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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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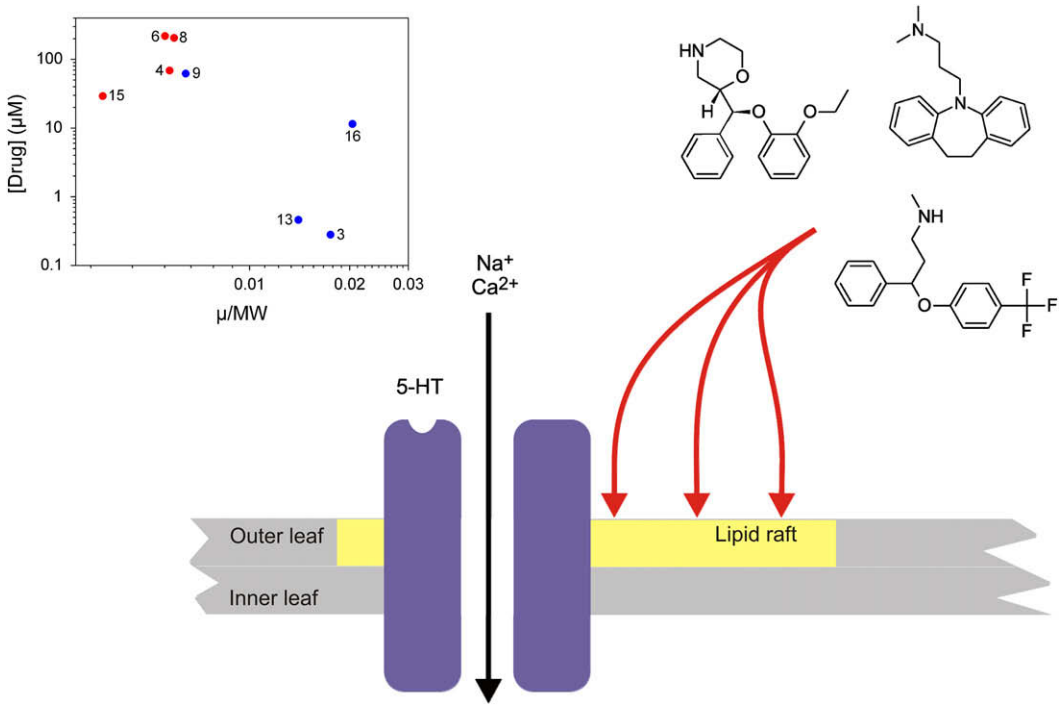

Fig. 1. The 5-HT_{3A} receptor is a membrane bound non-selective cation channel, which upon activation by serotonin (5-HT) allows the passage of Na^+- and Ca^{2+}-ions. The receptor is concentrated within "lipid rafts", namely membrane domains with a high concentration of sphingomyelin and cholesterol 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.

2.5. The significance of the model

The tight interaction between sphingolipids and cholesterol results in a separation of cholesterol- and sphingolipid-enriched membrane domains from other lipids in the cell membrane. These distinct membrane domains are called *rafts* and exist primarily in the outer leaflet of the cell membrane [19,20] (Fig. 1). It is most likely that drug partition into raft-like membrane domains is responsible for the non-competitive inhibition of 5-HT_{3A} receptors (see Introduction). We therefore correlated the experimentally determined [15] concentrations of carbamazepine **3**, desipramine **4**, fluoxetine **6**, fluphenazine **8**, haloperidol **9**, moclobemide **13**, reboxetine **15** and risperidone **16** in lipid rafts with calculated μ/MW values. We found a negative correlation between the drug concentration and μ/MW ($r = -0.740$, $P < 0.05$, $n = 8$, Pearson two-tailed test, ln-transformed drug concentrations, ln-transformed μ/MW, see inset in Fig. 1). This underlines the significance of the SPAR model developed here.

The exact mechanism by which antipsychotic and antidepressant drugs non-competitively inhibit the 5-HT_{3A} receptor remains to be elucidated. There might be a direct interaction of the drugs with the receptor at the membrane–receptor interface. Drugs may reach the binding site of a target receptor by diffusion through the membrane. Alternatively, the drugs accumulated in the biomembrane might functionally inhibit the lipid degrading enzymes, such as sphingomyelinase [21], thereby altering the lipid composition of the rafts, which might have consequences for receptor function and relative concentration of signalling proteins in membrane rafts. Such an effect has been demonstrated for the α-subunit of the G-protein [22].

