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Interaction between Morphine and Lysine

Sachiko Nakai* and Fumio Yoneda

Fujimoto Pharmaceutical Corporation, 1-3-40 Nishi-Otsuka, Matsubara-shi, Osaka, 580-8503, Japan

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Abstract—The study by the molecular orbital theory displayed that morphine and lysine make two types of the interactions between them: type (A) by three hydrogen bondings and type (B) by one hydrogen bonding accompanied with a proton transfer. The stabilization energies were 45.3 and 34.9 kcal/mol for type (A) and type (B), respectively. The characters of these interactions are striking compared to the interactions of morphine with the other amino acids, suggesting that lysine is the binding point of morphine in the μ-opioid receptor. © 2001 Elsevier Science Ltd. All rights reserved.

For more than 4000 years, morphine[1] has been used as a powerful pain killing drug and no superior substitute for it has been found yet. Morphine is a selective opioid for the μ-opioid receptor, but its functional mechanism is not yet clear because of the complicated structure of the opioid receptors which are the membrane proteins. It was just a few years ago that the amino acid sequences of the opioid receptors were determined.[2] Furthermore, the experimental studies using the chimeric receptors have started to contribute to the determination of the ligand selectivity.[3] Using this technique, Fukuda et al.[3a] determined that the μ-selective alkaloids, like morphine, were bound to the region spanning the transmembrane segments TM-V to TM-VII of the receptors (vide infra). They indicated that it is possible for the extracellular loop EL-III to contribute to the ligand selectivity because of the amino acid sequence of this loop, which is more divergent among the receptors than those of the other loops. They also pointed out that the contribution of the transmembrane segments TM-V and TM-VI was referred, according to the ligand selectivity suggested in other peptide receptor systems.[4]

Figure 1 represents the schematic design of the opioid receptor in which the amino acid sequences of EL-III of human κ-, μ-, δ-receptors and ORL-1[5] (opioid receptor-like) are shown comparatively. Another experimental study,[6] has shown that methanethiosulfonate (MTS) derivatives bound with cysteine residue inhibited the binding of an antagonist, [^{3}H]diprenorphine, to the opioid receptors and that the reaction occurred within or in the vicinity of the binding pocket. According to the molecular dynamics simulations of the transmembrane domains of the opioid receptors by Strahs and Weinstein,[7] lysine in the μ-opioid receptor, 303K, is in the nearest vicinity of this cysteine, 321C (marked in the figure), and seems to be in a rather free state in the binding pocket. Taking account of the special state of the lysine described above, it would be worthwhile to pursue the theoretical interaction between morphine and lysine in the free state.

The calculations by the molecular orbital theory using the program Gaussian98[8] were done through B3LYP/6-31G(d)//HF/6-31G(d), that is, the geometry optimizations by Hartree Fock Self Consistent Field theory at 6-31G(d) level and then the single-point calculations of such optimized conformations by the density functional method B3LYP at 6-31G(d) level. The atomic charges are calculated by Mulliken population analysis.

The sketch of morphine in Chart 1 was put into a computer and minimized energetically. The conformation obtained was similar to the ones presented in the literature.[9] Lysine was extracted from a protein data base and optimized.

Figure 2 represents two types of the optimized conformations of the interactions between morphine and lysine. In type (A) there are three hydrogen bondings; the first one is O1...H(N)1–N, the second is O3...H(N)2–N and the third is O3-H(O3)...Oa.[10] In type (B), there is only one hydrogen bonding N...H(N)1–N17, of which the proton H(N)1 is transferred from lysine side. The conformational changes

*Corresponding author. Tel.: +81-723-32-5151; fax: +81-723-32-8482; e-mail: soyaku@fujimoto-pharm.co.jp

