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The contribution of α_2-adrenoceptor and opioid receptor mechanisms to antinociception differs in Lewis and Fischer 344 rats

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Abstract

Lewis and Fischer 344 (F344) rats differ in their physiological and pharmacological responses to a variety of environmental stimuli, which have been partially attributed to endogenous opioid function. Since opioid and α_2-adrenoceptor mechanisms are closely related, we have comparatively examined the contribution of both systems to antinociception in female Lewis and F344 rats by the tail-flick method. Basal responses of F344 and Lewis rats were found to be similar, both showing a slight but significant increase in reaction time along the experimental period which was not completely reversed by naloxone. Morphine exhibited a bell-shaped dose–response curve in Lewis rats, these animals being more sensitive than F344 at 1 and 5 mg/kg but less sensitive at 10 mg/kg. Clonidine up to 0.1 mg/kg was more active in F344 rats. The α_2-adrenoceptor antagonist yohimbine provoked a higher hyperalgesic effect in Lewis rats and decreased morphine antinociception in both strains. The existence of a balanced contribution of opioid and α_2-adrenoceptor mechanisms to control pain transmission in both strains is discussed.

Keywords: Antinociception; Lewis rat; F344 rat; Morphine; Yohimbine; Clonidine

1. Introduction

The comparative study of drug effects in different strains of laboratory animals is a widely used method to study the involvement of genetic factors in pharmacology. Fischer 344 (F344) and Lewis rats are two inbred strains that have been repeatedly used for this kind of comparisons, especially in the field of drug addiction, since Lewis rats are much more prone to drug abuse than F344. This has been observed in conditioned place preference studies with cocaine, nicotine and morphine (Guitart et al., 1992; Kosten et al., 1994; Horan et al., 1997) and also in self-administration experiments with cocaine, ethanol and different opioids (George and Goldberg, 1988; Suzuki et al., 1992). It has been repeatedly shown that Lewis and F344 rats markedly differ in the response of the hypothalamic–pituitary–adrenal axis to immune, inflammatory or environmental stressors, the former being hyporresponsive and latter hyperresponsive relative to some outbred strains (Sternberg et al., 1989a,b, 1992; Rosecrans et al., 1986; Dhabhar et al., 1993, and see review of Kosten and Ambrosio, 2002). This response could be related to many of the differences observed between Lewis and F344 rats, but sometimes the link is not easy to demonstrate. Thus, it has been shown that the relative hyporeactivity of the hypothalamic–pituitary–adrenal axis in Lewis with respect to F344 rats is not clearly associated with uniform behavioural hyporeactivity even when corticotropin-releasing factor-dependent behaviors are examined such as deambulation in the elevated plus maze test, acoustic startle response, schedule-induced polydipsia and conditional emotional response (Stöhr et al., 2000).

Differences between Lewis and F344 rats could be related at least in part to the function of the endogenous opioid system, which seems to be hypoactive in Lewis rats (Sternberg et al., 1989a,b; Nylander et al., 1995; Martín et al., 1999). Since these opioid mechanisms are deeply involved in nociception, one could expect that Lewis and F344 rats should differ in their pain control mechanisms; in fact, the comparative study of the antinociception elicited by exogenous opioid receptor agonists has revealed such heterogeneity, but these results are very dependent on the experimental paradigm used and sometimes apparently contradictory (Vaccarino and Couret, 1995; Woolfolk and Holtzman, 1995; Morgan et al., 1999). These changes in

