Buprenorphine in Combination with Samidorphan (ALKS 33) Results in Antidepressive-Like Effects in Two Distinct Rat Models

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INTRODUCTION

• The endogenous opioid system regulates mood and is dysregulated in patients with depressive illness.
• The use of µ-opioid agonists for the treatment of central nervous system (CNS) diseases and mood disorders such as major depressive disorder (MDD) has been hampered by their abuse liability and overdose potential.
• One strategy to increase the utility of opioids is balanced neuromodulation of µ-opioid agonist activity.
• ALKS 5461 represents a novel treatment for depression that targets the opioid µ-receptor (BUP) and samidorphan (SAMI), a potent full µ-opioid antagonist. Both BUP and SAMI have similar activity at a and k receptors.
• In a recent phase 2 clinical trial in MDD, ALKS 5461 was superior to placebo on a range of depressive symptoms.
• It is hypothesized that this combination results in balanced neuromodulation that regulates the pharmacodynamic effects of the agonist to minimize its potential for abuse and overdose while preserving therapeutic efficacy in the treatment of depression.
• Previously, it has been demonstrated that co-administration of BUP and SAMI dose-dependently attenuates buprenorphine-induced elevations of extracellular dopamine and serotonin in the nucleus accumbens and medial prefrontal cortex of rats (Deaver, et. al., ACNP, 2013; See Figure 2).
• Here, we used two models to examine the anxiolytic and antidepressant-like effects of this combination in rats.
• In the first model, an anxiogenic/depressive-like state was induced with chronic corticosterone treatment and saccharin consumption was measured.
• In the second model, the forced swim test, Wistar Kyoto (WKY) rats were used because they display a number of behavioral and hormonal deficits that are considered descriptive of depression features and are used in nonclinical models of learned helplessness.

METHODS

Drugs and Animals:
• Samidorphan was synthesized by Cambridge Major Laboratories (Cambridge, WI). Buprenorphine (Buprenex®; 0.3 mg/kg) was purchased from Bristol Myers Animal Health Supply (Chicago, IL).
• Rates were purchased from Charles River Laboratories (Raleigh, NC).

Saccharin Consumption Test:
• Male Sprague-Dawley (SD) rats (300) were implanted with 100 mg slow-release corticosterone pellets (C-111, Innovative Research America, Sarasota, FL).
• Rats were individually housed to allow measurement of individual saccharine and water consumption (no bottle choice).
• On Day 7, rats were tested to confirm a reduction in saccharin consumption and then assigned to one of two groups in a 4x2 factorial design based on this consumption.
• On Day 14, rats were treated subcutaneously (SC) with an 0.0% saccharine, 0.1 mg/kg buprenorphine, 0.1 mg/kg of combination, 0.3 mg/kg samidorphan, or 0.5 mg/kg buprenorphine + 0.3 mg/kg Sami in combination with 3% saccharine.
• Rates were then returned to their home cage for a second test.
• Saccharin consumption was calculated based on the change in bottle weights during the 15-20 hour overnight access and calculated as grams.

Forced Swim Test:
• Male SD rats (n = 9) were randomly assigned to one of three treatment groups.
• The swim chambers were 45 cm x 20 cm x 47 cm and filled to 26-31 cm with water (24 ± 2°C) for 15 min.
• On Day 1, rats were placed in the water-filled tanks for 15 minutes, then removed, towel dried, and placed in a warm enclosure for 15 minutes before being returned to the colony.
• Following the initial trials, rats were tested three days of 0% saline solution for injection (1 ml/kg SC), 0.3 mg/kg buprenorphine, 0.1 mg/kg in combination with 0.3 mg/kg samidorphan, SC, or 0.3 mg/kg samidorphan SC for 30 minutes.
• On Day 7, rats were returned to the swim chambers for 15 consecutive minutes; after the first trial.
• One hour after the last test injection, rats were placed in the water-filled tanks for a second time for 260 seconds under the same conditions as Day 1.
• These trials were videotaped from the side of the cylinders and were scored manually for immobility time (in seconds) over the entire 360 second period using a stop watch by a rater blinded to the treatments. Because WKY rats did not display any clinging behavior, the time spent near the wall was not scored.
• A rat was judged to be immobile if it was making only movements necessary to keep it head above water.

