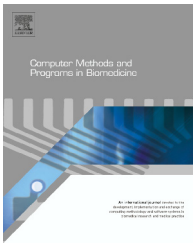
COMPUTER METHODS AND PROGRAMS IN BIOMEDICINE 111 (2013) 330–337

journal homepage: www.intl.elsevierhealth.com/journals/cmpb



The application of support vector regression for prediction of the antiallodynic effect of drug combinations in the mouse model of streptozocin-induced diabetic neuropathy

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ARTICLE INFO

Article history:
Received 12 May 2012
Received in revised form
16 April 2013
Accepted 25 April 2013

Keywords:
Diabetes-induced neuropathic pain
Dihydrofuran-2-one
Mechanical allodynia
Pregabalin
Streptozocin
Support vector regression

ABSTRACT

Drug interactions are an important issue of efficacious and safe pharmacotherapy. Although the use of drug combinations carries the potential risk of enhanced toxicity, when carefully introduced it enables to optimize the therapy and achieve pharmacological effects at doses lower than those of single agents. In view of the development of novel analgesic compounds for the neuropathic pain treatment little is known about their influence on the efficacy of currently used analgesic drugs.

Below we describe the preliminary evaluation of support vector machine in the regression mode (SVR) application for the prediction of maximal antiallodynic effect of a new derivative of dihydrofuran-2-one (LPP1) used in combination with pregabalin (PGB) in the streptozocin-induced neuropathic pain model in mice. Based on SVR the most effective doses of co-administered LPP1 (4 mg/kg) and PGB (1 mg/kg) were predicted to cause the paw withdrawal threshold at 6.7 g in the von Frey test. In vivo for the same combination of doses the paw withdrawal was observed at 6.5 g, which confirms good predictive properties of SVR.

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1. Introduction

Neuropathic pain is a drug-resistant type of pain which still remains a serious medical problem worldwide. Neuropathies with concomitant spontaneous pain episodes occur as a consequence of nerve injuries caused by a large variety of factors, including diseases of nerves and neuronal tissue injuries with subsequent dysfunctions of the central or peripheral nervous system. The pharmacotherapy used for the relief of neuropathic pain comprises several pharmacological classes, of which antiepileptic drugs (AEDs), antidepressants, opioid analgesics and local anesthetic agents play a pivotal role [1–7]. For instance, lacosamide has been recently approved for the treatment of epilepsy, while its possible use in the treatment of neuropathic pain is still under clinical investigation [8,9]. Two other, the second generation AEDs, namely gabapentin (GBP) and pregabalin (PGB) bind to the auxiliary $\alpha_2\delta$ subunit of N-type voltage-gated calcium channels (VGCCs) in the central nervous system (CNS) [6,10] and this action can be beneficial not only as an add-on treatment of partial seizures, but also in many non-epileptic indications, including bipolar disorder, anxiety, hot flashes and chronic pain [10]. In view of the enhanced expression of VGCCs in the

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http://dx.doi.org/10.1016/j.cmpb.2013.04.018

neuropathic and other chronic pain syndromes [11], recently GBP and PGB have become the first-line treatment of postherpetic neuralgia, trigeminal neuralgia, migraine, reflex sympathetic dystrophy and diabetic neuropathy [10]. In animal models the analgesic activity of GBP and PGB was also confirmed. Many lines of evidence demonstrate their effectiveness in the formalin model of tonic pain (the second-inflammatory phase) [12], carrageenan-induced paw edema [13,14] and neuropathic pain (partial sciatic nerve ligation, spinal nerve ligation, chronic constriction injury and diabetic neuropathy) [4,6,10,15] with no effect in some acute pain models [10,13,16].

The growing knowledge about pain phenomenon gives the opportunity to affect novel drug targets for the attenuation of neuropathy-related nociceptive responses. The poor therapeutic efficacy of drugs used for neuropathic pain treatment and a significant number of drug-resistant patients on analgesic monotherapy [4] have recently led to the development of new therapeutic strategies to relieve pain, such as ziconotide [17–19]. The use of combinations of analgesics belonging to distinct pharmacological classes is also an important approach to this issue as it can provide synergistic or additive analgesic effects with the increased efficacy or reduced number of side effects. The application of analgesic drugs in combinations was found very efficacious both in acute [20] and chronic [1] pain conditions. Such a strategy enables to reduce the effective doses of individual drugs and it aims at the achievement of main therapeutic goals, including the facilitation of patient compliance, improvement of efficacy without increasing adverse reactions or reduction of adverse effects without loss of their efficacy [20]. Among the examples of such drug combinations there is paracetamol used either with non-steroidal anti-inflammatory drugs (NSAIDs) [20] or tramadol [5,21], nortriptyline and GBP [4], GBP and clonidine [7], PGB and tapentadol [1].

