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The effect of hyperglycemia on the pharmacokinetics of valproic acid studied by high-performance liquid chromatography with electrochemical detection

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ABSTRACT

The effects of hyperglycemia on the pharmacokinetics of valproic acid (VPA) were examined by time-concentration profiles of plasma VPA accompanied with blood glucose (BG) changing. In addition, time-concentration profiles of plasma free fatty acids (FFAs) were also obtained to examine the interaction between VPA and FFAs *in vivo*. For the experiments *in vivo*, normal rats, given multiple doses of maltose orally, and diabetic rats, which were made to maintain hyperglycemia, were used. Plasma VPA and FFA were determined by high-performance liquid chromatography with electrochemical detection (HPLC–ECD) systems based on the reduction of quinone for the selective determination of acids, respectively. BG was determined by pocket-size glucose meter. The maximum plasma concentrations (C_{max}) of VPA in normal rats given multiple doses of maltose orally and in diabetic rats were remarkably decreased in comparison with those in the control rats. From the present study, it was shown that the metabolism of plasma VPA is accelerated under hyperglycemia. Moreover, we also found that VPA was preferentially metabolized in comparison with the plasma FFA *in vivo*.

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1. Introduction

Valproic acid (VPA, 2-propylpentanoic acid), administrated as sodium valproate (VP-Na), is FDA-approved for the treatment of simple complex absence seizures, mixed seizures, bipolar I disorder (manic phase, adult only), and migraine prophylaxis (adults only). Its off-label uses include acute treatment of manic symptoms in bipolar II disorder (BP II) and bipolar disorder not-otherwise-specified (BP NOS), and maintenance treatment of BP I, II, and NOS in both adult and pediatric populations [1]. During VPA-therapy, the dysregulation of the hypothalamic system [2], inhibition of insulin metabolism in the liver [3], b-cell dysfunction on insulin secretion [4,5], and an increase in plasma free fatty acid (FFA) level [6–8] have been reported to occur. As such, VPA can cause a considerable increase in body weight, with serum insulin, therefore VPA-induced obesity seems to be associated with many metabolic and endocrine disturbances [9–12]. The weight gain and the associated increase in insulin resistance might result in an increase in patients' cardiovascular risk [13,14]. Thus, plasma VPA level is intimately involved in glycolipid metabolism. However, detailed kinetic profiles and interaction for blood glucose (BG), plasma FFA, and plasma VPA are not well known, especially when a patient also has hyperglycemia. For the VPA therapy for hyperglycemia patients, it is important to examine the kinetic profiles for plasma VPA and FFA accompanied with BG changing and to determine a suitable therapeutic concentration range of VPA.

Several methods have been employed for the determination of plasma VPA, based on gas chromatography (GC) with flame ionization detection (GC–FID) [15] or mass spectrometric detection (GC–MS) [16] and high-performance liquid chromatography with ultraviolet detection (HPLC–UV) [17], fluorescent detection (HPLC–FL) [18], or mass spectrometric detection (LC–MS) [19]. However, there have not been any reports of the use of electrochemical detection methods in HPLC for determining VPA since carboxylic acids are less active electrochemically.

The authors developed a new voltammetric method for the determination of FFAs in fats and oils, based on the reduction of quinone [20]. The electrode redox process of quinone involves a two-electron transfer coupled with a two-proton transfer in protic solvent. The presence of a small amount of acid in a solution

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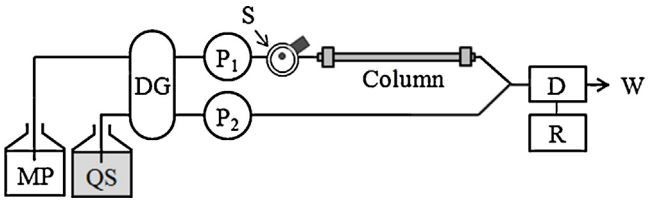

Fig. 1. Block diagram of the HPLC–ECD system. MP, mobile phase; QS, quinone solution; DG, degasser; P_1 and P_2, pump; S, sample injector; column, reversed-phase C_{30} column (Develosil C30-UG-3, 250 mm × 1.0 mm *i.d.*); D, electrochemical detector, electrochemical cell and potentiostat; R, recorder; W, waste. For the determination of VPA, an acetonitrile–water (70:30, v/v) mixture and one containing 6 mmol/L DBBQ and 20 mmol/L $LiClO_4$ served as a MP and QS, respectively. For the determination of FFA, acetonitrile–ethanol (90:10, v/v) mixture and one containing 6 mmol/L DBBQ and 0.1 mol/L $LiClO_4$ served as a MP and QS, respectively.

of quinone such as 3,5-di-*t*-butyl-1,2-benzoquinone (DBBQ) in unbuffered protic solvents was found to cause a new peak (termed a prepeak) at a more positive potential than the original reduction wave of DBBQ itself [21]. The occurrence of the prepeak can be ascribed to the increased availability of protons from the added acid. The current height of the prepeak increases with increasing amounts of acid in proportion to the acid concentration, which is a basis for the amperometric detection of acids. The method was applied to high-performance liquid chromatography with electrochemical detection (HPLC–ECD) for the determination of carboxylic acids in biological samples and food [20]. However, an experimental system including the sample preparation for the determination of plasma VPA with this electrochemical detection has not yet been established.