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opioid function could be expected to extend to those neurotransmitter systems that are closely related, as it is the noradrenergic system in the case of antinociception. A broad range of preclinical and clinical studies on analgesia has demonstrated that opioid and α_2-adrenoceptor mechanisms are interdependent. It is widely known that α_2-adrenoceptor stimulation enhances the antinociceptive effect of μ-opioids (Wilcox et al., 1987; Yeçilyurt and Tayfun Uzbay, 2001), while α_2-adrenoceptor antagonists such as yohimbine or idazoxan are generally hyperalgesic and attenuate morphine analgesia in several pharmacological tests (Browning et al., 1982; Iglesias et al., 1992; Herrero and Solano, 1999). Some works tend to show that this interaction could be placed at the spinal cord, where α_2-adrenoceptors participate in the antinociception that follows opioid activation of descending noradrenergic inhibitory pathways (Camarata and Yaksh, 1985; Wigdor and Wilcox, 1987; Solomon and Gebhart, 1988). The close relationship between the antinociceptive effects of opioids and α_2-adrenoceptor agonists extends to the chronic conditions that give rise to neuroadaptations. Thus, repeated exposure to morphine leads to α_2-adrenoceptor downregulation in the central nervous system (Smith et al., 1989, but see Gabilondo and García-Sevilla, 1995) and analgesic cross-tolerance with α_2-adrenoceptor agonists (Yamazaki and Kaneto, 1985; Stevens et al., 1988; Solomon and Gebhart, 1988). Even when opioid receptor/α_2-adrenoceptor interactions are prominent in analgesia, as well as in many other circumstances, neither the analgesic effect of α_2-adrenoceptor agonists nor the interactions with opioid analgesics have been comparatively studied in Lewis and F344 rats. We have tried to examine this question since it could reveal how these systems work together in two rat strains that exhibit considerable differences concerning pain control mechanisms. A preliminary report of this work has been presented (Herradón et al., 2000).

2. Methods

Female Lewis and F344 rats (7 weeks old; Harlan, Spain) were used. Animals had free access to water and standard diet and were maintained in a controlled environment (20–22 °C, 12 h/12 h dark/light cycle) throughout the experiments. The drugs used were morphine sulphate (Alcaliber, Spain), clonidine hydrochloride, naloxone hydrochloride and yohimbine hydrochloride (Sigma, Spain). All these drugs were dissolved in physiological saline for i.p. administration (10 ml/kg). This assay has been carried out in accordance with the Guide for the Care and Use of Laboratory Animals promulgated by the National Institutes of Health.

Nociception was studied with the tail-flick method (D'Amour and Smith, 1941) using a heat-radiating lamp. The intensity of the stimulus was adjusted to a value previously shown to elicit baseline latencies close to 6 s in outbred Sprague–Dawley rats, and was kept constant for all the experiments. A cut-off latency of 15 s was used to minimize tissue damage.

After a 1-h habituation period to plexiglas holders, the basal nociceptive thresholds were established and then the animals were assigned at random to the different drug-treatment groups. Rats showing basal latencies greater than 10 s (three of the F344 strain and one Lewis) were no longer used for this study. Immediately after drug treatment, animals were restrained again for the remaining experimental period, tail-flick latencies being redetermined at 30, 60 and 120 min postinjection. In the experiments performed to evaluate the effects of morphine, yohimbine and the possible influence of yohimbine over morphine antinociception, animals were pretreated either with saline or yohimbine (2 mg/kg) and 5 min later they received another injection of either saline or morphine (0.2–10 mg/kg). The effects of naloxone (1 mg/kg) and clonidine (0.004–0.1 mg/kg) were studied after single injection. The different pharmacological treatments were always run in parallel in Lewis and F344 rats to enable statistical comparison between strains.

Dose–response curves for morphine and clonidine were constructed by using the percentage of the maximum antinociceptive effect for each dose; these results were fitted to a hyperbolic function, which served to calculate EC_{50} values (95% confidence intervals are shown in brackets). Statistical comparison between different treatments and

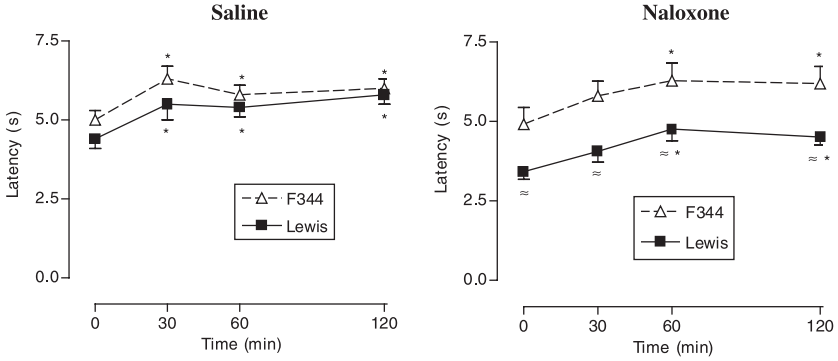

Fig. 1. Latencies in the tail-flick test in animals treated with saline or naloxone (1 mg/kg). Points represent means and S.E.M. from at least nine determinations. *$P<0.05$ vs. basal latency, ≈ $P<0.05$ vs. F344.