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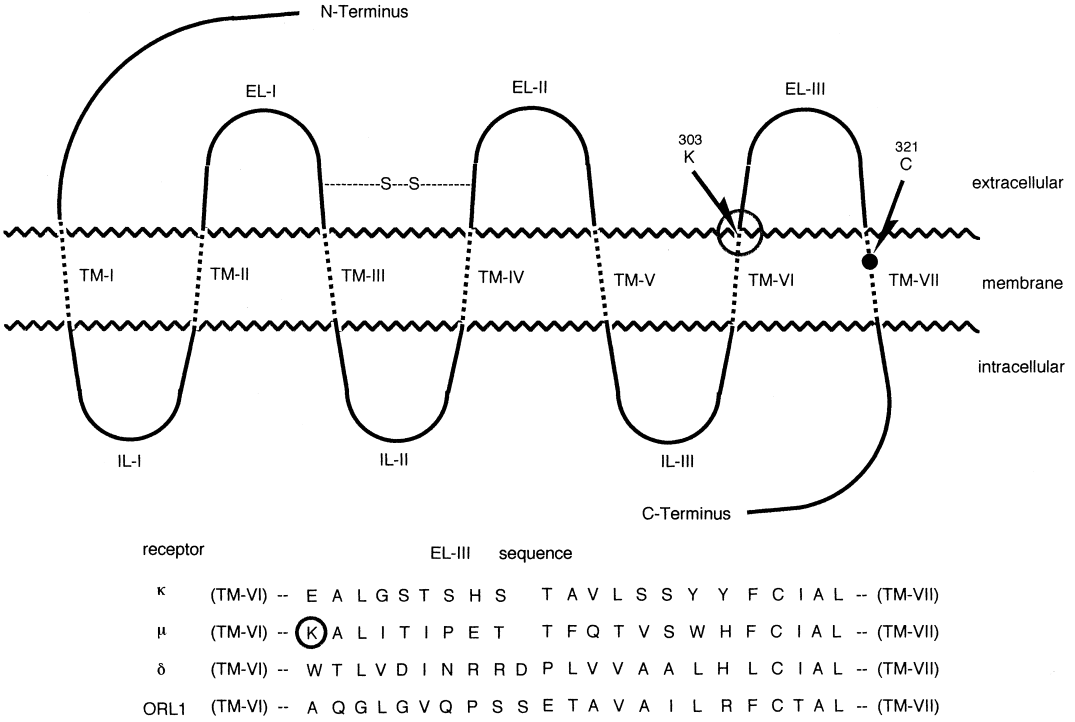

Figure 1. Schematic representation of the opioid receptor. The amino acid sequences of EL-III of human κ-, μ-, δ-receptors and ORL1 are shown. The circles indicate the sites of lysine (303K) and cysteine (321C) of μ-receptor.

through the interactions from the separated states were very small. The maximum differences in the interaction type (A) were in the length C3–O1 by 0.03 Å and in the angle C4–C3–O1 by 2.7° on the morphine side, and those on the lysine side were in the length Cε–N by 0.02 Å and in the angle Na–Cα–C by 8.0°. The maximum differences in the interaction type (B) were in the length C9–N17 by 0.06 Å and in the angle N17–C18–H(C18)1 by 4.1° on the morphine side, and those on the lysine side were in the length Cε–N by 0.045 Å and in the angle Na–Cα–C by 8.0°.

On the other hand, the energy descents from the separated state by 45.3 and 34.9 kcal/mol for type (A) and type (B) interactions, respectively, were exceptionally large, considering that one hydrogen bonding energy is typically in the range of 2–15 kcal/mol,[11a] and that in the interaction between guanine and cytosine in DNA, a famous example of one including strong three hydrogen bondings, the stabilization energy is 23.8 kcal/mol by the method MP2/6–31G*[11b] (30.3 kcal/mol by our calculation with the same method employed in the present work). Our results were without correction for basis set superposition error (BSSE) which was less than 0.4 kcal/mol for the system of morphine and lysine.

Figure 3 represents the atomic charge density distributions of morphine and lysine in the separated and the interacted situations. In type (A) interaction, the total charges of morphine and lysine parts were 0.137 and 0.863, respectively, namely the electron moved by 0.137 from morphine toward lysine through the three hydrogen bonds. In type (B) interaction, those of the morphine part, including the transferred proton H(N)1, and lysine part were 0.874 and 0.126, respectively, meaning