A simple division of molecular descriptors by chemical sample size creates size-intensive descriptors. It has been shown [23] (1) that the size-intensive form of a descriptor is only weakly correlated with either the descriptor or the chemical sample size, (2) that these descriptors appear in the best QSAR models and (3) that size-intensive descriptors can produce more compact models. This finding is confirmed by the model developed here: The best model uses a size-intensive descriptor and is compact.

The model developed here uses a concentration like information μ/MW. How can this descriptor be interpreted in relation to non-competitive inhibition of 5-HT_{3A} receptors? To the best of our knowledge, the descriptor μ/MW has not been investigated in the context of drug-membrane or drug–receptor interactions. However, the components of this descriptor, namely μ and MW have been studied in this context. These descriptors are related to solubility [24,25], sorption to solid phases [26–28] and appear in QSAR models describing human intestinal absorption [29] and in a large number of QSAR equations quantifying biological activity of drug compounds [30]. Intermolecular dipole–dipole interactions occurring in drug–membrane interactions therefore depend on the dipole moment μ of the molecules. Raft-like membrane domains are characterized by strong hydrophobic interactions between cholesterol and the ceramide moiety of sphingomyelin. The preferential accumulation of drugs with a low dipole concentration (low μ/MW) in raft-like membrane domains is, therefore, plausible.

2.6. Limitations of the findings presented here

(1) The set of compounds is rather small ($n = 19$). Nevertheless, the physicochemical properties and molecular structures of the compounds are diverse (see Table 1). The set contains tricyclic compounds, monocyclic compound, compounds with low and high pK_a values, compounds with low and high *X* log *P* values, and the set contains licensed drugs as well as experimental compounds. The model developed here may also be valid for other small drug-like molecules with similar properties. However, the ability of the model to predict the effects of non drug-like molecules should be thoroughly tested. (2) Quantitative IC_{50} values for non-competitive inhibition of sodium currents through 5-HT_{3A} receptors were available for only 10 of the 19 compounds included in this study. We therefore developed the model shown above using qualitative data for all 19 compounds (see also Data set selection). We also tried to develop a quantitative model using the IC_{50} values as response variable: The quantitative data available for 10 compounds [11,12] did not allow a classical model development, with splitting of the data set into training set and validation set. A linear regression learner was applied to these data, correlating the values of molecular descriptors with IC_{50} values. The descriptor with highest LOO cross-validated squared correlation was *X* log *P*/MW ($r^2 = 0.88$). Allowing models with 2 or 3 independent variables did not improve r^2. This shows that the cross-validated linear regression analysis on the small quantitative data set results in a compact model with a single MW-related size-intensive descriptor, comparable to the decision tree analysis in the whole qualitative data set.

2.7. Strengths of the study

(1) While a number of studies on structure–property–activity relationship (SPAR) have been published to characterize competitive 5-HT_3 receptor antagonists [31–35], this is the first SPAR study investigating non-competitive inhibition of 5-HT_{3A} receptors. (2) We used simple to interpret molecular descriptors and a learner that develops an easily interpretable model (decision tree, in contrast to neuronal networks or support vector machines). The final resulting model is maximally simplified, in that it is based on only a single molecular descriptor. (3) Although using a relatively small data set, we applied a classical internal (LOO cross-validation within the training set) as well as external validation approach (validation set). The model was stable when using different partitions of the complete data set into training and validation sets. Furthermore, the accuracy of the model was clearly above random as indicated by the *Y*-scrambling test. (4) The descriptor μ/MW is plausible in the context of drug-lipid raft interactions. (5) In addition to predicting 5-HT-induced Na^+ currents, the descriptor μ/MW is significantly negatively correlated to a second biological phenomenon, namely the drug concentration reached in lipid rafts. This means that the results of the present study might be more widely applicable, namely that the descriptor μ/MW might predict pharmacological phenomena that are related to the drug concentration in lipid rafts. (6) This study confirms that the use of size-intensive descriptors [23] results in compact chemo-informatic models. (7) To the best of our knowledge and according to a recent review [36], this is the first chemo-informatic study using the machine learning suite RapidMiner [37]. This open-source software might facilitate QSAR and SPAR studies.

3. Conclusion

The present *in silico* SPAR model can predict the non-competitive inhibition of 5-HT_{3A} receptors of unknown CNS-active drug-like molecules with a reasonable degree of accuracy. The interaction of psychotropic drugs with lipid rafts obviously requires molecular properties that are different from those required, for instance, for interaction with lysosomal membranes [21]. The study confirms the notion [23] that size-intensive descriptors allow more compact models, which in turn allow the development of decision trees even in small data sets.

