in the microdialysate are analyzed by means of an instrumental analysis. As the sample size of the microdialysates is very small of ～20 μL, a high sensitive and selective method is required for the determination of the compounds.
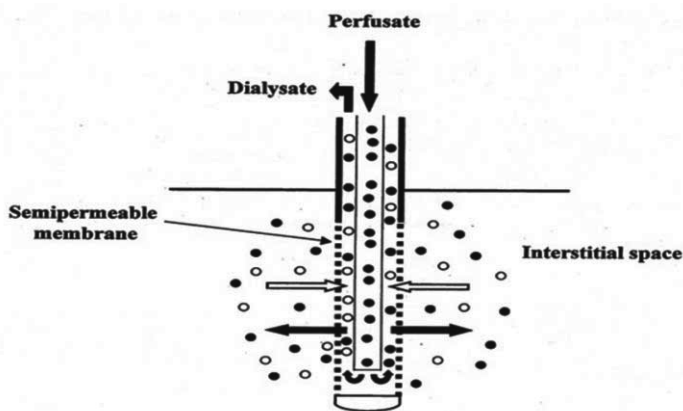

Fig. 1　Diagram of microdialysis probe

2) Evaluation of drug-drug interaction using microdialysis

3,4-Methylenedioxymethamphetamine (MDMA), an amphetamine analog that has come a popular recreational drug among young people, and its metabolite, 3,4-methylenedioxyamphetamine (MDA) were studied on their interaction with caffeine by Tomita et al. (2007).[26] They developed the sensitive HPLC−FL method for determination of MDMA and MDA in rat blood and brain microdialysates with as low as 1.2 and 4.2 ng/mL of detection limits, respectively. By using the determination method, pharmacokinetic parameters of these drugs in the microdialysates after administration of MDMA (5 mg/kg, i.p.) with or without caffeine (20 mg/kg, i.p.) were evaluated (Fig. 2). As a result, the AUC_{0-300} ($53\pm5\,\mu g\cdot$ min/mL) of MDMA in blood significantly increased to $91\pm5\,\mu g\cdot$min/mL ($p<0.01$), and clearance (CL) of MDMA (96 ± 10 mL/min/ kg) decreased by half to 51 ± 4 mL/min/kg. No change of C_{max} and AUC for MDA was observed, which suggested that caffeine may interfere with renal clearance of MDMA. On the other hand, the C_{max} of MDMA ($1,009\pm28$ ng/mL) and MDA (168 ± 17 ng/mL) in brain significantly decreased to 496 ± 80 ng/mL ($p<0.01$) and 93 ± 21 ng/mL ($p<0.05$). Moreover, the T_{max} and the mean residence time (MRT) of MDMA and MDA were considerably prolonged, but the elimination half-life ($T_{1/2}$) of MDMA and MDA were unchanged. These results suggested that caffeine inhibits the transportation of MDMA and MDA to brain via the blood-brain barrier, although the exclusions of MDMA and MDA from
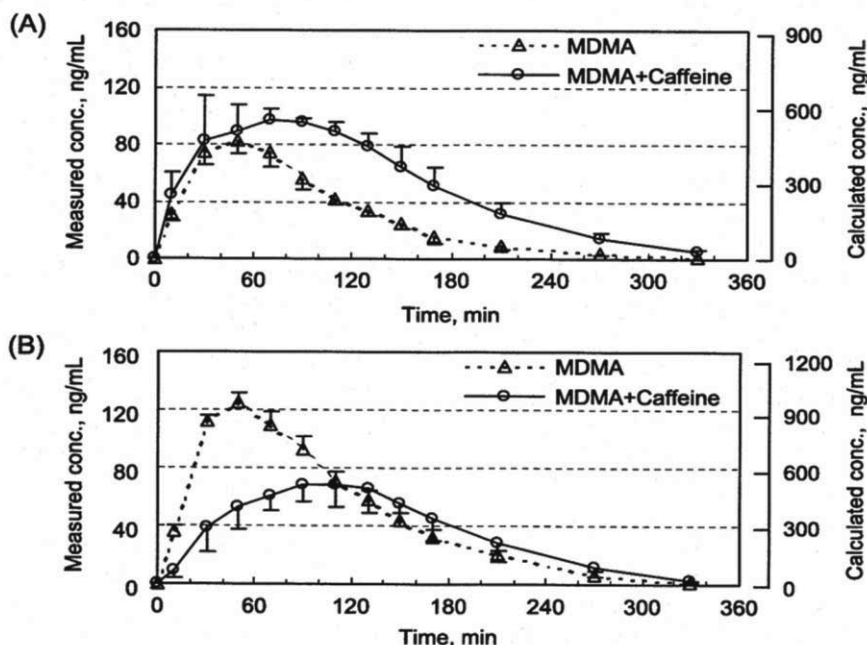