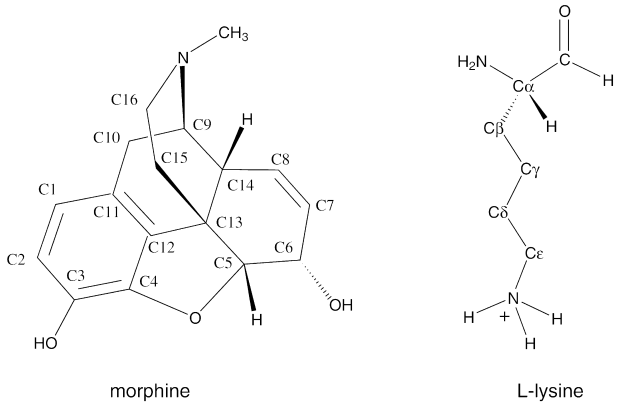

Chart 1.

that the original charge on the lysine side moved almost all toward the morphine side together with the proton which had the charge 0.436. It is observed in the figure that the charge variations on hydrogen atoms were relatively large, particularly in type (B) interaction where the total charge variations of all hydrogens in morphine and lysine sides were 0.710 and −0.451, respectively. Thus, the large charge transfer between morphine and lysine was due not only to the transferred proton but also the overall charge variations on the hydrogens. On the morphine side, it is also remarked that N17 gained more electron by 0.149, responding to the coming proton. In type (A) interaction, the charge variations on the hydrogens were large only on the morphine side which were in total 0.348 and it was noticed in the figure that the relatively large changes took place on the few atoms near the hydrogen bonds.

