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Physico-chemical profiling of semisynthetic opioids

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ABSTRACT

Species-specific acid–base and partition equilibrium constants were experimentally determined for the therapeutically important semisynthetic opioid receptor agonist hydromorphone, dihydromorphine, and mixed agonist-antagonist nalorphine and nalbuphine. The acid–base microequilibria were characterized by combining pH-potentiometry and deductive methods using synthesized auxiliary compounds. Independent of the pH, there are approximately 4.8 times as many zwitterionic microspecies than non-charged ones in nalbuphine solutions, while for nalorphine it is the non-charged form that predominates by the same ratio. The non-charged microspecies is the dominant one also in the case of hydromorphone, although its concentration exceeds only 1.3 times that of its zwitterionic protonation isomer. The pH-independent partition coefficients of the individual microspecies were determined by a combination of experimentally measured, pH-dependent, conditional distribution constants and a custom-tailored evaluation method, using highly similar auxiliary compounds. The pH-independent contribution of the zwitterionic microspecies to the distribution constant is 1380, 1070, 3160 and 72,440 times smaller than that of the inherently more lipophilic non-charged one for hydromorphone, dihydromorphine, nalbuphine and nalorphine, respectively.

1. Introduction

Morphine and other opioid compounds have long been used to treat severe acute and chronic pain. The three principal classes of opioid receptors, μ, κ, δ (mu, kappa, delta), are all G-protein coupled receptors acting on GABAergic neurotransmission. Activation of the μ-opioid receptors is associated with analgesia, sedation, euphoria, physical dependence, and respiratory depression [1]. Morphine is the parent compound of several valuable therapeutic agents with agonistic or antagonistic activities on the opioid receptors. The constitutional formulas of the compounds investigated in this study can be seen in Fig. 1.

Hydromorphone (dihydromorphone, **1a**) is a semi-synthetic derivative of morphine, approximately 5 times as potent as morphine, with two structural alterations relative to morphine: the 6-OH is oxidized and the 7,8 double bond is reduced. Hydromorphone is widely used for acute pain, chronic cancer pain and to a lesser extent, in chronic non-malignant pain [2]. Hydrocodone (dihydrocodone, **1b**) is the 3-methoxy version of hydromorphone. The loss of the 3-OH group yields a compound that is approximately 4–5 times less potent than hydromorphone, thus about equal to morphine. Unlike codeine, the agonist activity of hydrocodone does not require 3-O-demethylation, although it does occur via CYP2D6. The protected 3-position has better brain penetration, and the 7,8-dihydro-6-keto C ring enhances its binding to the μ-receptor. Like codeine, hydrocodone is also marketed as an antitussive agent [1].

The 3-methoxy version of dihydromorphine (hydromorphine, **2a**) is dihydrocodeine (hydrocodeine, **2b**), which is also used as an antitussive agent [3]. After parenteral administration, dihydrocodeine is twice as potent as codein [4].

Nalbuphine (**3a**) is the 14-beta-hydroxy version of dihydromorphine, with a cyclobutylmethyl group on the nitrogen. It was introduced in 1979 as a mixed agonist-antagonist with the hope of becoming an effective pain reliever with little abuse potential. It has agonist activity at the κ-receptor and antagonist activity at the μ-receptor. Used as the sole opioid agent, nalbuphine has been used successfully to treat the pain of labour, cesarean section, dental extraction, hip replacement, and hysterectomy surgery [1]. The analgesic efficacy of nalbuphine is comparable to morphine, but nalbuphine provides a better safety profile than morphine in the aspect of certain side-effects, especially related to pruritus and respiratory depression [5].

Nalorphine (**4a**) is a competitive antagonist at the μ-receptor but it has agonistic actions at the κ-receptor, thus it is also a mixed

