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Short communication

Molecular properties of psychopharmacological drugs determining non-competitive inhibition of 5-HT_{3A} receptors

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ABSTRACT

We developed a structure–property–activity relationship (SPAR)-model for psychopharmacological drugs acting as non-competitive 5-HT_{3A} receptor antagonists by using a decision-tree learner provided by the RapidMiner machine learning tool. A single molecular descriptor, namely the molecular dipole moment per molecular weight (μ/MW), predicts whether or not a substance non-competitively antagonizes 5-HT-induced Na^+ currents. A low μ/MW is compatible with drug-cumulation in apolar lipid rafts. This study confirms that size-intensive descriptors allow the development of compact SPAR models.

1. Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is a major neurotransmitter in the mammalian central nervous system (CNS) that acts through several membrane bound receptor subtypes, which are mostly coupled to G proteins thereby mediating slow modulatory responses via second messenger signalling. Only the 5-HT_3 receptor subtype constitutes a ligand-gated non-selective cation channel. Activation of 5-HT_3 receptors causes membrane depolarization and an increase in intracellular Na^+ and Ca^{2+} [1,2] (Fig. 1). Functional 5-HT_3 receptors exist either as homomeric 5-HT_{3A} or as heteromeric 5-HT_{3AB} receptors [3–5]. Competitive as well as non-competitive antagonists at the 5-HT_3 receptors have a broad range of clinical applications. These drugs, similarly to ondansetrone, prevent emesis induced by cytostatic drugs that are commonly employed in cancer therapy [6]. Furthermore, 5-HT_3 receptor antagonists display anxiolytic and atypical antipsychotic properties [7,8]. Further clinical indications might include cognitive disturbances, Alzheimer's disease, cerebella tremor, Parkinson's disease, inflammatory pain and appetite disorders [1,9]. It has recently been shown that a wide range of CNS-active drugs acts as non-competitive antagonists at 5-HT_{3A} receptors [10–14]. The exact mechanism by which these drugs interact with the 5-HT_{3A} receptors is not clear. However, it has been shown (1) that 5-HT_3 receptors are localized within raft-like membrane domains, (2) that antidepressant and antipsychotic drugs are markedly enriched in these raft-like domains, and (3) that the concentration of these drugs was strongly associated with their inhibitory potency against 5-HT_3-induced Na^+ currents [15]. This indicates that drug–membrane interactions might be important for the observed effects of antidepressant and antipsychotic drugs on 5-HT_3-induced cation currents (Fig. 1). The aim of the present study is to investigate the structural and/or property–activity relationship for non-competitive inhibition of 5-HT_{3A} receptors by antidepressant and antipsychotic drugs. We attempted to build an easily interpretable model

Abbreviations: 5-HT, serotonin; CNS, central nervous system; HEK, human embryonic kidney; LOO, leave-one-out; μ, molecular dipole moment; QSAR, quantitative–structure–activity relationship; SPAR, structure–property–activity relationship.

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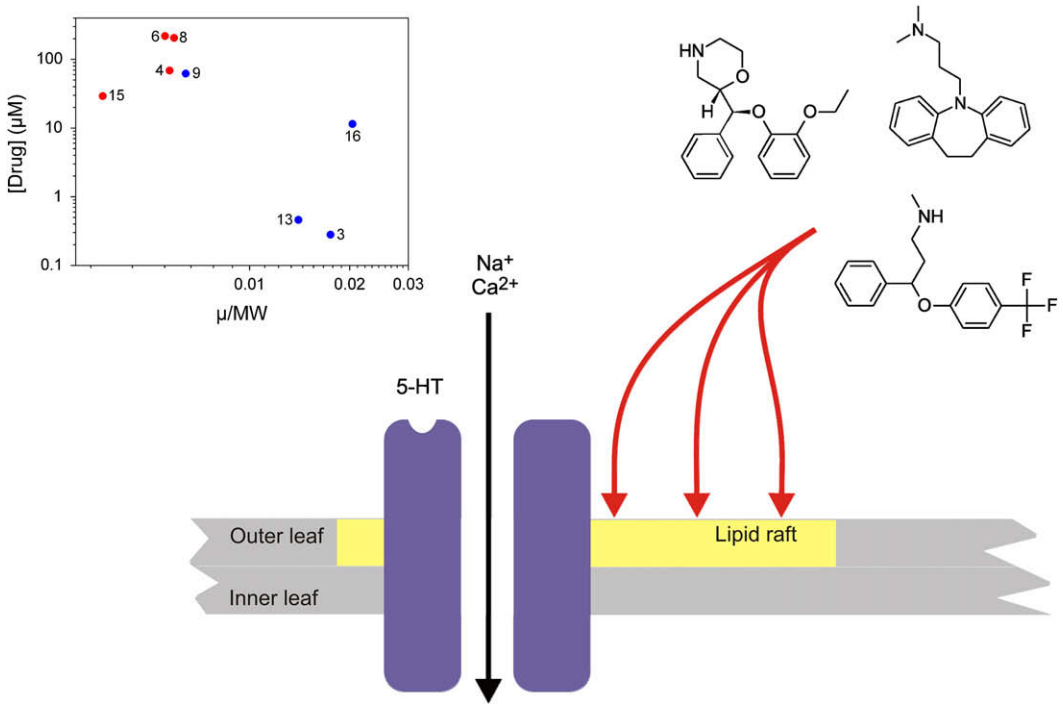