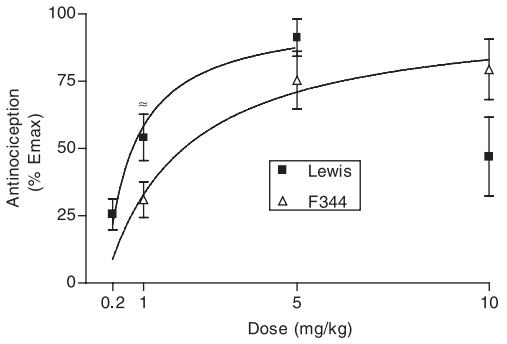

Fig. 2. Dose–response curves to morphine in Lewis and F344 rats. Points represent means and S.E.M. from at least eight rats. ≈ $P<0.05$ vs. F344.

strains was performed by two-way analysis of variance followed by multiple comparison post hoc tests (least significant differences). Significance was considered at the 0.05 level.

3. Results

The basal latencies exhibited by the animals in the tail-flick test tended to be higher in the case of F344 rats in the whole experiments, but this result did achieve statistical significance only in two of the experimental sets. Saline-treated animals of both strains exhibited a slight but significant increase of the latencies along the experimental period considered; this increase was also present in naloxone-treated animals (Fig. 1).

Morphine injection increased latencies in a dose-related fashion in both strains up to 5 mg/kg, but opiate sensitivity tended to decrease at a higher dose in Lewis rats; accordingly, the dose–response curve to morphine was bell-shaped in Lewis but not in F344 animals (Fig. 2). The calculated EC_{50} of morphine was 2 mg/kg (0.9–3.2) for F344 rats and 0.7 mg/kg (0.2–1.2) for Lewis rats (taking into account only the ascending part of the dose–response curve).

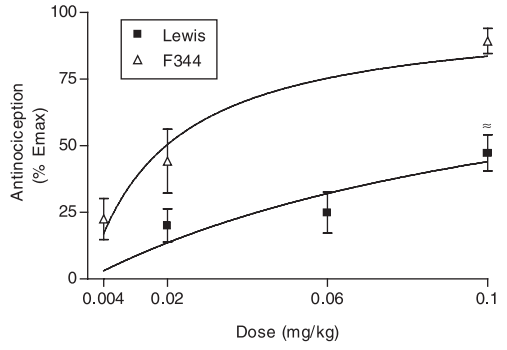

Fig. 3. Dose–response curves to clonidine in Lewis and F344 rats. Points represent means and S.E.M. from at least eight rats. ≈ $P<0.05$ vs. F344.

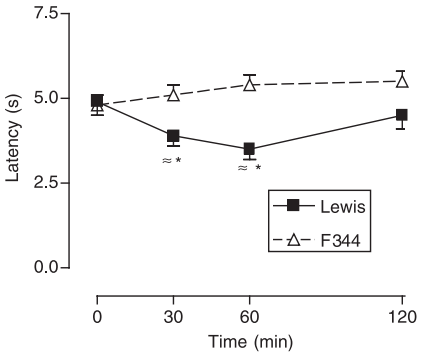

Fig. 4. Latencies in the tail-flick test in F344 ($n=17$) and Lewis ($n=18$) rats treated with yohimbine (2 mg/kg). Points represent means and S.E.M. *$P<0.05$ vs. basal latency, ≈ $P<0.05$ vs. F344.

The effects of α_2-adrenoceptor ligands were markedly different in both strains. Clonidine was more potent in F344 rats (Fig. 3), the EC_{50} being 0.02 mg/kg (0.01–0.04) for F344 and higher than 0.1 mg/kg for Lewis. On the other hand, the hyperalgesic effect of yohimbine was more pronounced in Lewis rats (Fig. 4). Opioid antinociception was blocked by yohimbine pretreatment in both strains (Fig. 5).

