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QSAR of 3-methylfentanyl derivatives studied with neural networks method[1]

TANG Yun, WANG Hong—Wu, CHEN Kai—Xian, JI Ru—Yun (*Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 200031, China*)

AIM: To use neural networks, which simulate the functions of living nervous systems, in QSAR studies; **METHODS**: Using the back-propagation neural networks program devised by us, combining with partial least squares (PLS) method, we studied the relationships of quantum chemical indices and analgesic activities of 25 3-methylfentanyl derivatives; **RESULTS**: Through learning process, a good QSAR model was established, and the activities of these compounds were predicted; the correlation between the activities and quantum chemical indices: the net charge of the atom N_1, the net charge of the atom O_{16}, the torsional angle of atoms C_{10}-C_9-N_8-C_4, the interatomic distance between atom C_7 and the center of phenyl plane C_{9-14} (PhA), is quite well-matched. Based on these results, an interactive pattern between 3-methylfentanyl derivatives and opioid receptors was suggested; **CONCLUSION**: Not only are the results of neural networks superior to those of PLS method but they also provide accurate predictions of the activity of the compounds and also combine the PLS method with neural networks.

KEY WORDS neural networks (computer); 3-methylfentanyl; analgesics; structure-activity relationship

The formulation of quantitative structure-activity relationships (QSAR) has had a momentous impact upon medicinal chemistry in the past 30 years. The biological activities of drug molecules can be matched to a linear combination of the physicochemical parameters of the corresponding drug[1]. There have been many attempts to include cross-product terms in the regression analysis, but this only added complexity to the study and did not achieve in significant improvements.

The method of partial least squares (PLS)[2] is generally used in handling regression problems with latent variables. The power of PLS is due to the fact that latent variables describe the maximum predictive variance of a data set, and at the same time provide maximal fit to the model. By using only a significant number of latent variables in the procedure, a noise filtering effect was obtained which resulted in an improved predictive ability of PLS. However, PLS remains a linear evaluation method.

There has been a growing interest in the application of neural networks in the field of QSAR[3-5]. This new technic is superior to the traditional Hansch approach. Neural networks system is a computer-based one derived from a simplified concept of the brain in which a number of nodes, called processing elements or neurons, are interconnected in a network-like structure. The key strength of the neural networks is that in the presence of hidden layers, neural networks are able to perform non-linear mapping of physicochemical parameters to a corresponding biological activity implicitly. However, there is a hidden danger of "overfitting," namely, the number of vari-

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ables under the control of the neural networks may exceed the number of data points that are needed to describe the hypersurface.

This study is to use the PLS method to select the variables to overcome the danger of "overfitting," compare the performance of neural networks combined with PLS method with the ability to predict activity as a main criterion, and explore the relationships of quantum chemical indices and analgesic activity of 3-methylfentanyl derivatives in order to give more information for designing new drugs.

METHODS

The basic processing element of neural networks is the neuron or unit (Fig 1).

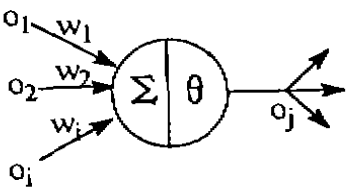


Fig 1. A model of the neuron.

A neuron has some inputs and one output. After some inputs have entered into the neuron, a summation is calculated[4],

$$i_j = \Sigma w_{ji} o_i + \Theta_j$$

where o_i is the ith input, w_{ji} is the weight of the bond connecting unit j with input unit i, Θ_j is the weight of the bond connecting unit j to the input bias unit, i_j is the input summation of unit j.

Then, through a nonlinear transfer function, the output is attained[4]:

$$o_j = f(i_j) = \frac{1}{1 + \exp(-\beta i_j)}$$

where o_j is the output of unit j, β is a gain, being able to adjust the form of the function, usually $\beta = 1$.

Every input must be scaled between 0 and 1 before.

Many neurons are interconnected to form neural networks. The method of back-propagation neural networks is widely used in supervising learning for multiple-layer nets, which seems to be best adapted for solving pattern recognition problems. It has at least 3 layers-one input layer, one or more hidden layers, and one output layer (Fig 2), where b is a bias.

