POSSIBILITY OF ANAESTHETICAL ACTIVITY PREDICTION OF *N*-(PYRROLIDINYL)ETHYL ESTERS OF ALKOXY-PHENYLCARBAMIC ACIDS

Stefan HATRIK[a], Jozef LEHOTAY[b] and Jozef CIZMARIK[c]

[a] *Department of Chemistry, Comenius University, 841 15 Bratislava, Slovak Republic*
[b] *Department of Analytical Chemistry, Slovak Technical University, Bratislava, Slovak Republic*
[c] *Department of Pharmaceutical Chemistry, Comenius University, 841 15 Bratislava, Slovak Republic*

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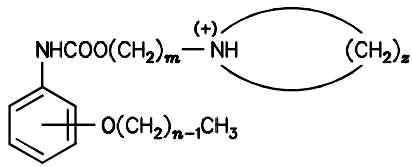
A back-propagation-type neural network consisting of three layers was used for predicting of surface and infiltration anaesthetical activity of pyrrolidinylethyl esters of 2- and 3-alkoxyphenylcarbamic acids. The prediction of local anaesthesia was based on the knowledge of this property for piperidinylethyl esters, piperidinylpropyl esters and azepanylethyl esters of 2- and 3-alkoxyphenylcarbamic acids. The structural formulas of compounds pre-processed to the numerical input and RP-HPLC capacity factors (characterizing the lipophility of tested compounds) were used for generating inputs for the neural network. Anaesthetical activities of tested drugs calculated by neural network were in a good agreement with the experimentally measured data. Average error of predicted values ranges from 2% for the surface anaesthesia of pyrrolidinylethyl esters of 2-alkoxyphenylcarbamic acids to 15% for the infiltration anaesthesia of pyrrolidinylethyl esters of 3-alkoxyphenylcarbamic acids.

The problem of the property prediction is one of the basic problems of the quantitative structure–activity relationship studies. The basic assumption is that the compounds with similar structure lead to the similar biological activity. Therefore it can be assumed that the property values change smoothly over structurally similar compounds[1].

Neural networks seem to be valuable tools for the prediction of a property at given conditions based on the knowledge of this property under other conditions[2]. The success of the neural network methods for solving of this kind of problems is due to the above mentioned continuous character of input/output functional relationships. Once trained, neural networks are quick and have a tolerance to incomplete of noisy data. This makes them helpful in a real-world environment such as biological systems considered in the presented work[3–5]. Self-adjusting algorithm of neural network can generalize the knowledge without the need of postulated models.

The homologous series of some esters of 2- and 3-alkoxyphenylcarbamic acids represent an important group of compounds because of their high local anaesthetical activity[6–8]. The aim of this work was to employ the three layer perceptron, that was trained by the back propagation of errors for predicting of surface and infiltration anaesthesia of pyrrolidinylethyl esters of 2- and 3-alkoxyphenylcarbamic acids of general formula *I*. Neural network was trained on the known data of piperidinylethyl esters, piperidinylpropyl esters and azepanylethyl esters of 2- and 3-alkoxyphenylcarbamic acids.



I

EXPERIMENTAL

The local anaesthetics under study (formula *I*) were prepared according to ref.[9] and the values of surface and infiltration anaesthesia were taken also from this papers. The experimental details of HPLC system used for the determination of capacity factors of tested local anaesthetics were published previously[10].

TABLE I
Encoded structural information[a] of some tested local anaesthetics

Drug	*n*	*P*	*z* + 1	*m*
Pyrrolidinylethyl ester of 2-ethoxyphenylcarbamic acid	2	1	5	2
Pyrrolidinylethyl ester of 3-propoxyphenylcarbamic acid	3	2	5	2
Piperidinylethyl ester of 2-butoxyphenylcarbamic acid	4	1	6	2
Piperidinylethyl ester of 3-pentyloxyphenylcarbamic acid	5	2	6	2
Azepanylethyl ester of 2-hexyloxyphenylcarbamic acid	6	1	7	2
Azepanylethyl ester of 3-heptyloxyphenylcarbamic acid	7	2	7	2
Piperidinylpropyl ester of 2-octyloxyphenylcarbamic acid	8	1	6	3
Piperidinylpropyl ester of 3-nonyloxyphenylcarbamic acid	9	2	6	3

[a] *n* Number of C-atoms in a side alkoxy chain; *P* position of the side alkoxy chain on the benzene ring; *z* + 1 number of atoms in the ring of N-containing substituent; *m* number of C-atoms in the interconnecting aliphatic chain.