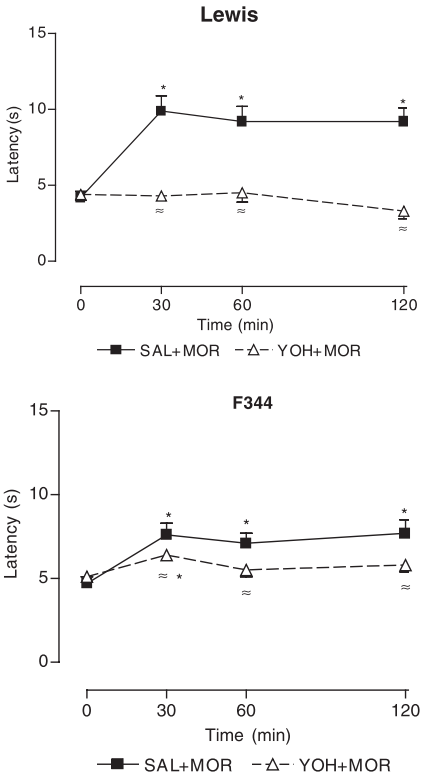

Fig. 5. Latencies in the tail-flick test in Lewis and F344 rats treated either morphine (MOR, 1 mg/kg). Animals ($n=8$) were pretreated either with saline (SAL) or yohimbine (YOH, 2 mg/kg) 5 min before morphine administration. Points represent means and S.E.M. *$P<0.05$ vs. basal latency, ≈ $P<0.05$ vs. SAL + MOR.

4. Discussion

The results obtained in our study clearly show that Lewis and F344 rats exhibit different behaviours in the tail-flick paradigm, especially after injection of analgesic drugs as previously noted by other authors. However, additional studies using other kind of nociceptive stimuli and habituation procedures should be considered to fully understand the meaning of these differences and the involvement of stress. In fact, the tail-flick response is sensitive to changes in skin temperature (Hole and Tjolsen, 1993), which in turn may be closely dependent on stress-induced vasoconstriction. Therefore, we cannot rule out a potential contribution of these temperature changes to the observed differences in tail-flick latencies. Another point to bear in mind when interpreting both our results and those obtained by others is the possible contribution of strain-related pharmacokinetic differences to the drug effects obtained. We have not found in the literature any report showing significant differences in drug metabolism between Lewis and F344 rats affecting the drugs used in this study, but we cannot discard this possibility on the basis of the present experiments.

The basal responses of F344 and Lewis rats did not show prominent differences in our experiments. Although F344 rats tended to exhibit higher basal latencies, this difference was not of great magnitude and only achieved statistical significance in two of the experiments performed. Animals from both strains injected with saline also showed a comparable increase of the latencies along the experimental period, which seemed to be non-opioid in nature at least partially, since it was not completely blocked by naloxone. These findings were very similar to those reported by Woolfolk and Holtzman (1995) and together showed that the basal reactions of Lewis and F344 rats in the tail-flick test were alike under the experimental conditions selected for this study.

The finding that the antinociceptive effect of morphine in Lewis rats was bell-shaped in the range of doses studied could explain some apparent discrepancies found in the literature when the effect of the opiate was comparatively examined in Lewis and F344 rats. Thus, Woolfolk and Holtzman (1995) studied the effect of morphine up to 5.6 mg/kg and showed that Lewis rats were more sensitive to this drug, as it happens with the lower doses of opiate in our study. Conversely, Vaccarino and Couret (1995) concluded that F344 rats were more sensitive to morphine since this drug at doses higher than 5 mg/kg was more potent in F344 rats, which is in agreement with our results obtained with morphine at 10 mg/kg. It therefore seems that these previous studies failed to describe the biphasic change of morphine sensitivity between strains just because they examined a narrow range of doses. Morgan et al. (1999) examined the effect of morphine and other opioids in different rat strains including Lewis and F344, and they found a higher effect in F344, closely dependent on the intensity of the nociceptive stimulus, at doses generally above 1 mg/kg. It is important to note that these authors obtained a very poor antinociceptive effect with this last dose both in Lewis and F344 rats; this finding clearly reflects that there should be striking differences in the experimental conditions with respect to our study, since we have obtained a very potent effect after injection of 1 mg/kg of morphine. One of the possible reasons for this difference is that Morgan et al. unrestrained animals during their experiments, which is important since it has been reported that stress-induced activation of the hypothalamic–pituitary–adrenal axis is different in both strains (Sternberg et al., 1992) and this affects morphine analgesia (Vaccarino and Couret, 1995). Other possible experimental variations cannot be addressed since Morgan et al. did not mention the sex, weight or age of the rats in the original paper. In other study, Cook et al. (2000) did not find consistent differences regarding the antinociceptive effectiveness of various opioids in F344 and Lewis females. However, the animals used in that study were 3–6 months old, while in our work, the rats used were 7 weeks old; this could be the reason of the apparent discrepancies since there are prominent age-dependent changes in opioid function in the rat (see for instance Parra et al., 1997).

