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Low doses of risperidone and morphine interact to produce more analgesia and greater extrapyramidal effects in rats

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ABSTRACT

The search for non-narcotic drugs that will enhance the analgesic effects of opiates without enhancing their side effects has included the investigation of psychoactive drugs already approved for other uses. Some research has supported an analgesic effect of risperidone (RIS), an atypical neuroleptic. However, the analysis of the analgesic efficacy of RIS alone or as an adjuvant to morphine (MOR) has not considered the production of adverse motor effects that would limit its usefulness as a treatment for pain. We tested whether low doses of RIS would enhance the analgesic action of opiates without inducing untoward motor effects. The analgesia induced by a range of RIS doses (0.1–1.0 mg/kg, SC) was assessed alone and in combination with MOR (5 mg/kg, IP) in male Long–Evans (hooded) rats using two different algesiometric assays: hotplate and tail-flick test. The presence or absence of ptosis, vacuous chewing, and abnormal stationary postures was recorded to evaluate dyskinetic effects. No dose of RIS alone altered pain threshold. However, the highest dose of RIS, 1.0 mg/kg SC, significantly increased the analgesic effects of MOR. Dyskinetic effects of RIS were dose-dependent and enhanced in RIS + MOR treatment. These results do not support the hypothesis that RIS, alone or in combination with MOR, elevates pain threshold without also inducing motor side effects. These findings suggest caution in the use of RIS as either a primary treatment or opiate adjuvant treatment for pain.

Introduction

The search for non-narcotic drugs that enhance the analgesic effects of opioids without enhancing their side effects has included the investigation of psychoactive drugs already approved for other uses (e.g., neuroleptics). The main support for the idea that typical neuroleptics (e.g., phenothiazines and butyrophenones) have properties consistent with an analgesic action in humans includes that haloperidol, a butyrophenone, is structurally similar to the opiate meperidine and binds weakly to opioid receptors [12], chlorpromazine, a phenothiazine, effectively treats neuropathic pain and headache [7], and methotrimeprazine, another phenothiazine, induces analgesia comparable to that of a low dose of MOR [1]. However, the utility of typical neuroleptics as analgesics is limited by adverse side effects, which include extrapyramidal symptoms (EPS) like akinesia, rigidity, dystonia, and tremors that are linked to the antagonist action of neuroleptics on the dopamine D_2 receptor [15].

Atypical neuroleptics, at therapeutic doses, produce fewer EPS than do typical neuroleptics [20] presumably because their primary action is not limited to the dopamine D_2 receptor but also involves serotonin, norepinephrine, and histamine. For this reason, atypical neuroleptics may offer a distinct advantage as a pain management tool. RIS is a candidate analgesic from this class of compounds [5,17] that antagonizes serotonin 5-HT_2 receptors, α_1 and α_2 adrenergic receptors, histamine H_1 receptors, and dopamine D_2 receptors [3]. Schreiber et al. [17] reported that RIS alone induces analgesia, and, when combined with MOR, enhances the analgesic action of MOR: RIS (10–40 mg/kg, SC) increased pain threshold in mice using a tail-flick test and RIS (5 mg/kg, SC) enhanced MOR-induced antinociception. These results suggest that RIS + MOR have additive analgesic actions that may allow for lower doses of each drug to be given to achieve analgesia with minimal side effects. However, this conclusion implies that the combination of drugs does not also enhance RIS-induced side effects. Schreiber et al. [17] did not directly assess the action of RIS alone, or in combination with MOR, on motor side effects. They did note, but only casually, that EPS were present, but not dose-dependent, across the dose range of 10–40 mg/kg, SC, in mice. One possibility is that even their lowest dose (10 mg/kg, SC) was sufficient to produce the maximum EPS,

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and leaves untested the question of whether lower doses of RIS, those that produce minimal EPS, can be useful to induce or enhance analgesia. This is significant because EPS greatly reduce compliance to neuroleptic regimens and increase discomfort in humans, an outcome that is counterproductive in pain treatment.

The present investigation was designed to examine the utility of RIS as an analgesic agent and analgesic adjuvant to MOR with consideration of the intensity of EPS. Toward that end, we used a low dose range of RIS alone and in combination with a low-to-moderate dose of MOR and measured antinociception and atypical motor behavior in rats.

Methods

Subjects

Subjects were 123 experimentally naïve, male Long–Evans (hooded) rats, weighing 380–650 g. Rats were purchased from Harlan Animal Laboratories (Indianapolis, IN) or were the first generation offspring of rats from that laboratory. Rats were maintained under standard conditions: 14:10 h light/dark cycle, *ad libitum* food and water, and constant temperature of 21 ± 2 °C. All experiments received approval from Buffalo State College Institutional Animal Care and Use Committee.

Drugs

RIS (1 mg/ml) was supplied by Janssen Pharmaceutica (Titusville, NJ) or purchased from Sigma–Aldrich (St. Louis, MO) and administered SC. Morphine sulfate was purchased from Sigma (St. Louis, MO) and was administered IP (1 ml/kg). For both drugs, vehicle (VEH) preparations were used for control injections (see Supplementary data for drug preparation details). MOR was selected because it is a relatively nonselective opioid-receptor agonist [6]. A low dose of MOR, 5 mg/kg, was used to increase the likelihood that antinociception enhancement by RIS, if present, could be detected in our assay.

