Discovery and Development of Nalfurafine hydrochloride, a novel κ-Opioid Receptor Agonist

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For the past three decades, considerable efforts have focused on the search for an opioid κ-selective agonist without the undesirable morphine-like side effects (e.g., respiratory depression, constipation, physical dependence, etc.). In 1982, U-50488H was discovered to be a highly selective κ-agonist. Subsequently, many research groups modified its structure and succeeded in preparing more selective and potent κ-agonists. All these compounds had potent antinociceptive effects in animal models and also lacked the morphine-like side effects. However, the compounds were not developed for clinical use since they, too, had side effects such as dysphoria and psychotomimetic effects. These analogous compounds share a structure similar to the [N-C-C-N(sp^2)] pharmacophore sequence of U-50488H. They lack the tyrosine structure which is essential for opioid activity from the viewpoint of endogenous opioid chemistry. Therefore, we designed a new type of κ-agonist which incorporated tyrosine moiety. Our compound (TRK-820) showed potent analgesic effect and no aversive and psychotomimetic effects. However, when the compound was applied to post-operative patients, the unexpected strong sedation was appeared with antinociceptive effect. So, we changed the indication to antipruritus for kidney dialysis patients. As we expected, the compound afforded strong antipruritic effect without aversive and psychotomimetic effects. As the result, TRK-820 (nalfurafine) was launched in Japan on May in 2009. The compound is also expected to be effective in pruritus of atopic dermatitis patients. Now the clinical trial is going on.