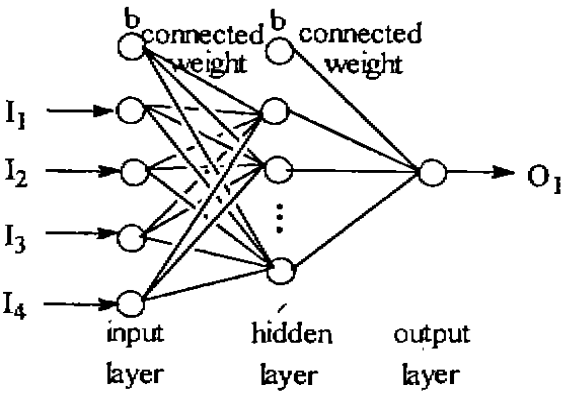


Fig 2. A model of 3-layer back-propagation neural networks with 4-*x*-1 configuration.

Before the beginning of learning process, an error function E should be defined as follows[4]:

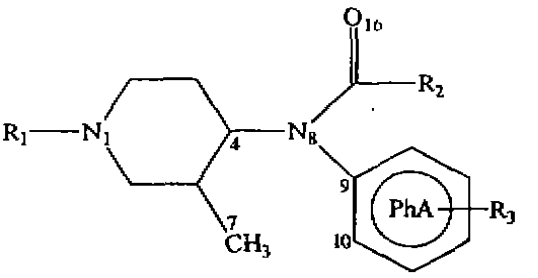
$$E = \Sigma E_p = 0.5 \Sigma \Sigma (t_{pl} - o_{pl})^2$$

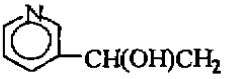
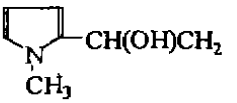
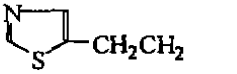
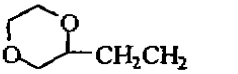
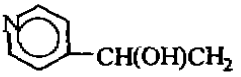
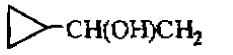
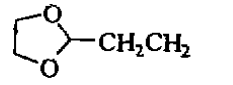
where E_p is the error of pth learning pattern, t_{pl} is the target output, o_{pl} is the actual output.

Learning through the neural networks is achieved by minimizing E, usually using gradient descent method. Following the learning process, a fixed model is attained, then it can be used to test some new cases.

3-Methylfentanyl is a highly potent analgesic, acting selectively on opioid receptors, and its analgesic effect is over 1000 times more potent than that of morphine. Some previous papers had studied the relationships between the physicochemical parameters and the activity of 3-methylfentanyl derivatives[6], and showed that the correlation was not well accorded. Therefore, the relationships between quantum chemical indices and the activity were studied.

At first, 25 3-methylfentantyl derivatives (Fig 3) synthesized by our institute were calculated by MNDO method on a microcomputer AST PII486/33. The crystal structure was taken as initial conformation for ohmefentanyl (1) which possessed the most potent analgesic activity so far attained. Similar structures were selected as initial conformations for other compounds. After these conformations had been minimized, many chemical indices was obtained.



Compound	R_1	R_2	R_3
1	$C_6H_5CH(OH)CH_2$	C_2H_5	H
2		C_2H_5	H
3	$C_6H_5CH_2CH_2$	C_2H_5	H
4	$C_6H_5CH_2CH(CH_3)$	C_2H_5	H
5		C_2H_5	H
6		C_2H_5	H
7		C_2H_5	H
8	$C_6H_5CH(OH)CH(CH_3)$	C_2H_5	H
9		C_2H_5	H
10		C_2H_5	H
11		C_2H_5	H

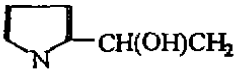
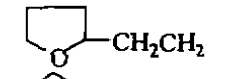
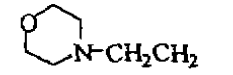
Compound	R_1	R_2	R_3
12		C_2H_5	H
13		C_2H_5	H
14		C_2H_5	H
15	$C_6H_5COCH_2$	C_2H_5	H
16	$C_6H_5CH_2CH_2$	$CH_3(CH_2)_2$	H
17	$C_6H_5CH_2CH_2$		H
18	$C_6H_5CH_2CH_2$	CH_3	H
19	$C_6H_5CH_2CH_2$	$CH_3(CH_2)_3$	H
20	$C_6H_5CH_2CH_2$	$C(CH_3)_3$	H
21	$C_6H_5CH_2CH_2$	$CH(CH_3)_2$	H
22	$C_6H_5CH_2CH_2$		H
23	$C_6H_5CH_2CH_2$	C_2H_5	H
24	$C_6H_5CH_2CH_2$	C_2H_5	3'-OH
25	$C_6H_5CH_2CH_2$	C_2H_5	3'-OCH_3

Fig 3. Structures of 3-methylfentanyl derivatives.

