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论文

药物分子设计的策略: 分子的宏观性质与微观结构的统一

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摘要：

药物与机体的相互作用，包含机体对药物的处置和药物对机体的作用。机体对药物的处置，所进行的物理和化学、时间和空间的处置，遵循一般的规律，具有共性特征，即分子的整体和宏观性质影响药代动力学行为。药物对机体的作用，是药物分子与靶标蛋白的物理或化学结合，引发药理(或毒理)作用，起因于药物的特异性作用，是药物分子的个性表现，受制于药物分子中特定的原子或基团与靶标分子在三维空间的结合，这种微观结构就是药效团。药物分子可视作宏观性质与微观结构的集合，统一在分子的整体结构之中，宏观性质决定药代和物化性质，微观结构决定药理作用。认识宏观与微观同药代与药效的内在相互关系，可以深化对药物作用的认识，指导药物分子设计。决定分子宏观性质的因素是相对分子质量、水溶性、电荷、脂溶性(分配性)和极性表面积等，通常是由分子骨架和整体分子所决定，无特异性的结构要求；决定活性的微观结构因素有氢键给体、氢键接受体、正电中心、负电中心、疏水中心和芳环中心。不同的生物活性取决于这些不同特征的组合及其空间排布。分子的宏观性质，包含了微观结构中原子和基团的贡献；在改变分子的结构以调整宏观性质时，往往影响微观结构的空间位置。药物分子设计的技巧是整合这两个因素成最佳配置，在早期研究阶段，应兼顾宏观性质与微观结构，使药效强度和选择性、药代动力学和药物的物理化学性质达到最佳的匹配，为此，要求表征药代的空间与药效学的选择性空间有结构交盖。

关键词： 药物分子设计 宏观性质 微观结构 药代动力学 药效学

Strategy of molecular design of drugs: the unification of macro-properties and micro-structures of a molecule

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Abstract:

The interaction of a drug with the organism involves both the disposition of a drug by the organism and the action of a drug on the organism. The disposition of various exogenous substances, including drugs, complies with general rules. The underlying physical and chemical changes to different drugs in view of time and space, i.e. pharmacokinetics, share common characteristics, that is the tout ensemble of a molecule and its macroscopic properties convey direct effect on the pharmacokinetic behavior as the tendency and consequence of biological evolution. The action of a drug on the organism, on the other hand, implicates the physico-chemical binding of a drug molecule to the target protein, which induces pharmacological and toxicological effects. The biological reactions, no matter beneficial or adverse, are all specific and individual manifestation of the drug molecule and determined by the interactive binding between definitive atoms or groups of the drug molecule and the macromolecular target in three-dimension. Such critical atoms, groups, or fragments responsible for the interaction reflect the microscopic structures of drug molecules and are called pharmacophore. In this context, a drug molecule is presumed as an assembly of macroscopic property and microscopic structure, with the macroscopic properties determining the absorption, distribution, metabolism and elimination of drugs and the microscopic structure coining pharmacological action. The knowledge of the internal relationship between macroscopy/microscopy and PK/PD conduces to comprehension of drug action and guides molecular drug design, because this conception facilitates the identification of structural features necessary for biological response, and the determination of factors modulating the physico-chemical and pharmacokinetic properties. The factors determining macro-properties include molecular weight, solubility, charge, lipophilicity (partition), and polar surface area, etc., which are destined by molecular scaffolds and/or side chain(s) apart from pharmacophore. The features of micro-structures contributing to specific activity contain hydrogen bonding donor and acceptor, positive and negative charge centers, hydrophobic centers and centers of aromatic rings. Different combinations and spacial arrangements of these features determine the distinct activity presented. The macro-property and micro-structure are integrated into a single molecule, and are inseparable. The macro-property reflects overall contribution of atoms and groups in the micro-structure. On the other hand, structural changes aimed to adjust macroscopic property usually alter the relative position of the microscopic structure. The goal of molecular drug design is to integrate the macroscopic and microscopic factors in optimized manner. In

the early stage of molecular design, both macroscopic property and microscopic structure should be considered to make pharmacodynamics, pharmacokinetics, and physico-chemical properties in optimal match. Therefore, it required the existence of structural overlapping among acceptable pharmacokinetics, visible developing potential and specific pharmacodynamics. The larger the scope of overlapping, the higher the possibility to be a drug.

Keywords: macroscopic property microscopic structure pharmacokinetics pharmacodynamics molecular drug design

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