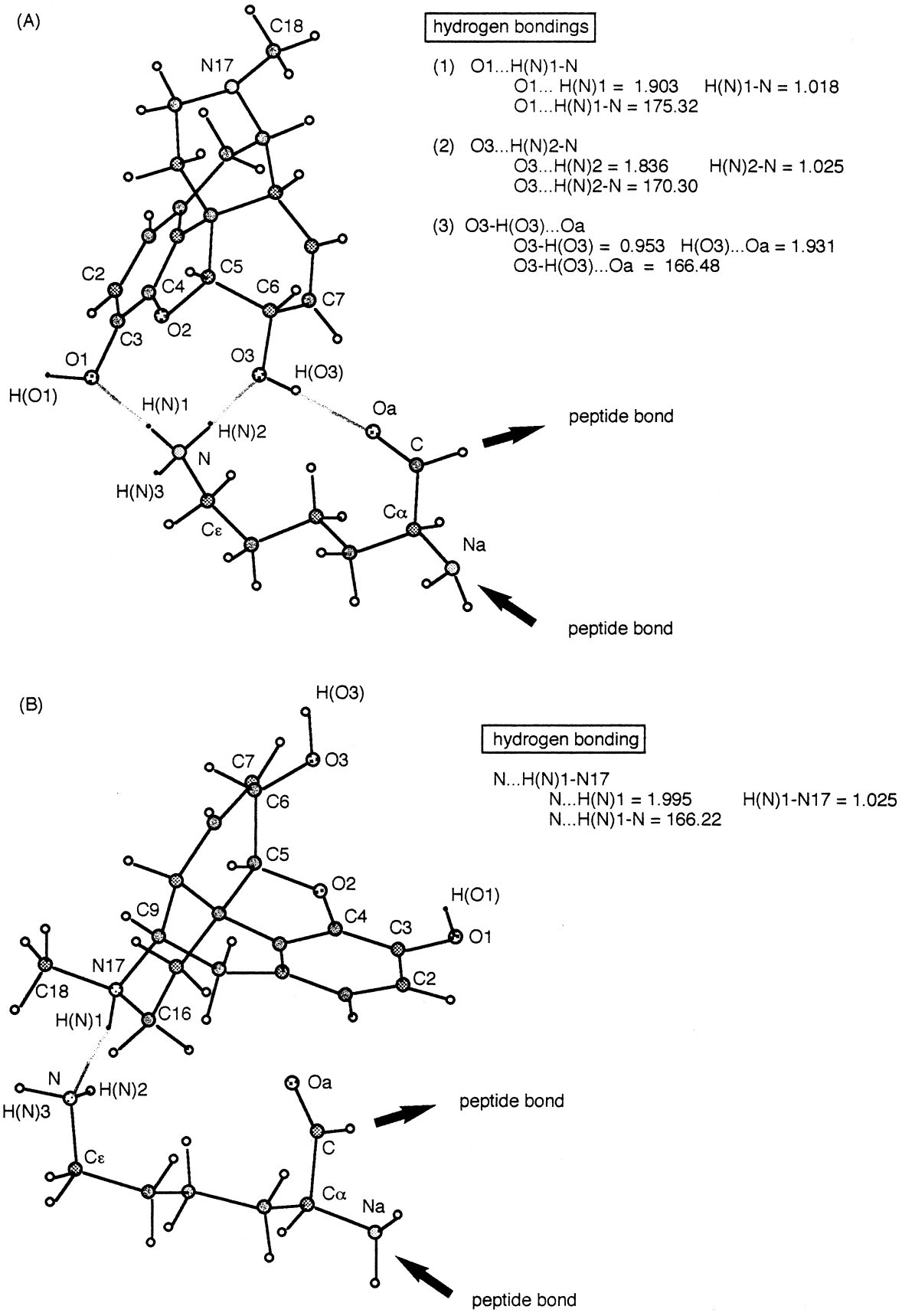

Figure 2. Optimized conformations of the interactions of types (A) and (B). The data about the hydrogen bondings are shown. The additional notations are also designated.

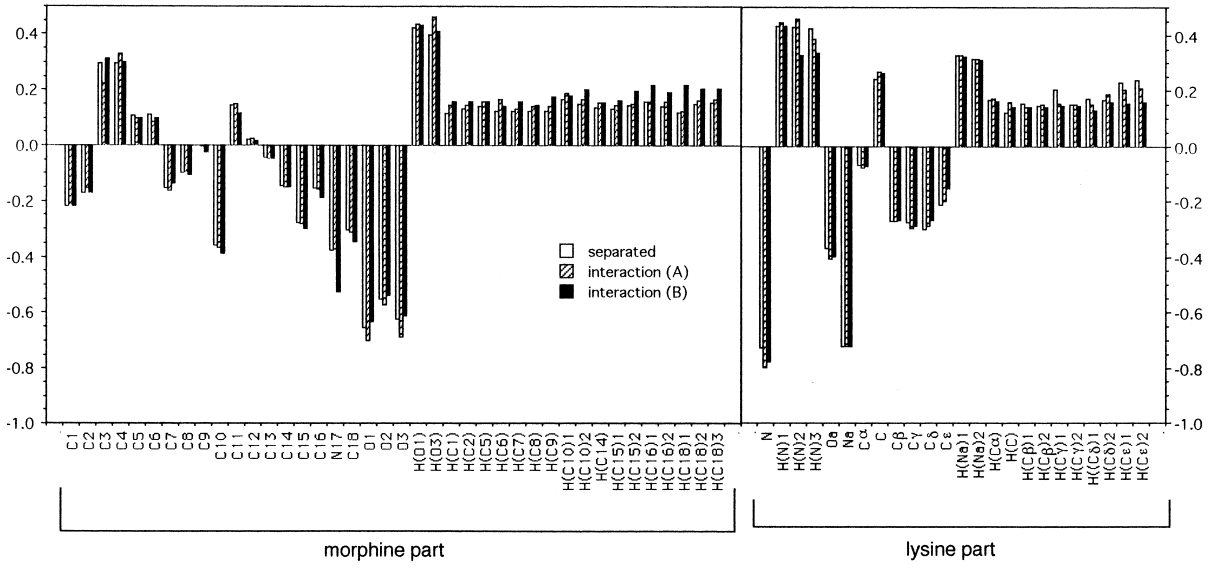

Figure 3. Atomic charge density distributions of morphine and lysine in the separated state and in the interacted ones of types (A) and (B).

