Department of Pharmacy[1], Zhejiang University City College, Department of Chemistry[2], Zhejiang University, College of Pharmaceutical Sciences[3], Zhejiang University, Hangzhou, P.R. China

Prediction of plasma protein binding of cephalosporins using an artificial neural network

X. C. Fu[1], G. P. Wang[2], J. Q. Gao[3], S. Y. Zhan[3], W. Q. Liang[3]

Received October 20, 2005, accepted February 14, 2006

Prof. Xuchun Fu, Department of Pharmacy, Zhejiang University City College, Hangzhou, 310015, P.R. China
Fuxc@zucc.edu.cn

Pharmazie 62: 157–158 (2007)
doi: 10.1691/ph.2007.2.5735

An artificial neural network model is developed to predict the fraction of cephalosporins bound to plasma proteins (f_b) from their molecular structural parameters. These molecular structural parameters are the molecular weight (MW), the surface area occupied by oxygen and nitrogen atoms ($S_{O,N}$), and the surface area occupied by hydrogen atoms attached to oxygen or nitrogen atoms (S_H). For a training set of 20 cephalosporins and a test set of 3 cephalosporins, root mean squared errors (RMSE) between experimental f_b values and calculated/predicted f_b values are 0.036 and 0.045, respectively.

Binding to plasma proteins, mostly to serum albumin, α_1-acid glycoproteins, and lipoproteins, is a significant factor in the transport and release of many drugs in the human body, strongly influencing their disposition and excretion. The portion of a drug bound to plasma protein is inactive in terms of receptor/enzyme activity, metabolism, and elimination, so, the pharmacological effect of a drug is related to the unbound concentration of drug in plasma (e.g. the free drug concentration) rather than total concentration (Fichtl et al. 1991; Benet et al. 1996). Drug-protein complexes in plasma also serve as drug reservoir for free drug concentration, as the drug is removed from the body by various elimination processes, and prolong the duration of drug action. Thus, the extent of protein binding of a drug may influence pharmacokinetic parameters, i.e. the clearance and the apparent volume of distribution, and pharmacodynamic processes. The prediction of plasma protein binding is important in the design, optimization, and selection of candidates for the development of novel drugs, and several predictive models for plasma protein binding from physicochemical or molecular properties have been reported (Deschamps-Labat et al. 1997; Zlotos et al. 1998; Saiakhov et al. 2000; Kratochwil et al. 2002; Turner et al. 2004; Aureli et al. 2005). In this paper, we report an artificial neural network model for prediction of plasma protein binding of cephalosporins.

Artificial neural networks were established to predict the fraction of cephalosporins bound to plasma proteins (f_b). The back-propagation algorithm with a modified learning rule, normalized cumulative delta was used to train the network. A tanh function was used as the transfer function. The neural network model is a three-layer network that includes an input layer, a hidden layer, and an output layer. The initial learning coefficients are 0.3 and 0.15 for hidden layer and output layer, respectively. The initial momentum is 0.4. Epoch size is 4. F′ offset is 0.1. Transition point is 10000 and learning coefficient ratio is 0.5. Inputs to the neural network consist of the molecular weight (MW), the surface area occupied by oxygen and nitrogen atoms ($S_{O,N}$), and the surface area occupied by hydrogen atoms attached to oxygen or nitrogen atoms (S_H). Both S_H and $S_{O,N}$ were obtained from the molecular conformations optimized using the semiempirical self-consistent field molecular orbital calculation AM1 method (Dewar et al. 1985) and the atomic radii used by Clark (1999). The hidden layer consists of five neurons and the output layer consists of a single neuron, f_b. The network architecture is shown in the Fig.

The calculated/predicted f_b values from the neural network model obtained after 50000 training cycles are listed in the Table along with experimental f_b values taken from the reference (Benet et al. 1996) and the molecular structural parameters (MW, S_H, and $S_{O,N}$).

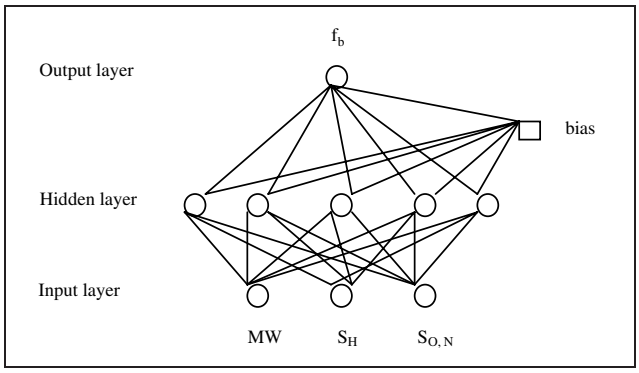

Fig.: Architecture of the neural network

Table: Fraction of cephalosporins bound to plasma proteins and their molecular structural parameters