Architecture of the Neural Network

A back–propagation–type neural network used in experiments had a following architecture. In our experiments the best number of hidden "neurons" was determined by training several different sized networks and picking the best. The experiments used five input "neurons" which partly characterized the molecules of local anaesthetics (number of carbon atoms in the side aliphatic chain: from one to ten; position of this chain on the benzene ring: 2-, 3-; number of atoms in a ring of nitrogen containing substituent; nuber of C-atoms in the interconnecting chain – see formula *I* and LC chromatographic capacity factor). Hidden layer consists of eight elements and output one element (logarithm of activity in the infiltration anaesthesia or surface anaesthesia, respectively). All had a feed-forward layered structure with connections only allowed between adjacent layers. Program of neural network was written in Turbo-Pascal 7.0 and run on a PC-AT computers.

TABLE II
The training set[a] of local anaesthetics

P	*n*	Piperidinylethyl esters			Azepanylethyl esters			Piperidinylpropyl esters		
		k	log (*A*)	log (*B*)	*k*	log (*A*)	log (*B*)	*k*	log (*A*)	log (*B*)
2	2	–	–	–	–	–	–	1.98	0.49	0.56
	3	–	–	–	2.06	0.55	1.27	2.11	0.68	0.78
	4	1.80	1.10	1.34	2.47	1.02	1.18	2.57	1.07	1.16
	5	2.15	1.46	2.00	2.92	1.77	1.88	3.10	1.70	1.83
	6	2.76	1.96	2.02	3.58	1.80	1.42	3.71	1.87	2.24
	7	3.30	2.00	2.23	4.34	2.06	2.28	4.70	2.08	2.41
	8	4.08	1.98	2.17	–	–	–	6.10	2.42	1.27
	9	5.21	1.97	1.43	–	–	–	7.50	2.21	1.22
	10	6.82	1.43	0.85	–	–	–	–	–	
3	2	1.18	0.20	1.46	–	–	–	1.59	0.59	0.59
	3	1.41	1.04	1.55	1.92	1.43	1.97	1.74	1.34	0.52
	4	–	–	–	2.35	1.76	1.60	2.31	1.46	1.73
	5	2.03	1.90	2.13	2.94	1.81	1.78	2.86	1.98	0.94
	6	2.65	1.92	1.89	3.56	1.78	1.44	3.43	1.77	0.90
	7	3.37	1.83	1.78	–	–	–	4.26	2.10	1.00
	8	–	–	–	5.69	0.08	0.83	5.50	1.74	0.96

[a] *n* Number of C-atoms in a side alkoxy chain; *P* position of the side alkoxy chain on the benzene ring; *k* HPLC capacity factor; log (*A*) logarithm of surface anaesthetical activity; log (*B*) logarithm of infiltration anaesthetical activity.

RESULTS AND DISCUSSION

The success of neural network method strongly depends on the pre-processing of the knowledge about the properties of the compounds into a form acceptable for neural network. Reversed phase chromatography (especially with C_{18} stationary phase) can be successfully employed for the characterization of lipophility of tested derivatives of phenylcarbamic acid[11,12]. Therefore the lipophilities of tested drugs which strongly influence the transport of the drug to the receptor were characterized by the capacity factors measured with C_{18} reversed phase chromatography[10]. The structural information of tested drugs was simply coded as can be seen in the following examples (Table I).