RESULTS

Figure 1: Subcutaneous administration of buprenorphine dose-dependently increased extracellular concentrations of dopamine in rat nucleus accumbens shell.

Figure 2: Concurrent administration of samidorphan dose-dependently attenuated buprenorphine-induced increases in F) DA, B) DOPAC, C) HVA, and D) 5-HIAA. Importantly, lower doses of samidorphan (0.3 mg/kg or 1.0 mg/kg) did not completely block the effects of buprenorphine on DA, DOPAC, HVA or 5-HIAA.

Figure 3: Effects of BUP and SAMI combinations on saccharin consumption in corticosterone treated SD rats

Figure 4: Effects of BUP and SAMI combinations in the forced swim test in WKY rats

CONCLUSIONS

• Samidorphan dose-dependently attenuated buprenorphine-induced elevations in dopamine and serotonin.
• In both behavioral paradigms, the dose combination that attenuated, but did not completely block buprenorphine-induced elevations in monoamines, demonstrated anxiolytic and antidepressant-like effects in rats.
• In rats, these data suggest a balanced neuromodulation of µ-opioid agonist activity is required to maintain efficacy in these paradigms.
• However, a potential role of δ- and κ-receptor opioids cannot be ruled out.

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Buprenorphine in combination with samidorphan (ALKS 33) results in antidepressive-like effects in two distinct rat models
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ALKS 5461 represents a novel treatment for depression that combines buprenorphine (a partial mu agonist) with samidorphan (a potent full mu antagonist), formerly referred to as ALKS 33. In a recent phase 2 clinical trial in Major Depressive Disorder, ALKS 5461 was superior to placebo on a range of depressive symptoms. There is a substantial body of nonclinical and pharmacologic research indicating that endogenous opioid systems regulate mood and are dysregulated in patients with depressive illness [1,2]. Additionally, opioid receptors and their endogenous ligands are expressed in areas of the brain that have been associated with regulating mood and depression, including the nucleus accumbens, prefrontal cortex, hippocampus, thalamus, caudate and amygdala [3]. Unfortunately, the use of mu opioid agonists for the treatment of CNS diseases and mood disorders such as Major Depressive Disorder has been hampered by their abuse liability and overdose potential. One strategy to increase the utility of opioids is to balance the activity of known partial or full mu opioid agonists with a pharmacologically active mu opioid antagonist. It is hypothesized that such a combination would modulate the pharmacodynamic effects of the agonist molecule so as to minimize its potential for abuse and overdose while preserving therapeutic efficacy. Previously, it has been demonstrated that co-administration of buprenorphine with samidorphan dose-dependently attenuated buprenorphine-induced elevations of extracellular dopamine and its metabolites in the nucleus accumbens and medial prefrontal cortex in rats (Deaver, et al., ACNP 2013).

Corticosterone-induced decreases in saccharin consumption and the forced swim test are models commonly used to study the antidepressant-like effects of drugs. In the first model, rats were induced into a depressive-like state with chronic exposure to corticosterone, as indicated by a decrease in saccharin consumption. In the forced swim test, Wistar-Kyoto rats were used because they are a spontaneously hypertensive strain that demonstrate endogenous hormonal and behavioral abnormalities often used in nonclinical models of behavioral despair. Antidepressant drugs reverse corticosterone-induced decreases in saccharin consumption and reduce immobility time in the forced swim test. Here, two doses of samidorphan (0.3mg/kg and 3.0mg/kg) were administered with a fixed dose of buprenorphine (0.1mg/kg) and data were analyzed using one-way analysis of variances. Buprenorphine, combined with 0.3mg/kg samidorphan, reversed corticosterone-induced decreases in saccharin consumption and decreased immobility in the forced swim test. However, when buprenorphine was combined with the higher dose of samidorphan (3.0mg/kg), the positive effects observed with the lower dose were reversed in both the saccharin consumption test and forced swim test. Thus, balanced modulation of opioid pharmacology may unlock the potential therapeutic value of known opioids by improving their safety. Together, the current data suggest that modulation of mu receptor activity plays an important role in the observed effects in these rat models of depression-like behavior.


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