Compound	MW	S_H (Å^2)	$S_{O,N}$ (Å^2)	f_b	
				Exp.[a]	Calc.[b]
Training set					
Cefaclor	367.8	16.0	109.7	0.25	0.21
Cefadroxil	363.4	20.1	127.8	0.20	0.16
Cefamandole	462.5	12.9	151.8	0.74	0.73
Cefazolin	454.5	8.7	157.1	0.89	0.84
Cefixime	453.5	21.2	183.9	0.67	0.67
Cefmetazole	471.5	8.6	166.6	0.70	0.73
Cefonicid	542.6	17.0	210.8	0.98	0.92
Cefoperazone	645.7	17.2	233.4	0.91	0.92
Ceforanide	519.6	21.5	180.1	0.81	0.82
Cefotaxime	455.5	17.2	179.4	0.36	0.37
Cefotetan	575.6	19.4	215.3	0.85	0.86
Cefoxitine	427.5	16.1	144.7	0.73	0.70
Cefpodoxime	427.5	16.5	135.9	0.27	0.30
Ceftazidime	547.6	21.7	179.5	0.21	0.21
Ceftizoxime	383.4	17.1	133.0	0.28	0.31
Cefuroxime	424.4	17.0	177.2	0.33	0.33
Cephalexin	347.4	15.8	109.2	0.14	0.22
Cephalothin	396.4	8.6	128.9	0.71	0.72
Loracarbef	349.8	16.1	110.8	0.25	0.17
Moxalactame	520.5	15.6	215.7	0.60	0.61
Test set					
Ceftriaxone	554.6	21.6	200.2	0.93	0.91
Cephapirin	423.5	8.7	139.0	0.62	0.69
Cephradine	349.4	16.7	115.1	0.14	0.12

[a] From reference (Benet et al. 1996)
[b] Calculated from neural network model

The calculated/predicted f_b values of the cephalosporins from the neural network model are in good accordance with the respective experimental ones. For the training set of 20 cephalosporins and the test set of 3 cephalosporins, root mean squared errors (RMSE) between experimental f_b values and calculated/predicted f_b values are only 0.036 and 0.045, respectively. The polar molecular surface areas (S_H, $S_{O,N}$, or the sum of S_H and $S_{O,N}$) are clearly related to the capacity of a compound to form hydrogen bonds. They have been widely used to predict human intestinal absorption (Clark 1999; Fu et al. 2005a), blood-brain barrier penetration (Fu et al. 2005b), corneal permeability (Fu et al. 2001), and so on. Since hydrogen bonding is one of main factors responsible for the plasma protein binding, the polar molecular surface areas are also good predictors of plasma protein binding.

Some physicochemical parameters such as pKa, octanol/water or octanol/buffer partition coefficient are usually used to predict plasma protein binding of drugs (Gobburu and Shelver 1995; Morris and Bruneau 2000). These physicochemical parameters are determined experimentally. The major advantage of the current technique is that the predictors, MW, S_H, and $S_{O,N}$, can be easily calculated from the chemical structure of the drug, thus making preliminary physicochemical studies unnecessary and prediction of plasma protein binding convenient.

References

Aureli L, Cruciani G, Cesta MC, Anacardio R, De Simone L, Moriconi A (2005) Predicting human serum albumin affinity of interleukin-8 (CXCL8) inhibitors by 3D-QSPR approach. J Med Chem 48: 2469–2479.

Benet LZ, Kroetz DL, Sheiner LB (1996) Pharmacokinetics: The dynamics of drug absorption distribution and elimination. In: Hardman JG, Limbird LE (ed.) Goodman & Gilman' The pharmacological basis of therapeutics, 9th ed. New York, McGraw-Hill, pp. 3–27.

Clark DE (1999) Rapid calculation of polar molecular surface area and its application to the prediction of transport phenomena. 1. Prediction of intestinal absorption. J Pharm Sci 88: 807–814.

Deschamps-Labat L, Péhourcq F, Jagou M, Bannwarth B (1997) Relationship between lipophilicity and binding to human serum albumin of arylpropionic acid non-steroidal anti-inflammatory drugs. J Pharm Biomed Anal 16: 223–229.

Dewar MJS, Zoebisch GE, Healy EF, Stewart JJP (1985) AM1: A new general purpose quamtum mechanical molecular model. J. Am. Chem. Soc. 107: 3902–3909.