Nociceptive threshold assays

A hotplate (Life Science Instruments, model 39D), set at 52 °C, was used to measure nociceptive response latency [22]. A rectangular Plexiglas chamber (28-cm high) with removable top was used to confine the rat to a 28.8 cm × 26.6 cm hotplate surface during testing. Nociceptive threshold was quantified as latency (in seconds) to lick the hindpaw or jump vertically (all paws simultaneously leaving the plate surface) after placement of the rat on the hotplate. Immediately after response latency measurement, the rat was removed from the hotplate (30-s cutoff). Each rat was tested once to avoid learning effects on hotplate performance. All testing was performed by a tester who was blind to experimental conditions in a separate testing room.

A constant temperature hot-water tank (Precision Scientific, Model 181), set at 55 °C, was used to measure nociceptive threshold in Exp 3 using the standard tail-withdrawal assay [8]. Rats crawled into a black cotton sock, and the distal third of the rat's tail was immersed in water. The time required for the rat to remove its tail was measured (30-s cutoff). Tail-withdrawal latency was the mean of the last 3 of 4 trials; trials were separated by 30-s intervals. Two tests (baseline and post-treatment, 1 h apart) were conducted on each rat.

All rats were habituated to testing procedures to minimize stress effects on nociceptive threshold [9,21]. Before testing, each rat was hand-held by the experimenters for 5–10 min/day for 6 days and exposed to a room-temperature hotplate for 5 min/day for 6 days and, in Exp 3, an empty hot-water tank in a black-sock restrainer for 5 min/day for 3 days.

Behavioral observations

Initial observations indicated that RIS-treated rats showed a range of atypical motor behaviors, including ptosis, abnormal stationary posture (i.e., a motionless stance that is characterized by muscle rigidity not characteristic of a resting posture), and vacuous chewing. The presence of these behaviors was noted at 5-min intervals for the 60-min period between RIS injection and antinociception determination in all experiments. For each 5-min observation period, rats were scored for the presence of none (0), one (1), or more (2) of these atypical motor behaviors. Observation reliability was confirmed by comparison of scores obtained by the experimenter and an independent observer, blind to the experimental condition, on 12% of the observation periods; the agreement exceeded 95%.

Procedures

In Exp 1, the analgesic effect of RIS (0, 0.1, 0.3, or 1 mg/kg, SC), alone, was evaluated 60 min after administration using the hotplate test. In Exp 2, the combined analgesic action of RIS (0, 0.01, 0.03, 0.1, or 1 mg/kg, SC) and a single dose of MOR (5 mg/kg, IP) was assessed using the hotplate test; MOR was administered 30 min after RIS and nociceptive threshold was measured 30 min later (60 min after RIS). In Exp 3, the effect of RIS (1 mg/kg, SC), or VEH, in combination with MOR (5 mg/kg, IP), or VEH, was assessed as in Exp 2, but using both the hot-water tail-withdrawal assay and the hotplate test. Exp 3 tested the possibility that the increased jump/lick latency observed after combined administration of RIS + MOR was due to motor dysfunction (i.e., increased EPS-like behavior) rather than reduced pain sensitivity by using a hot-water tail-withdrawal assay. The behavioral endpoint for the tail-withdrawal assay is organized at the spinal level and therefore less influenced by motor dysfunction [11]. A single hotplate measure was taken immediately after the last hot-water test to evaluate the concordance between the two pain threshold assays. Assignment to experimental condition was random in all three experiments.

Statistics

Group differences in hindpaw jump/lick latency or tail-withdrawal latency were assessed by analysis of variance (ANOVA)

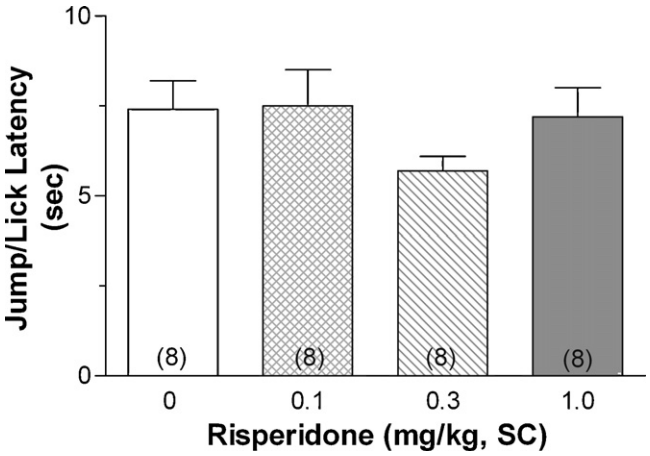

Fig. 1. Effect of risperidone on nociceptive threshold (mean ± SEM) assessed with the hotplate assay. No differences in latency to jump or lick the hindpaw were found among groups. Parentheses contain n/group.