Note added in proof. Since completion of these experiments we have carried out in vivo trials in older animals (16-month-old rats at commencement of the trial), with piracetam and centrophenoxine, using similar dosage schedules to those described. Again, there was no reduction in brain lipid peroxidation after drug treatment in these aged rats.

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Naloxone reduces abdominal muscle tone in mice and rats

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Summary. The effect of naloxone on muscle tone was investigated in mice and rats at various times after administration. The naloxone effect was also tested in diazepam-pretreated animals. Naloxone was found to display muscle relaxant activity. This effect appeared to be additive to that of diazepam.

The demonstration of endogenous opioid peptides in the mammalian organism has led to intense efforts to elucidate the physiological significance of the endorphinergic system(s). The opiate antagonist naloxone should represent a convenient tool for such investigations, since this compound is believed to compete selectively for opioid binding sites when administered at low doses[2]. Indeed, several reports have demonstrated certain effects of naloxone in the absence of exogenous opiates[3–6], pointing to a regulatory function of endogenous opioids in somatic and psychic activities.

Catatonia and muscle rigidity, apart from analgesia, are among the most prominent effects observed on the administration of opioid agonists to animals[7]. Whether or not endogenous opioids are involved in the physiological control of muscle tone is not, as yet, known. The present study examines the possible muscle relaxant activity of naloxone in mice and rats not previously treated with opiates. The effects observed were compared to those obtained with diazepam, a centrally acting compound with pronounced muscle relaxant activity. The combination of naloxone plus diazepam was also studied.

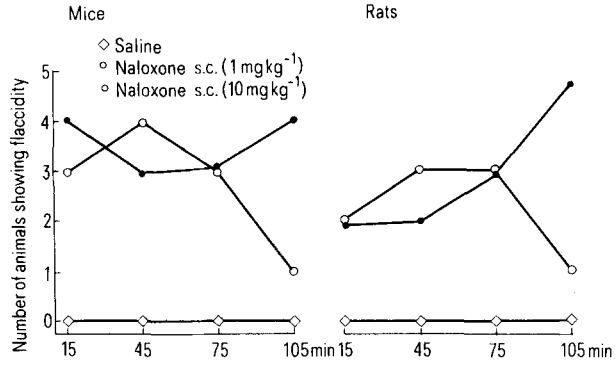

Figure 1. Effect of 1 and 10 mg kg^{-1} naloxone s.c. on the abdominal muscle tone of mice and rats at different times after administration, in comparison to saline-treated controls. The points represent the number of animals, out of a total number of 10 tested, showing a muscle relaxation. This effect of naloxone was shown to be significant by use of the Fisher-test 2×2 tables (2.5% for 1-side hypothesis), when compared to saline controls.