Fichtl B, Nieciecki A, Walter K (1991) Tissue binding versus plasma binding of drugs: General principles and pharmacokinetics consequences. Adv Drug Res 20: 118–166.

Fu XC, Liang WQ (2001) Prediction of corneal permeability using polar molecular surface areas. Pharmazie 56: 667–667.

Fu XC, Chen CX, Wang GP, Liang WQ, Yu QS (2005a) Prediction of human intestinal absorption using an artificial neural network. Pharmazie 60: 674–676.

Fu XC, Song ZF, Fu CY, Liang WQ (2005b) A simple predictive model for blood-brain barrier penetration. Pharmazie 60: 354–358.

Gobburu JVS, Shelver WH (1995) Quantitative structure-pharmacokinetic relationships (QSPR) of beta blockers derived using neural networks. J Pharm Sci 84: 862–865.

Kratochwil NA, Huber W, Müller F, Kansy M, Gerber PR (2002) Predicting plasma protein binding of drugs: a new approach. Biochem Pharmacol 64: 1355–1374.

Morris JJ, Bruneau PP (2000) Prediction of physicochemical properties. In: Bohm HJ, Schneider G (eds.) Virtual screening for bioactive molecules, Wiley-VCH Verlag GmbH, Weinheim, pp. 33–56.

Saiakhov RD, Stefan LR, Klopman G (2000) Multiple computer-automated structure evaluation model of the plasma protein binding affinity of diverse drugs. Perspec Drug Disc Des 19:133–155.

Turner JV, Maddalena DJ, Cutler DJ (2004) Pharmacokinetic parameter prediction from drug structure using artificial neural networks. Int J Pharm 270: 209–219.

Zlotos G, Bücker A, Jürgens J, Holzgrabe U (1998) Protein binding in a congeneric series of antibacterial quinolone derivatives. Int J Pharm 169: 229–238.

Shenyang Pharmaceutical University, Shenyang

Similar effects of clozapine and olanzapine on ethanol-induced ascorbic acid release in the prefrontal cortex of freely moving mice

YUE HOU, CHUN FU WU, JING YU YANG, PEI FEI GU, XIU LI BI, FANG DAI

Received August 30, 2006, accepted September 20, 2006

Dr. C. F. Wu, Department of Pharmacology, Shenyang Pharmaceutical University, Wenhua Road 103, Shenyang 110016, P.R. China
wucf@syphu.edu.cn

Pharmazie 62: 158–160 (2007)
doi: 10.1691/ph.2007.2.6692

Previous studies have shown that acute systemic administration of ethanol induced ascorbic acid (AA) release in mouse striatum and prefrontal cortex. Clozapine and olanzapine showed similar effects on ethanol-induced AA release in mouse striatum. However, their effects on ethanol-induced AA release in mouse prefrontal cortex have not been reported. Thus, their effects on this neurochemical event were further investigated in the present study. The results showed that ethanol (4.0 gkg i.p.) significantly stimulated AA release in the prefrontal cortex by about 200 of baseline in mice. Clozapine and olanzapine, at the dose of 1.0 mgkg s.c., had no effect on basal AA or ethanol-induced AA release. However, both drugs, at the dose of 10 mgkg s.c., significantly inhibited ethanol-induced AA release. The present study demonstrated for the first time that similar actions were exhibited by clozapine and olanzapine for the regulation of ethanol-induced AA release in the mouse prefrontal cortex.

Ascorbic acid (AA) is a normal constituent of the brain, and its concentration in the brain of several mammalian species, including man, is higher than that in any other organ with the exception of the adrenal cortex (Mefford et al. 1981; Schenk et al. 1982). It has been shown recently that AA acts not only as an antioxidant, but also as a neuromodulator in the central nervous system (Grunewald 1993; Rebec and Pierce 1994). For example, AA directly alters striatal dopamine binding sites (Dorris 1987; Hadjiconstantinou and Neff 1983; Kayaalp et al. 1981) and inhibits the binding of dopamine antagonists to dopamine receptors (Heikkila et al. 1982). More recently, it has been shown that acute administration of ethanol significantly enhanced the release of AA in the striatum and prefrontal cortex of freely moving mice (Hou et al. 2005, 2006). Further studies have also shown that clozapine and olanzapine similarly regulated ethanol-induced AA release in mouse striatum (Hou et al. 2005). However, their effects on ethanol-induced AA release in mouse prefrontal cortex have not been reported. Thus, in the present study, their effects on this neurochemical event were further investigated.