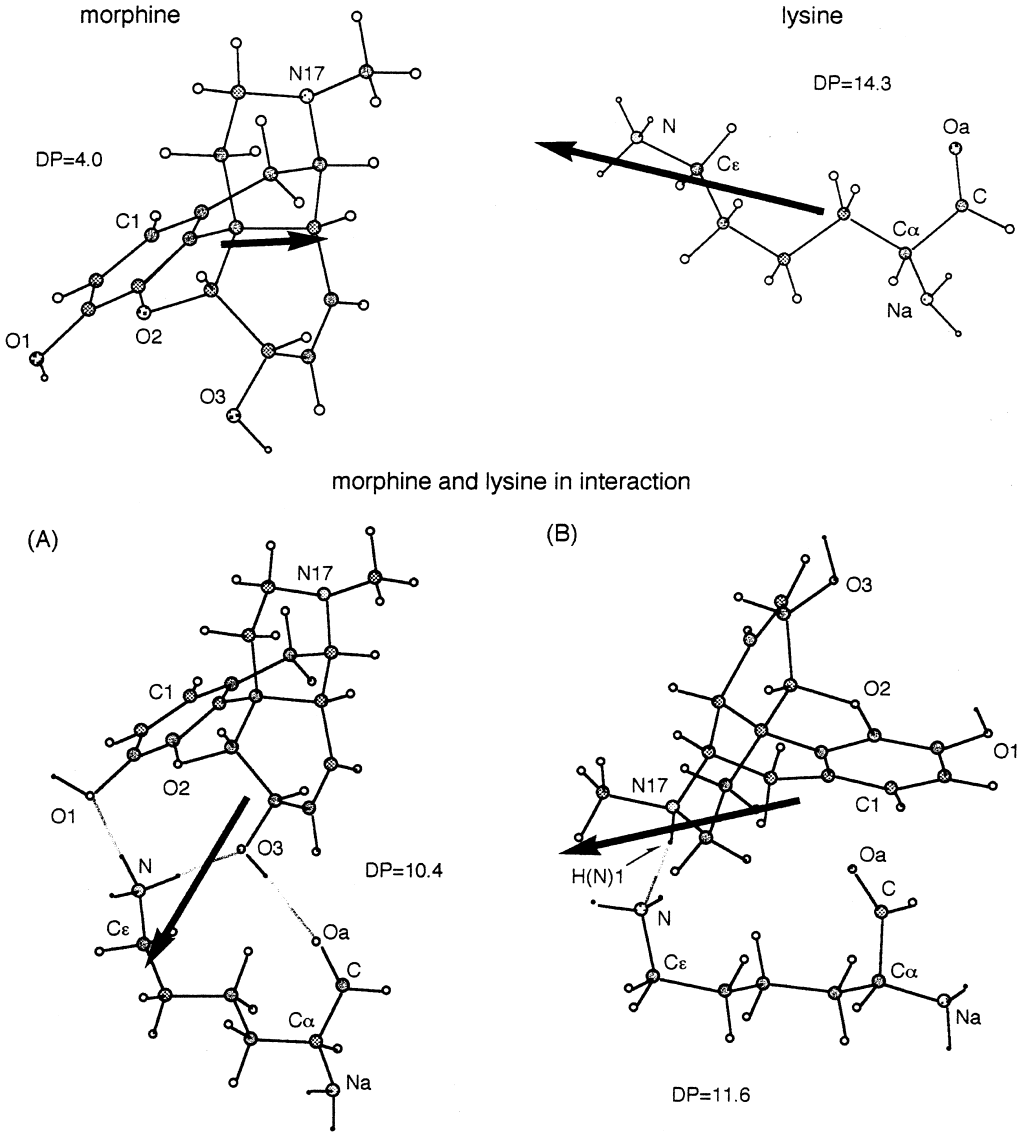

Figure 4. Dipole moments (DPs) of morphine, lysine and interactions (A) and (B). The unit of DP is the debye.

Figure 4 shows the dipole moments of morphine, lysine and two situations of the interactions. The dipole moment of lysine, a positively charged molecule, was large (14.3 debyes) in the direction along the side chain, while the one of morphine was small (4.0 debyes). It was remarked in type (A) interaction that the magnitude and direction were changed largely from the separated ones, while the dipole moment in type (B) interaction was nearly an added vector of the respective ones of morphine and lysine.

We have checked the interactions of morphine with the possible other amino acids one by one and found that none of them showed such strong binding as types (A) and (B). Thus, it is theoretically predicted that lysine, 303K, is the most potent candidate amino acid residue of the μ-opioid receptor with which morphine makes contact. Even though either of the interactions of type (A) or (B) may occur, the strong binding between morphine and lysine accompanied with the large energy descent could stimulate the receptor to send the signal which would trigger the analgesic action.

Acknowledgements

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