Table 1
Literature set.

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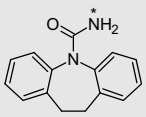
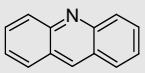
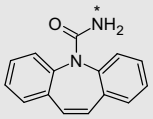
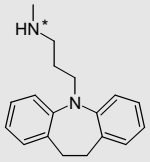
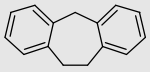
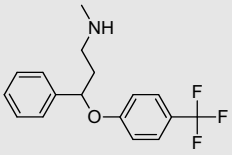
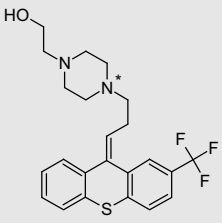
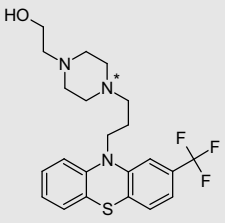
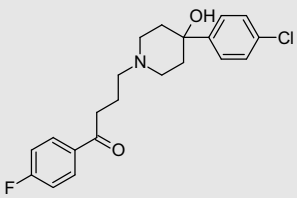
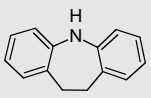
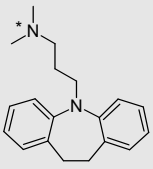
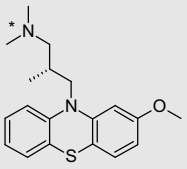
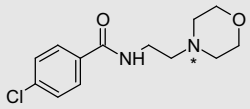
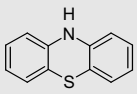
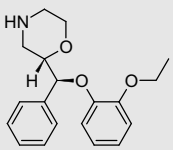
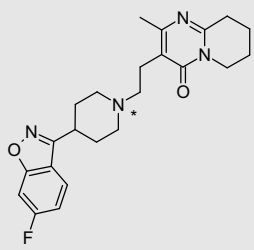
1		10,11-Dihydrocarbamazepine class = 0 [11]	**2**		Acridine class = 0 [12]
3		Carbamazepine class = 0 [11]	**4**		Desipramine class = 1 [11]
5		Dibenzosuberane class = 0 [11]	**6**		Fluoxetine class = 1 [11]
7		Flupenthixol class = 1 [12]	**8**		Fluphenazine class = 1 [12]
9		Haloperidol class = 0 [12]	**10**		Iminodibenzyle class = 1 [11]
11		Imipramine class = 1 [11]	**12**		Levomepromazine class = 0 [12]
13		Moclobemide class = 0 [11]	**14**		Phenothiazine class = 0 [12]
15		Reboxetine class = 1 [11]	**16**		Risperidone class = 0 [12]

Table 1 (*continued*)

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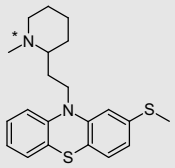
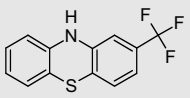
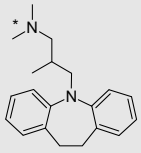
17		Thioridazin class = 1 [12]	**18**		Trifluoromethylphenothiazine class = 0 [12]
19		Trimipramine class = 1 [11]			

Class = 1: more than 50% inhibition of 5-HT_{3A}-induced Na^+ peak currents at 10 μM or higher concentrations of the drug. Class = 0: 50% or less inhibition. *: In the case of two or more nitrogen atoms, the most basic nitrogen atom, as determined by the ACD/Log *D* Suite is marked by an asterisk. This nitrogen atom was used to calculate the descriptors pK_a, *k* and nNH.