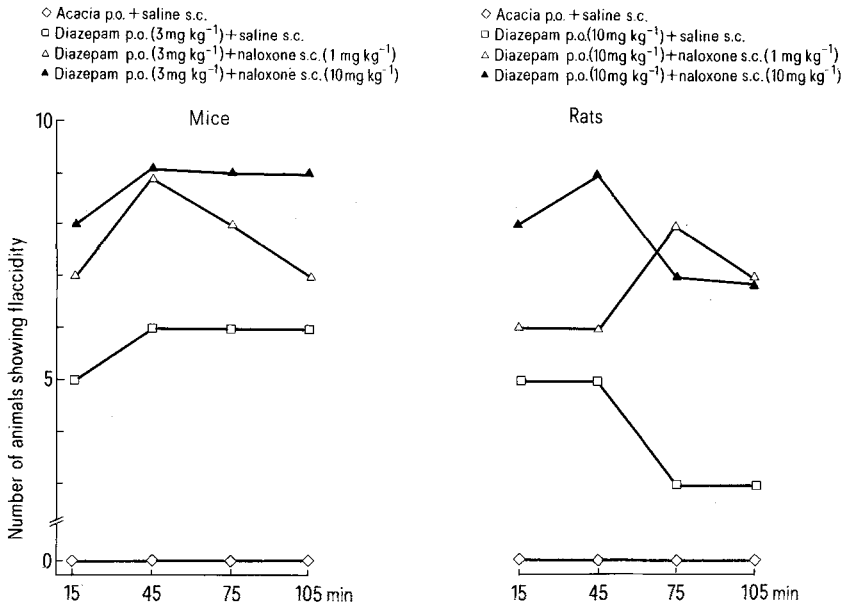

Figure 2. Effect of 1 and 10 mg kg^{-1} naloxone on abdominal muscle tone in diazepam-pretreated mice and rats in comparison with diazepam alone, at different times after drug administration. Diazepam or acacia were administered 30 min, naloxone or saline 15 min prior to the start of the experiment. The points represent the number of the animals out of a total number of 10 tested, showing a muscle relaxation.

The animals used were male specific pathogens free (SPF) albino mice, weighing 17–20 g, and male SPF albino rats, weighing 80–100 g, of the Füllinsdorf strain (rats: Wistar origin). A total of 120 animals per species was employed in the present study. Mice and rats were randomly assigned to the treatment groups (20 animals per dose and species). The treatments were: naloxone s.c. (1 and 10 mg kg^{-1}) or saline s.c. in both mice and rats. Diazepam was given p.o. at doses of 3 and 10 mg kg^{-1} in mice and rats, respectively, in 5% of gum arabic (acacia) 15 min before naloxone or saline. Controls received the vehicle only.

Muscle tone in each animal was assessed at various times after drug administration by palpation of the abdomen with the ball of the index finger as described by Irwin[8]. Care was taken not to stretch the skin of the abdominal region in any way when holding the animal. The individual animals were tested for the presence or absence of flaccidity in the abdominal region, no attempt being made to grade the score. Subjective assessment of muscle relaxation was blind as to treatment and dose used. Quantification of effects was done by taking the number of animals showing flaccidity in a dose group of 10. Significance was tested by Fisher's test for 2×2 tables (1-side hypothesis).

Both doses of naloxone (1 and 10 mg kg^{-1}, s.c.) produced a similar degree of muscle relaxation when assessed by this method, although a difference between the 2 doses was found in the duration of the effect (fig. 1). Preliminary experiments also revealed some muscle relaxant activity of naloxone at even lower doses (0.1 and 0.3 mg kg^{-1}, s.c., data not shown).

Although naloxone must be considered to display pharmacological effects unrelated to its opiate antagonistic activity[2], the low dose of 1 mg kg^{-1} employed here may be taken as specific for the blockade of opiate receptors. It is well documented that exogenously administered opiates and opioid peptides produce catatonia and muscle rigidity in rodents[7], an effect which is reversed by naloxone and is thus probably opiate receptor-specific in nature. Accordingly, the effects observed in the present investigation could indicate that naloxone antagonizes the effects of endogenous opioids on muscle tone.

The ability of naloxone to reduce abdominal muscle tension was compared with that of diazepam. On the basis of the criteria employed here, naloxone and diazepam displayed very similar effects (fig. 2). In the light of earlier reports demonstrating diazepam-induced changes in the striatal and hypothalamic enkephalin content in rats[9], the muscle relaxant activity of naloxone was also examined in diazepam-pretreated animals. The effects of both compounds appeared, however, to be 'additive'. Several lines of reasoning suggest separate mechanisms for the 2 drugs in affecting muscle tone: e.g. if we relate some of diazepam effects to the GABA system[10], then this suggestion gains support from reports demonstrating that the effects of opiates and muscimol on muscle activity are mediated in different brain areas[11,12]. In conclusion, the present results show a muscle relaxant effect of naloxone and a 'synergistic' interaction between naloxone and diazepam on muscle tone. While a 'synergism' was observed between diazepam and naloxone in the present investigation, an antagonistic interaction was found in a conflict behavior situation[13].

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