The training of the neural network was accomplished by repeated cycling through the training data (data of piperidinylethyl esters, piperidinylpropyl esters and azepanylethyl esters of 2- and 3-alkoxyphenylcarbamic acids, see Table II), presenting patterns at the input elements and indicating associations of all elements. In the prediction the outputs (log (*A*) – surface anaesthesia, log (*B*) – infiltration anaesthesia) were calculated according to the weights obtained in the training process. The results of training process were evaluated by the average sum-of-squares error (*SSO* = 0.023) of calculated and experimental outputs, the gradient of function (grad = 0.0102) and the index of correlation (I_c^2 = 0.975). The results of prediction process are listed in Table III. As can be seen in Table III an average error of predicted values ranges from 2 to 15%. The errors depend both on the position of a side alkoxy chain and the type of the anaesthetical

TABLE III
The results[a] of the prediction of surface and infiltration anaesthesia for the pyrrolidinylethyl esters of 2- and 3-alkoxyphenylcarbamic acid

n	log (*A*) *o*-position		log (*B*) *o*-position		log (*A*) *m*-position		log (*B*) *m*-position	
	exp	calc	exp	calc	exp	calc	exp	calc
5	0.95	1.00	1.20	1.30	1.61	1.59	1.78	1.58
6	1.92	1.95	1.64	1.84	1.34	1.32	1.04	1.07
7	2.11	2.12	1.82	1.95	1.46	1.11	1.20	0.95
8	2.31	2.22	1.65	1.41	1.20	0.98	0.85	0.72
e_{av}	2.1		9.3		11.3		14.6	
e_{min}	0.5		8.3		1.2		2.9	
e_{max}	3.9		12.2		24.9		29.4	

[a] *n* Number of C-atoms in a side alkoxy chain; log (*A*) logarithm of surface anaesthesia; log (*B*) logarithm of infiltration anaesthesia; exp experimentally measured anaesthesia; calc anaesthesia predicted by neural network; e_{av} average error (%); e_{min} minimal error (%); e_{max} maximal error (%).

activity. The success of anaesthesia prediction of 2-substituted drugs in comparison with 3-substituted drugs can be explained by the lower solubility of *meta* derivatives. They can form nonhomologenous solutions at the concentration under study. The fact that the prediction of the surface anaesthesia in comparison with infiltration anaesthesia was more successful can be explained by the higher precision of the surface anaesthesia measurements. During the surface anaesthesia measurements studied drug interacts directly with receptor and on the other hand in the case of infiltration anaesthesia it must penetrates through a lipophilic layer. By this way the drug can be partly sorbed and this phenomena can commonly decrease the reproducibility of anaesthesia measurements.

REFERENCES

1. Kerzic D., Blazic B. J., Batagelj V.: J. Chem. Inf. Comput. Sci. *34*, 391 (1994).
2. Gakh A. A., Gakh E. G., Sumpter B. G., Noid D. W.: J. Chem. Inf. Comput. Sci. *34*, 832 (1994).
3. Rowe R. C., Mulley V. J., Hughes J. C., Nabney J. T., Debenham R. M.: LC-GC *7*, 36 (1994).
4. Aoyama T., Ichikawa H.: Chem. Pharm. Bull. *39*, 372 (1991).
5. Aoyama T., Suzuki Y., Ichikawa H.: J. Med. Chem. *33*, 2583 (1990).
6. Cizmarik J., Borovansky A., Svec P.: Cesk. Farm. *25*, 118 (1976).
7. Cizmarik J., Borovansky A., Svec P.: Acta Fac. Pharm. Univ. Comenianae *26*, 53 (1976).
8. Cizmarik J., Borovansky A., Tumova I.: Pharmazie *42*, 702 (1987).
9. Cizmarik J., Polasek E., Svec P., Racanska E.: Cesk. Farm. *42*, 88 (1993).
10. Cizmarik J., Lehotay J., Pham Thi Viet Nga, Bednarikova A.: Pharmazie *49*, 368 (1994).
11. Lehotay J., Bednarikova A., Cizmarik J., Pham Thi Viet Nga: Pharmazie *48*, 470 (1993).
12. Lehotay J., Cizmarik J., Pham Thi Viet Nga, Bednarikova A.: Pharmazie *49*, 286 (1994).