The results of quantum chemical calculation had been analyzed by the PLS method, and 4 indices showing high accordance with analgesic activity were selected from all the quantum chemical indices. These were: the net charge of the atom N_1, the net charge of the atom O_{16}, the torsional angle of atoms C_{10}-C_9-N_8-C_4, the interatomic distance between atom C_7 and the center of phenyl plane C_{9-14}(PhA) (Tab 1).

Then, the back-propagation neural networks program written by us in Turbo C programming language was used. The 4 indices chosen were regarded as the input data of neural networks, and the target output datum was the analgesic activity lg (1/C) of 3-methylfentanyl derivatives excerpted from the literature, where C was ED_{50} tested with hot plate method in mice. The input nodes was 4 and the output nodes

was 1. The calculation was also carried out on the microcomputer AST PII486/33.

RESULTS AND DISCUSSION

The input data were normalized to give values between 0.1 and 0.9. Training continued until there was no further decrease in overall error after a period of 10 000 cycles. The quality of QSAR was assessed by 2 statistical variables: the correlation coefficient (CC) and the residual variance (RV). They were defined by the following expressions[5]:

$$CC = 1 - \frac{\Sigma(\text{activity}_{\text{observed}} - \text{activity}_{\text{predicted}})^2}{\Sigma(\text{activity}_{\text{observed}} - \text{activity}_{\text{observed,average}})^2}$$

$$RV = \frac{\Sigma(\text{activity}_{\text{observed}} - \text{activity}_{\text{predicted}})^2}{\text{number of compounds} - 1}$$

The number of hidden nodes is important in the network's performance. In order to determine the number of hidden nodes, the 25 compounds were divided into 2 data sets. One testing set of 4 compounds randomly selected (**3, 8, 15, 24**) was used as a guide to the accuracy of the trained networks and the remaining 21 served as a training set. Five networks were constructed with a configuration of 4-x-1, where x = 2 — 6. The number of input nodes was 4, that of the hidden nodes was x and of the output nodes 1. Each was simulated at least 4 times. When x = 2, 3, 4, 5, 6, the smallest RV for the testing set in each configuration were 0.461, 0.262, 0.235, 0.287, 0.399, respectively. There was the lowest

Tab 1. Input data of neural networks from the calculated results of quantum chemistry MNDO method and the observed analgesic activity of each derivative of 3-methylfentanyl.

Compound	Charge O_{16}	Charge N_1	Angle C_{20}-C_9-C_8-C_4	Distance C_7-PhA	Activity lg (1/C)
1	−0.3498	−0.4226	80.599	4.3758	8.539
2	−0.3310	−0.4184	84.861	5.2298	7.602
3	−0.3306	−0.4278	84.330	5.1987	7.545
4	−0.3299	−0.4237	83.791	5.2716	7.328
5	−0.3327	−0.4192	86.395	5.1656	7.152
6	−0.3310	−0.4236	84.695	5.1730	7.082
7	−0.3325	−0.4282	85.695	5.1755	7.012
8	−0.3372	−0.4260	86.445	5.1153	6.928
9	−0.3336	−0.4222	85.833	5.1644	6.870
10	−0.3330	−0.4219	85.740	5.1817	6.559
11	−0.3323	−0.4266	85.379	5.1745	6.556
12	−0.3580	−0.4232	84.119	4.8721	6.524
13	−0.3314	−0.4236	86.195	5.1488	6.499
14	−0.3315	−0.4303	86.469	5.1935	6.383
15	−0.3392	−0.4227	86.871	5.0935	6.056
16	−0.3313	−0.4245	84.547	5.1697	6.921
17	−0.3335	−0.4293	86.187	4.9249	6.866
18	−0.3383	−0.4259	86.463	5.1292	6.456
19	−0.3320	−0.4282	86.338	5.1334	6.229
20	−0.3270	−0.4293	86.683	5.1417	6.157
21	−0.3331	−0.4304	85.170	5.1273	6.014
22	−0.3339	−0.4284	86.362	5.1417	5.963
23	−0.3447	−0.4290	86.164	4.9646	5.462
24	−0.3312	−0.4274	85.659	5.1756	6.726
25	−0.3301	−0.4288	85.952	5.1717	6.427

testing RV when x=4, ie, x=4 was the best configuration. Because the 4 compounds were randomly selected, they were conceivably representative to the results. Therefore, the configuration of 4-4-1 was constructed for the following task.

