QSAR ANALYSIS OF ANTIARRHYTHMIC PHENYLPYRIDINES USING PARTIAL LEAST SQUARES METHOD

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Abstract - Antiarrhythmic activity data of phenylpyridines were investigated by the PLS method. The PLS equation supported for the modulated-receptor hypothesis in Na channels on cardiac muscle cell. From the obtained PLS modelling equation, the potent antiarrhythmic agents can be produced by increasing the MR value of the substituent R on benzene ring, increasing the proton affinity (corresponding to pKa) of an amino group of a phenylpyridine.

Key word phenylpyridines, PLS, antiarrhythmic activity, QSAR

Antiarrhythmic agents are compounds that improve cardiac overexcited states such as atrial fibrillation, atrial flutter, and paroxysmal tachycardia. The antiarrhythmic agents were classified into 4 classes by Vaughan Williams [1]. Phenylpyridines are one of the most popular antiarrhythmic agents which is considered to belong to class 1 such as procainamide, lidocaine, and phenytoin etc. It is very important to reveal a quantitative structure-activity relationships (QSAR) of antiarrhythmic phenylpyridines for design of new agents.

Recently, Shigyou et al. have synthesized phenylpyridines and evaluated these compounds in mice for antiarrhythmic activity against chloroform-induced arrhythmia [2]. We have performed a partial least squares (PLS) analysis in order to seek the relationships between the antiarrhythmic activity data and physico-chemical parameters. PLS is a relatively new multivariate statistical method for QSAR analysis developed by Wold [3,4,5]. This method relates the systematic variance within a data set y to some dependent properties x using latent variable t . In this study, y and x are antiarrhythmic activity data and physico-chemical parameters of phenylpyridines, respectively. The fourteen phenylpyridines with known antiarrhythmic activities have been studied. The chemical structures are shown in Fig. 1.

Fig. 1. The chemical structures of phenylpyridines

A y -variable was created with the value 0 for 7 inactive compounds and 1 for 7 active compounds according to the experimental values which were inhibition rate of chloroform-induced arrhythmia. Three physico-chemical parameters MR, TOR, PA were used in the PLS analysis. MR is a molar refractivity of R. TOR is a torsion angle between amide function and aromatic ring. PA is a proton affinity of an amino group calculated by the semiempirical AM1 method [6,7].

The biological and physico-chemical parameters were autoscaled to unit variance. The number of PLS components A , that is the number of latent variables, are determined to maximize a predicted correlation coefficient R_{pred} .

A two-component significant PLS model equation was obtained ($A=2$).

$$y = 0.566MR + 0.288TOR - 0.633PA \quad (1)$$

If $y \geq 0.5$ and $y < 0.5$, then the compound was classified to be active and inactive, respectively. The recognition rate was 86%. The validity of PLS model was confirmed by leave-one-out procedure. The predictive ability was 79%. Because the predictive ability is high enough, the PLS model is reliable for the prediction of antiarrhythmic activity. From the obtained PLS modelling equation, the potent antiarrhythmic agents can be produced by increasing the MR value of the substituent R on benzene ring, increasing the torsion angle between amide function and benzene ring and decreasing the proton affinity (corresponding to pK_a) of an amino group of a phenylpyridine.

The modulated-receptor hypothesis was proposed by Hille [8,9] as a mechanism of the antiarrhythmic agent-action for Na channels. According to this hypothesis, there is a receptor site for the antiarrhythmic agents in Na channels and by binding to this receptor site the agents consequently close a h-gate and generate an antiarrhythmic action. Then increasing the dispersion force (MR) of substituent R leads to the stronger interaction to the receptor site in Na channels and h-gate is closed more tightly and as a result more increasing activity is generated [8] (Fig. 2). The PLS model equation corresponds to this Hille hypothesis. The sign of PA in equation (1) means that weakening the

Fig. 2. Diagram of an antiarrhythmic agent binding in the site of a Na channel. By binding to this receptor site the agent closes a h-gate. The agent binding to the receptor site can block an influx of Na ions (Na currents) from extracell to intracell.

basicity of an amino group is advantage for the activity, because a neutral form of the agent actually has an action. The sign of TOR in equation corresponds to the QSAR equations of antiarrhythmic activity of α -amino-anilides [10,11]. Thus we have analyzed the antiarrhythmic activity data of phenylpyridines and supported for the modulated-receptor hypothesis in Na channels on cardiac muscle cell by the PLS model.

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