Despite the fact that there are many therapeutic approaches to neuropathic pain treatment, there is still a great need for seeking new analgesic compounds which could be used alone or in combination with available drugs. Recently we have demonstrated pronounced analgesic and local anesthetic activities of 3-[4-(3-trifluoromethylphenyl)-piperazin-1-yl]-dihydrofuran-2-one dihydrochloride (LPP1) in rodent models of acute pain and local anesthesia [22,23]. We also used the support vector machine in the regression mode (SVR) as an effective tool for the prediction of toxic dose regimens in the mouse model of electroconvulsive threshold [24].

In the following paper we demonstrate the possible application of SVR for prediction of the analgesic effect of LPP1 and PGB administered in a variety of dose combinations in the mouse model of diabetes-induced neuropathic pain. We use SVR as a tool to forecast the influence of different combinations of LPP1 and PGB on the mechanical (tactile) allodynia threshold measured using von Frey analgesia meter. Based on the results obtained in this study we compare the analgesic efficacy of diverse combinations of LPP1 and PGB (simultaneous administration) to the effects obtained when each of these two drugs is applied alone. In addition, as a part of the research, the dose set for mixtures giving the maximal analgesic effect is predicted by SVR and the efficacy of this computer simulation is then confirmed in vivo. Noteworthy, the use of SVR simulation enables to limit the number of animals used for behavioral research and this remains in agreement with the recommendations of ethical committees. Since SVR investigates the tested compounds more thoroughly than it is possible using live animals, this method seems to be a very helpful tool for the preliminary prediction of additional dose combinations at which maximum efficacy of co-administered drugs is observed.

2. General procedure and background

2.1. *Specifications for study design – general procedure*

In this study we first evaluated the analgesic activity of LPP1 and PGB administered alone to establish pain reactivity thresholds for mechanical stimulation for each of these compounds. Then, the same procedure was conducted for various dose combinations of PGB and LPP1. The highest tested dose of LPP1 or PGB administered alone was 30 mg/kg. For the prediction the mixtures were also prepared to obtain cumulative doses that did not exceed 30 mg/kg in total.

The following steps of the study were distinguished:

I. The evaluation of mechanical allodynia threshold for LPP1 in the von Frey test: doses 1, 10, 30 mg/kg (intraperitoneal pretreatment).
II. The evaluation of mechanical allodynia threshold for PGB in the von Frey test: doses 1, 10, 30 mg/kg (intraperitoneal pretreatment).
III. The evaluation of mechanical allodynia threshold for combinations of LPP1 and PGB. The doses used in this experiment are shown in Table 2.
IV. Preprocessing phase. Data from I to III were randomly divided into learning and testing data. The model for mixtures was built – learning and SVR testing.
V. Prediction phase for various combinations (1–30 mg/kg) of LPP1 and PGB.
VI. Based on results from prediction phase (V) the establishment of doses of the mixture (LPP1 + PGB) for which the antiallodynic effect achieves its maximum.
VII. Confirmation of the method's effectiveness under in vivo conditions. Evaluation of the analgesic activity of predicted in simulations (VI) combined doses of LPP1 and PGB giving maximal efficacy.

2.2. *Background on support vector regression*

The basis of support vector machines (SVM) have been laid by Vapnik [25] and the methodology is gaining popularity ever since. SVMs that deal with classification problems are called support vector classification (SVC) and SVMs dealing with modeling and prediction are called support vector regression. Because the formulation of SVR is based on structural risk minimization, the SVR typically shows better performance than the conventional algorithms based on empirical risk minimization such as artificial neural network and partial least squares. Support vector regression (SVR) [26] has been successfully used to solve forecasting problems in many fields,

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