At first, the activities of 25 compounds were fitted, and the results were excellent (Tab 1).

Then, in order to test the predictive capability of the network, a cross-validation procedure was carried out. In this process 1 compound was removed from the data set, and the remaining 24 served as the training set. After training, the indices of the removed compound were put into the network and the predicted activity was evaluated. This procedure was repeated 25 times and the predicted activities of the entire data set were obtained (Tab 2). The cross-validated CC and RV were 0.839 and 0.0651, respectively. It was confident that the neural networks were able to provide reliable predictions of analgesic activities of the novel 3-methylfentanyl derivatives.

Tab 2. Results of neural networks analysis for 3-methylfentanyl derivatives and comparison with PLS method.

Compound	Observed activity lg (1/C)	Neural nets Fit[a]	Res[b]	Neural nets Pre[c]	Res[b]	PLS Pre[c]	Res[b]
1	8.539	8.541	−0.002	7.868	0.671	8.478	0.061
2	7.602	7.562	0.040	7.447	0.155	7.486	0.116
3	7.545	7.598	−0.053	7.462	0.083	7.091	0.454
4	7.328	7.279	0.049	7.409	−0.081	7.535	−0.207
5	7.152	7.127	0.025	7.299	−0.147	6.861	0.291
6	7.082	6.937	0.145	6.954	0.128	7.238	−0.156
7	7.012	6.769	0.243	6.723	0.289	6.518	0.494
8	6.928	6.550	0.378	6.575	0.353	6.241	0.687
9	6.870	6.875	−0.005	6.815	0.055	6.826	0.044
10	6.559	6.778	−0.219	6.809	−0.250	6.892	−0.333
11	6.556	6.805	−0.249	6.735	−0.179	6.744	−0.188
12	6.524	6.523	0.001	6.459	0.065	6.542	−0.018
13	6.499	6.518	−0.019	6.624	−0.125	6.706	−0.207
14	6.383	6.367	0.016	6.135	0.248	6.135	0.248
15	6.056	6.078	−0.022	5.974	0.082	6.239	−0.183
16	6.921	7.012	−0.091	7.225	−0.304	7.221	−0.300
17	6.866	6.865	0.001	6.329	0.537	6.387	0.479
18	6.456	6.549	−0.093	6.364	0.092	6.187	0.269
19	6.229	6.249	−0.020	6.306	−0.077	6.337	−0.108
20	6.157	6.027	0.130	6.010	0.147	6.344	−0.187
21	6.014	5.986	0.028	6.269	−0.255	6.564	−0.550
22	5.963	6.297	−0.334	6.269	−0.306	6.232	−0.269
23	5.462	5.476	−0.014	5.665	−0.203	5.928	−0.466
24	6.726	6.624	0.102	6.581	0.145	6.637	0.089
25	6.427	6.470	−0.043	6.507	−0.080	6.489	−0.062
Comparison CC		0.948		0.839		0.751	
Comparison RV		0.0209		0.0651		0.1008	

[a] Fitted activity, [b] Residual = obsd (lg 1/C) − calc (lg 1/C), [c] Predicted acitivity.

To investigate the relationships between the 4 indices and the analgesic activity, based on the former learning pattern, the variation of the activity was monitored by changing the value of 1 input while keeping the remaining 3 inputs constant at 30 % of their maximal ranges (Fig 4). On the basis of the resulting plots, the biological activity seems to be nonlinear with the 4 indices, among which, the net atomic charges of atom N_1 and O_{16} were important to the analgesic activity. We suggested that N_1 and O_{16} be the negative electric centers and bind to the positive electric centers of the receptor. The interatomic distances of C_7-PhA and the torsional angles of C_{10}-C_9-N_8-C_4 were also important to the analgesic activity, which indicated that the 3-methyl group and the phenyl (PhA) group bound to the hydrophobic pockets of the receptor.