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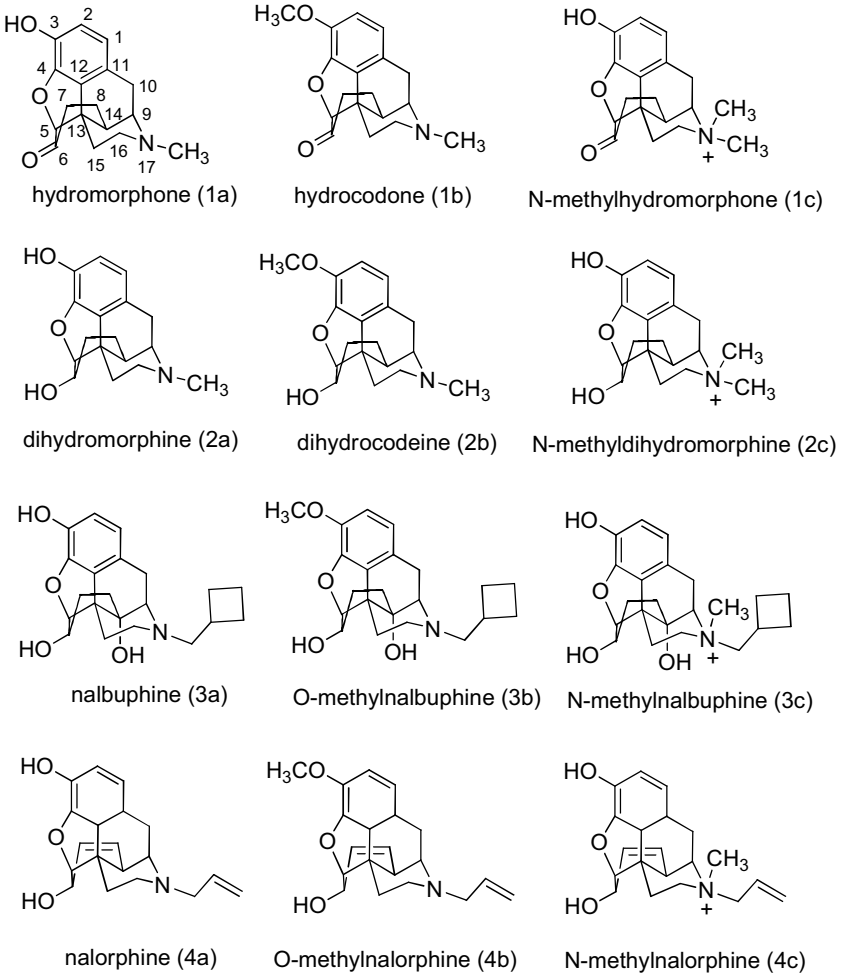

Fig. 1. The structure and ring numbering of the examined compounds.

agonist-antagonist. Previously used as an antidote to reverse opioid overdose, its clinical use is limited because it produces side-effects such as hallucinations due to the activation of the κ-receptor. The chemical structure of nalorphine resembles that of morphine, the only difference being the substitution of the N-methyl group with an allyl (prop-2-enyl) group [3,6].

Species-specific basicity and lipophilicity are two fundamental physico-chemical parameters in drug action [7]. Basicity of the protonation sites of multidentate ligands can only be correctly characterized in terms of microscopic protonation constants. Also, they are the analytical tools to quantify the concentration of the various protonation forms, of which not necessarily the major one is reactive in biological and chemical processes [8–10].

Hydromorphone (**1a**), dihydromorphine (**2a**), nalbuphine (**3a**) and nalorphine (**4a**) exist in solutions in four microscopic protonation forms (microspecies), including the cationic, zwitterionic, non-charged and anionic ones [11]. The protonation scheme of hydromorphone is depicted in Fig. 2. K_1 and K_2 are the stepwise macroconstants, k^N, k^O, k^O_N, k^N_O are the microconstants, indices O and N designate phenolate and tertiary amino site oxygen and nitrogen atoms, respectively. Superscripts of the microscopic protonation constants indicate the group protonating in the given microequilibrium protonation process, whereas the subscript (if any) stands for the group holding proton during the process [11].

A review on some of the physicochemical properties of morphine and related compounds has been published, where we tabulated all the literature data on their acid–base properties and lipophilicity [6]. Lipophilicity expresses the affinity of the molecule for a lipophilic environment [12–14], and its applications include drug design for targeted delivery, liquid–liquid extraction of compounds, quantitative structure-activity relationships, intramolecular forces of recognition [15–17].

log$P$ is the logarithm of the partition coefficient, the concentration ratio of a solute present in a single electrical state and in equilibrium between two immiscible solvents. The organic solvent of choice is usually octanol. When more than one electrical species are present in solution, the observed ratio of concentrations is the distribution coefficient (D), which takes into account the intrinsic lipophilicity of the various electrical species present (p_i), and their mole fractions in the aqueous phase (x_i).

For amphoteric molecules that exist in solution in anionic (Ani), non-charged (Non), zwitterionic (Zwi) and cationic (Cat) forms (see also Fig. 2), the distribution coefficient is the sum of four products:

$$D_{(pH)} = \Sigma x_i p_i = x_{Ani} p^{Ani} + x_{Non} p^{Non} + x_{Zwi} p^{Zwi} + x_{Cat} p^{Cat} \quad (1)$$

where x_i mole fractions are pH-dependent, while p_i parameters are pH-independent ones. The lipophilicity profile (the variation of log$D$ as a function of the aqueous pH) of a drug is essential in understanding its pharmacokinetic, toxicokinetic and even pharmacodynamic properties [18].

Contrary to the widespread misbelieve, passive diffusion into lipophilic media is not necessarily predominated by the non-charged species. Ions and zwitterions can dominate the distribution of a drug over the most lipophilic non-charged form, provided the