4. Experimental

4.1. Data set selection

The set consists of compounds with proven effects on 5-HT_{3A} receptors [11,12] (Table 1, substances **1**–**19**). All compounds had been tested with regard to their effects on 5-HT-induced inward Na^+ currents recorded from lifted human embryonic kidney (HEK) cells stably expressing the *human* 5-HT_{3A} receptor. Compounds with a competitive antagonistic effect on 5-HT_{3A} receptors (mirtazapine [11], clozapine [12]), as evidenced by competition studies using [^{3}H]GR65630, were omitted. The set selected thus comprised 19 compounds (Table 1). IC_{50} values for the functional inhibition of 5-HT_{3A}-induced Na^+ peak currents were available for only 10 of the compounds (desipramine, fluoxetine, flupenthixol, fluphenazine, haloperidol, imipramine, levomepromazine, reboxetine, thioridazine, trimipramine). The remaining 9 compounds have been tested at a single high concentration (10 μM or higher). We therefore used qualitative data for model development. A substance was rated as functional inhibitor (class 1) if a 50% or higher inhibition of sodium-peak currents through 5-HT_{3A} receptors were achieved at 10 μM drug concentration. Otherwise, the drug was rated as inactive (class 0). The *X* log *P* values range from 1.5 to 5.9 and the MW from 179.2 to 437.6. All but one (benzosuberane) of the 19 substances possess a basic nitrogen atom with pK_a values ranging from −2.6 to 10.7. None of the compounds has acidic functional groups at physiological pH.

4.2. Structure entry

Molecular structures were obtained from the PubChem-Project page [38] with the exception of dibenzosuberone, which was drawn in ACD/ChemSketch 11 (Table 1).

4.3. Descriptor selection

Since it has been suggested that partitioning into membrane bilayers of psychotropic drugs is relevant for non-competitive inhibition of 5-HT_{3A} receptors [15], we used a number of intramolecular descriptors which had previously been shown to be relevant in describing interactions between xenobiotics and membrane bilayers [16,21,39–52]. These descriptors describe steric, electrostatic and hydrophobic attributes of drugs.

4.4. Computation of molecular descriptors

Molecular descriptors were calculated by the ACD/Log *D* Suite 10 [53] (log *D* 7.4, pK_a), ADRIANA.*CODE* 2.1 [54] [octanol/water distribution coefficient (*X* log *P*), approximate surface area [52] (ASA), mean molecular polarizability (Polariz), molecular dipole moment μ (Dipole), aqueous solubility (Log *S*), number of atoms (*NA*toms), molecular complexity (Complexity)], DRAGON 5.5 professional software [55] [molecular weight (MW), number of rotatable bonds (RBN), number of hydrogen bond donors (nHDon), number of hydrogen bond acceptors (nHAcc), hydrophilic factor (Hy), Ghose–Crippen molar refractivity (AMR), topological polar surface area using N, O polar contributions (TPSA-NO), topological polar surface area using N, O, S, P polar contributions (TPSA-Tot), average molecular weight (AMW), sum of topological distances between N···O (TN···O)] and by visual inspection of the molecules [number of heavy atoms at the most basic nitrogen atom [21] (*k*), number of hydrogen atoms at the most basic nitrogen atom (nNH)]. Further information on these descriptors is available in the literature [16]. In the case that there was more than one proton accepting centre in a single molecule, the one with the highest pK_a value (the most basic nitrogen atom) was used for SPAR model generation and statistical analysis. In addition to the 21 raw molecular descriptors we calculated size-intensive descriptors [23], which were shown to result in more compact and more stable models. These descriptors are calculated by dividing a descriptor related to structure or property (n = 18) with a size related descriptors (n = 3: MW, NAtoms, ASA). This resulted in 54 size-intensive descriptors and finally resulted in 75 attributes. Before applying classification learner, all molecular descriptors were normalized via *z*-transformation (mean centering and univariate scaling, i.e. the mean of each descriptor becomes 0 and the standard deviation 1).

4.5. Model construction

All learning and validation techniques were computed using RapidMiner 4.3 [37]. The data set was partitioned into a training (n = 14) and a validation set (n = 5) using a stratified random sampling in order to assure a similar distribution of classes between the training and the validation sets. This partition procedure was repeated 5 times using different random seeds. A decision tree analysis (binary decision, using a maximum of 2, 4 and 8 leaves) was used to generate cut-off values using the training set.

The information index was used as a split-criterion (i.e. the increasing information with increasing average purity of the subsets in the leaves of a tree as assessed by the entropy). Decision trees provide a nonparametric statistical technique [56] that is capable of solving classification. This technique has previously been successfully used in SPAR models [48,57–60]. The LOO cross-validation was used as internal validation when learning a model using a training set. Accuracy (number of correctly allocated cases divided by number of all cases) was chosen as a performance criterion. The predictive ability of the model was then evaluated using the validation set, again using accuracy as a performance criterion. The compounds in the validation set were not used for model generation, and therefore, represent unknown compounds.

4.6. Statistical analysis

Correlations (Pearson) and deviation from normal distribution (Kolmogoroff–Smirnov) were computed using SPSS (Version 15, Chicago, Illinois).

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