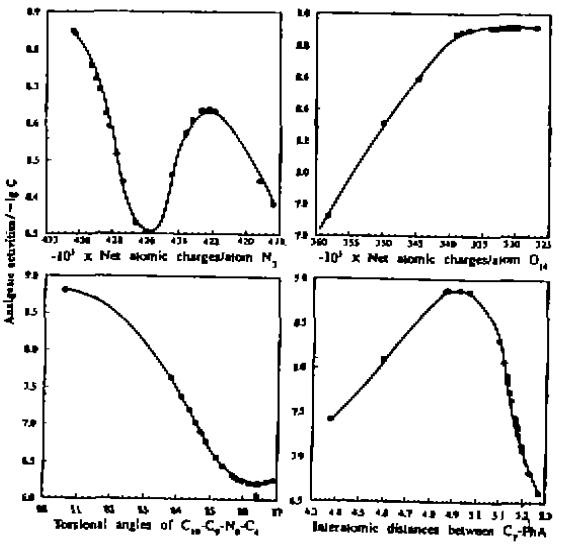


Fig 4. Relationships between analgesic activity and 4 indices.

Finally, a comparison of neural networks and PLS method was performed. Using PLS method to the same data analysis, results of QSAR were listed in the last 2 columns of Tab 3. The CC and RV of PLS method were 0. 751 and 0. 1008, respectively. It was clear that neural networks outperforms PLS method and provided a superior mapping of quantum chemical indices to the analgesic activity. However, PLS method has a higher capability to select parameters, and it was wise to combine the PLS method with neural networks.

CONCLUSION

Our results add to the growing support for the use of neural networks in QSAR studies. Not only are the results superior to those of PLS method but also they provide accurate predictions of the activity of the compounds and also combine the PLS method with neural networks. We suggest such an interactive pattern between 3-methylfentanyl derivatives and the opioid receptors: the electronegative centers on N_1 and O_{16} are essential structural features for their binding to the receptors; 3-methyl group can bind a small hydrophobic pocket on the receptor. 3-Methyl group also affects the position and orientation of the phenyl group (PhA), which binds another pocket on the receptor, the spatial position relationships of these 2 substituents exhibit a vital influence on the binding ability.

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应用神经网络方法研究3-甲基芬太尼类似物的定量构-效关系

唐 菁、王红武、陈凯先、嵇汝运 (中国科学院上海药物研究所，上海 200031，中国)

目的：应用神经网络这种新型的信息处理系统研究定量构-效关系。 **方法**：应用自编的逆传播神经网络算法，结合偏最小二乘法，研究了25个3-甲基芬太尼类似物的量子化学指数和镇痛活性之间的定量关系。 **结果**：得到了良好的QSAR模型，3-甲基芬太尼类似物的量子化学指数即 N_1 和 O_{16} 上净电荷、C_{10}-C_9-N_5-C_4 二面角、C_7-PhA 中心的距离与镇痛活性之间具有很好的相关性，并根据计算结果，提出了芬太尼类似物与阿片受体的结合模式。 **结论**：神经网络方法研究结果优于单纯偏最小二乘法的结果，且能对化合物活性进行准确的预测。

关键词 神经网络(计算机)；3-甲基芬太尼；镇痛药；结构－活性关系

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Assay of metoprolol and α-hydroxymetoprolol in human urine by reversed-phase liquid chromatography with direct-injection[1]

XIE Hong-Guang, ZHOU Hong-Hao
(Department of Pharmacology, Hu-nan Medical University, Changsha 410078, China)

AIM: To develop an HPLC method with direct injection for the simultaneous determination of metoprolol (M) and α-hydroxymetoprolol (HM) in human urine. **METHODS**: Urine (200 μl) was diluted with eluate and injected into the chromatograph. Samples were seperated on an ODS column by isocratic binary elution and monitored by fluorescence detection. **RESULTS**: No potential interfering peaks were identified. M and HM gave rapid elution and baseline resolution. The linear curves of both analytes ranged between 0.2 and 100 $mg \cdot L^{-1}$. The response sensitivity was approximately 0.1 $mg \cdot L^{-1}$ and the coefficients of variation in the assay were within 8 % for both compounds. A typical application in oxidation phenotyping was presented for one healthy volunteer who received 100 mg of oral metoprolol. **CONCLUSION**: The method can be used for the investigation of genetic polymorphism of metoprolol oxidation in the large populations.

KEY WORDS metoprolol; α-hydroxymetoprolol; high pressure liquid chromatography; urine

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