In this study, we developed HPLC–ECD systems for the determination of VPA and FFAs, respectively. Furthermore, we were able to get the time-concentration profiles of VPA and FFA accompanied with BG changing to examine the effect of hyperglycemia on the pharmacokinetics of VPA in rats.

2. Experimental

2.1. Materials

All chemicals and solvents were of reagent grade. 3,5-Di-*t*-butyl-1,2-benzoquinone (DBBQ, >99%) was purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). $LiClO_4$, acetonitrile, ethanol, palmitic acid (99.5%), stearic acid (99.5%), oleic acid (99%), linoleic acid (99%), valproic acid (VPA, 98%), sodium valproate (VP-Na, 98%), *n*-nonanoic acid (97%), alloxan monohydrate (98%), and maltose monohydrate (98%) were obtained from Wako Pure Chemical Industries (Osaka, Japan). Arachidonic acid (99%) and margaric acid (99%) were obtained from Funakoshi (Tokyo, Japan). FFAs and VPA were dissolved in an acetonitrile–ethanol (90:10, v/v) mixture and acetonitrile–water (70:30, v/v) mixture, respectively, to prepare the standard solution.

2.2. HPLC–ECD system

2.2.1. Apparatus

Two HPLC–ECD systems were established for the determination of VPA and FFA, respectively. The present HPLC–ECD system is shown in Fig. 1. It consists of a degasser (DG-980-50, Jasco, Tokyo, Japan), two pumps (301M, Flom, Tokyo, Japan) for the mobile phase and quinone solution, respectively, a sample injector fitted with a 5-μL sample loop (7725, Rheodyne, Cotati, CA, USA), a reversed-phase C_{30} microbore column (Develosil C30-UG-3, 250 mm × 1.0 mm *i.d.*, Nomura Chemical, Aichi, Japan), an electrochemical detector (LC-4C, BAS, Tokyo, Japan) with the electrochemical cell (Radial flow cell, BAS), and a recorder (807-IT, Jasco). The 12 μm thickness of the gasket was set between the working electrode and the flow-cell block in the electrochemical cell, thereby the cell volume was 0.33 μL.

2.2.2. HPLC conditions for determining VPA

An acetonitrile–water (70:30, v/v) mixture and one containing 6 mmol/L DBBQ and 20 mmol/L $LiClO_4$ served as the mobile phase and the quinone solution, respectively. The detection potential for monitoring the VPA was set at −0.15 V *vs.* Ag/AgCl. *n*-Nonanoic acid was used as an internal standard (IS). The mobile phase and quinone solution were deaerated by the degasser and made to flow at a rate of 30 μL/min and 60 μL/min, respectively, in each flow line. Then 5 μL of the test solution were injected into the microbore column maintained at 30 °C using a column oven.

2.2.3. HPLC conditions for determining FFA

An acetonitrile–ethanol (90:10, v/v) mixture and one containing 6 mmol/L DBBQ and 0.1 mol/L $LiClO_4$ served as the mobile phase solution and the quinone solution, respectively. The detection potential for monitoring the FFAs was set at −0.09 V *vs.* Ag/AgCl. Margaric acid was used as an IS. Other HPLC conditions such as the flow rate, injection volume, and column temperature were used the as same as in Section 2.2.2.

2.3. Procedure for animal experiments

2.3.1. Animals

Male Wistar rats (8 weeks old, 230–250 g) were purchased from Tokyo Jikken Dobutu Co. (Tokyo, Japan). To prepare a diabetic rat, an alloxan solution was intraperitoneally injected into the rats (200 mg/kg) for two days with a once-daily injection.

After 16 h fasting, VP-Na that was dissolved in water at a dose of 150 mg/kg was orally administered to the normal and diabetes rats. To maintain the hyperglycemia in the normal rats, maltose, which was dissolved in water at a dose of 1.8 g/kg, was orally ingested every 1 h after VP-Na administration.

2.3.2. Sample preparations

Fifty microliters of blood were drawn from the caudal veins of the rats before and after administration. BG was determined using 5 μL blood specimens by a pocket-size glucose meter (Glucocard, GT-1641, Arkray, Kyoto, Japan). Next, from the remaining 45 μL of the blood specimen, plasma for the determination of VPA and FFA, respectively, were obtained. The plasma was separated by centrifugation of the heparinized blood and stored at −30 °C until analysis.

For the determination of VPA, 10 μL of rat plasma with *n*-nonanoic acid as an IS was mixed with 0.1 mL of acetonitrile, and then this solution was sonicated for 1 min. The solution was filtered through a membrane filter (pore size, 0.45 μm) and 5-μL aliquots were injected into the HPLC–ECD system for determining VPA.

For the determination of FFA, another 10 μL of rat plasma, with margaric acid as an IS, was mixed with 0.1 mL of diethyl ether to extract the FFA from the rat plasma. This collection process by diethyl ether was repeated three times. The collected diethyl ether was evaporated using an evaporator at room temperature to obtained the lipid residue, which was then dissolved in an acetonitrile–ethanol (90:10, v/v) mixture. The solution was filtered through a membrane filter (pore size, 0.45 μm) and 5-μL aliquots were injected into the HPLC–ECD system for the determination of the FFA.

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