Fig. 2 Concentration-time profiles of MDMA in rat (A) blood and (B) brain microdyalysates after single administration of MDMA (5 mg/kg) with or without caffeine (20 mg/kg). Data are expressed as mean±SEM. Ref. 26.

brain to blood were not influenced by caffeine.

Wada et al. (2008)[27] developed the sensitive HPLC–FL detection method of morphine labeled with DIB–Cl, a fluorescent labeling reagent for amines, in rat brain and blood microdialysates and applied the method to evaluate the pharmacokinetic interaction between morphine (Mor) and diclofenac (Dic). No significant difference was observed for any pharmacokinetic parameter of Mor between rats administered Mor with/without Dic. However, they concluded that the basic findings might help clinical inference when Mor is coadministered with Dic to humans.

Pharmacokinetics of kadsurenone and its interaction with cyclosporine were studied by Huang et al. (2009).[28] Kadsurenone, a neolignan with specific antagonistic activity of platelet-activating factor, was investigated on its hepatobiliary excretion mechanism and whether the mechanism is associated with P-gp. They used a microdialysis system coupled with HPLC–UV to measure free-form kadsurenone in Sprague-Dawley rat blood and bile after i.v. administration of kadsurenone. The obtained results indicated that the hepatobiliary excretion ratio of kadsurenone on the cyclosporine treated group was 1.2 ± 0.1, which was not significantly different from those of kadsurenone alone (1.3 ± 0.2). Therefore, they concluded that kadsurenone goes through hepatobiliary excretion but might not be regulated by P-gp.

Varenicline is used for smoking cessation, which can reduce alcohol seeking and consumption in alcohol high-prefering rats. Ericson et al. (2009)[29] studied to explore whether interactions among varenicline, nicotine, and ethanol in the brain reward system could indicate the use of varenicline also for alcohol

dependence. By using in vivo microdialysis method, the effects of systematic injections of varenicline on the extracellular accumbal dopamine levels in response to a systemic challenge of ethanol, nicotine, or combination of nicotine and ethanol were investigated in rats. The results obtained demonstrate different effects of acute varenicline on nucleus accumbens dopamine response to ethanol in naive animals compared with varenicline-pretreated animals. Therefore, this antismoking drug may be beneficial for treating patients with alcohol dependence with (and possibly also without) concomitant nicotine dependence.

Hippalgaonkar et al. (2010)[30] investigated the effect of topically co-administrated P-gp substrates/inhibitors on the vitreal kinetics of systematically administered P-gp substrate using male rabbits. The concentration-time profile of quinidine was determined alone and with verapamil, prednisolone and erythromycin after i.v. administration of quinidine. The vitreal pharmacokinetic parameters of quinidine with these compounds were significantly different from those of the control. They concluded for the first time that topically applied P-gp inhibitors can diffuse to the retinal pigmented epithelium (RPE) and alter the elimination kinetics of a systemically administered P-gp substrate, probably through inhibition of RPE P-gp. And the degree of inhibition will depend on the physicochemical characteristics of the inhibitor and its affinity for P-gp and the concentration of the therapeutic agent in plasma or vitreous humor. According to the extensive use of herbal medicine in the modern world, herb-drug interaction has become a serious problem. Therefore, effects of