The mechanisms underlying dose-related variations in the effects of morphine are not clear. It is important to note that morphine-induced elevations of plasma corticosterone and prolactin have been described at doses higher than 1 mg/kg both in Lewis and F344 rats, and strain differences were only seen at 10 mg/kg (Baumann et al., 2000); therefore, it is possible that differences in antinociception could be closely related to variations of these neuroendocrine responses to morphine, since both corticosterone and prolactin have analgesic properties (Ramaswamy et al., 1989; Sutton et al., 1994).

Besides the differential contribution of opioid mechanisms to the final nociceptive response in Lewis and F344 rats, there is additional evidence to affirm that the neurochemical mechanisms that control pain exhibit substantial differences between these strains. This is particularly evident when the antinociceptive effect of substances such as nitrous oxide is tested in the tail-flick test, since both strains display a striking divergent response (Fender et al., 2000). Moreover, in the hot plate test, even the basal latencies of Lewis and F344 rats are clearly different, the former exhibiting a lower threshold for pain responses (Stöhr et al., 1998). Our results extend these strain differences to the role of α_2-adrenoceptor mechanisms in the control of pain. The hyperalgesic effect of yohimbine in Lewis rats reveals the existence of a tonic inhibitory control of pain transmission mediated by α_2-adrenoceptors in our experimental conditions, as it has been observed in outbred strains (Iglesias et al., 1992). On the contrary, F344 did show poor (if any) sensitivity to yohimbine injection. This is not the first time that F344 rats have proved to be resistant to alpha adrenoceptor blockade in experimental pain models: Sprague–Dawley, Wistar and especially Lewis rats show a phentolamine-sensitive hyperalgesia after nerve ligation that

is absent in F344 rats (Lee et al., 1997). It appears that the endogenous noradrenergic tone-controlling pain transmission is not prominent in F344 rats under these experimental conditions. At the same time, the finding that the antinociceptive effect of the exogenous α_2-adrenoceptor agonist clonidine was more potent in F344 rats leads to the suggestion that, in this strain, α_2-adrenoceptor-mediated antinociception could become hypersensitive as an homeostatic adaptation to lower endogenous stimulation. However, this possible correlation between neurochemical and behavioral responses remains to be seen.

Our results therefore show that the antinociception mediated by α_2-adrenoceptor and opioid receptor agonists is quantitatively opposite in Lewis and F344 rats. Due to the fact that both mechanisms are closely related, as shown by yohimbine reversal of morphine effects, it is tempting to speculate that the final antinociceptive response could result from the balanced influence of the opioid and the α_2-adrenoceptor systems. Thus, Lewis rats could be more sensitive to low and moderate doses of opioid receptor agonists and less sensitive to α_2-adrenoceptor agonists in comparison with F344 rats, but the resulting responses to noxious stimuli appear equilibrated in both strains.

At least in the case of opioid sensitivity, these strain differences could reflect the variations of the intrinsic opioid circuitry that have been previously described. Lewis rats exhibit lower enkephalin gene expression and endogenous dynorphin levels than F344 in several rat brain areas (Nylander et al., 1995; Martín et al., 1999), which could lead to an adaptative increase of the sensitivity to exogenous opioids. As we have mentioned before, such an increased sensitivity to morphine has been also described in studies of drug self-administration and conditioned place preference, but also in feeding (Gosnell and Krahn, 1993) and electroencephalographic activity (Mayo-Michelson and Young, 1993).

We did not find any detailed, comparative study dealing with noradrenergic function in Lewis and F344 strains. It is known that both the spontaneous firing rate and the tyrosine hydroxylase activity of locus coeruleus neurons are lower in F344 rats (Beitner-Johnson et al., 1991; Guitart et al., 1993); since the locus coeruleus is the main location of brain noradrenergic neurons, these findings probably reflect a decreased noradrenergic function in F344 rats, but the authors did not identify the cells studied and neither drafted any conclusion on this subject. Such a noradrenergic hypoactivity would fit very well with our proposed adaptative increase of sensitivity of F344 rats to exogenous noradrenergic agonists. Taking together all these ideas, we could hypothesize that different effects of morphine and clonidine in Lewis and F344 rats could be the result of adaptations to the specific influences of the endogenous opioid and noradrenergic systems in each strain. Although this balance hypothesis could be judged highly tentative on the basis of the present evidences, we think that it deserves attention and consequently further experiments to clarify that this point could be of interest.

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