Fig. 1. The 5-HT_{3A} receptor is a membrane bound non-selective cation channel, which upon activation by serotonin (5-HT) allows the passage of Na^+- and Ca^{2+}-ions. The receptor is concentrated within "lipid rafts", namely membrane domains with a high concentration of sphingomyelin and cholesterol primarily within the outer leaf of the plasma membrane. Several antipsychotic and antidepressant drugs, such as fluoxetine **6**, imipramine **11** and reboxetine **15** (see Table 1), non-competitively inhibit 5-HT-induced cation currents. This effect is correlated with the concentration of these drugs reached within membrane lipid rafts [15], indicating that the non-competitive effect on 5-HT_{3A} receptors is related to a drug–membrane interaction. Here, we describe that both drug-related phenomena, namely non-competitive inhibition of 5-HT-induced Na^+ currents and concentration reached in lipid rafts, may be predicted by the molecular descriptor μ/MW. The inset shows the relationship between concentration measured in lipid rafts [15] and μ/MW, with the colour coding indicative of the drug effect on 5-HT-induced Na^+ currents (red = inhibition, blue = inactive). For further details see text.

allowing classification of molecules into those which functionally inhibit the 5-HT_{3A} receptors and those that don't.

2. Results and discussion

2.1. Model development using training set

The data set was partitioned into a training ($n = 14$) and a validation set ($n = 5$), according to a split ratio of approx. 3:1. As a result of the stratified random partitioning, the distribution of the classes is almost the same in the entire data set, as well as in the training and validation data sets. We used a decision-tree learner and aimed to allow successively higher depths of the decision tree during model development. However, already the lowest depth (one root-node with two branches and two leaves) resulted in a sufficient model, with only a single molecular descriptor, namely molecular dipole moment/MW (μ/MW) [leave-one-out (LOO) cross-validated accuracy in the training set: 0.86] being required for prediction. More complicated models were, thus, not elaborated. This resulted in a split position of ≤ -0.354 of the z-transformed μ/MW. This corresponds to a split position of $\leq$0.00618 of the original μ/MW values, indicating that molecules with a low μ/MW such as fluoxetine **6**; imipramine **11**; reboxetine **15** (Fig. 1) are more likely to functionally inhibit 5-HT-induced Na^+ currents. The distribution of the μ/MW values had negative kurtosis with a nearly significant deviation from the normal distribution (Kolmogoroff–Smirnov test, $P = 0.074$).

2.2. Model validation using validation set

The application of the model to the validation set resulted in an accuracy of 0.80.

2.3. Repeated partitioning

Applying a decision-tree learner to five consecutive stratified randomly partitioned training and validation subsets resulted in a mean LOO cross-validated accuracy in the training set of 0.81 ± 0.08 (mean ± SD), in a mean split position of $\leq -0.331 \pm 0.037$ of the z-transformed μ/MW and in a mean accuracy in the validation set of 0.72 ± 0.11. This indicates that the result is independent of a particular partition.

2.4. Response permutation test

Whenever a QSAR or an SPAR model is built, there is a probability that the best model is chance correlation. We therefore performed a response permutation test (also known as Y-scrambling [16–18]). If a strong correlation remains between the descriptors selected and the randomly permutated response, then the significance of the proposed QSAR or SPAR model is regarded as suspect. The model (μ/MW) was recalculated for a randomly reordered response. This procedure was performed 30 times. This resulted in a mean 7-fold cross-validated accuracy of 0.53 ± 0.13 for the training set and a mean accuracy of 0.50 ± 0.17 for the validation set. The accuracy of the chosen model, μ/MW, applied to the original data set is therefore more than 1 SD above random (accuracy in the validation set 0.72 ± 0.11). The data set comprised 19 compounds, 10 of them in class 0 and 9 in class 1. A model assuming all compounds would belong to class 0 (zero rule model) would have an accuracy of 0.53. The accuracy of the chosen model applied to the original data set is significantly higher than the zero rule model, whereas the model applied to randomly reordered response values has a performance which is similar to the zero rule model.