Andrographis paniculate extract (APE) and its major component, andrographolide (AG) on theophylline pharmacokinetics in rats were studied using HPLC-UV by Chien et al. (2010).[31] Pretreatment of AG increased elimination of theophylline, and chronic use of Andrographis paniculata could elevate the concentration of theophylline in the blood. They suggested that there should be a warning for the interaction with APE and its herbal ingredients with CYP1A2 substrate. As a conclusion, patients who want to use CYP 1A2-metabolized drugs such as caffeine and theophylline should be advised of the potential herb-drug interaction, to reduce therapeutic failure or increased toxicity of conventional drug therapy.

Ikeda et al. (2011)[32] evaluated the pharmacodynamic effects of interactions caused by concomitants in MDMA tablets on extracellular dopamine and serotonin (5-HT) by microdialysis in the striatum of ethylcarbamate-anesthetized rats. After a single administration of MDMA (10 mg/kg, i.p.), a dramatic increase in extracellular dopamine and 5-HT levels was observed. Co-administration of methamphetamine with MDMA showed increase in dopamine level induced by MDMA in a methamphetamine-dose-dependence. In contrast, ketamine and caffeine showed synergistic effects on the monoamine levels induced by MDMA, whereas the individual administration of either of these drugs did not affected monoamine levels. In conclusion, the results suggested that exposure to multiple drugs in addition to MDMA can have neurotoxic effects.

Shaw and Tsai (2012)[33] developed a microdialysis technique coupled to HPLC system to measure free-form aspirin and salicylic acid for herbal-drug interaction in rat blood and brain. The pharmacokinetic data demonstrated that the area under the concentration-time curve (AUC) of aspirin was $2,031 \pm 266$ min·μg/mL after aspirin administration (100 mg/kg, i.v.). The AUC of salicylic acid was $12,660 \pm 1,799 \mu$g/mL, which suggested that aspirin was quickly hydrolyzed to salicylic acid in blood and metabolite can also be detected within 15 min in brain microdialysate. But, the herbal-drug pharmacokinetic interaction showed no significant effects. Spinosin, a major herbal ingredient, plays an important role in sedation and hypnosis.

Ma et al. (2012)[34] developed an in vivo microdialysis technique with LC-MS method, and used to investigate the pharmacokinetics of spinosin and its interaction with cyclosporin A in the brain, blood and bile of rats. Co-administration of these compounds significantly increased the AUC of spinosin in blood, bile and brain. They concluded that the results obtained demonstrated that cyclosporin A decreased the efflux of spinosin through the inhibition of P-gp efflux transporter and it might be used as a group of P-gp substrate. Further, as it was demonstrated that hepatobiliary excretion of spinosin was also increased after co-administration, other transporters or pathways might also be involved in the mechanism of spinosin.

Fuchigami et al. (2013)[35] evaluated the risks of co-administration of MDMA and methamphetamine based on drug distribution and monoamine level in rat brain. They monitored pharmacokinetic and pharmacodynamics variables for drugs and monoamines in the rat brain. AUCs for concentration-time of MDMA and dopamine after co-

administration of MDMA with methamphetamine significantly increased compared to those of sole MDMA administration. Therefore, they concluded that the co-administration of MDMA with methamphetamine confers greater risk than sole administration, and that adverse events of MDMA ingestion many increase when methamphetamine is co-administered.

The recent trend of drug-drug interaction was introduced. Many drug-drug or herb-drug interactions have been reported. These interactions sometime cause serious adverse reactions and make the risks of human health. Thus, the research to protect the adverse reactions from the human health, should be very important and will be developed more and more in a future.

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