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Impact of ageing on the antinociceptive effect of reference analgesics in the Lou/c rat

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1 Research on the evolution of experimental pain perception and on the achievement of analgesia with ageing has led so far to contradictory results.

2 This study investigated in the rat the impact of ageing on the antinociceptive effect of reference analgesics, acetaminophen (50, 100, 200, 400 mg kg^{-1} po), aspirin (50, 100, 200, 400 mg kg^{-1} sc), clomipramine (5, 10, 20, 40 mg kg^{-1} sc) and morphine (1.25, 2.5, 5, 10 mg kg^{-1} sc).

3 Lou/c rats were chosen because they provide a model of healthy ageing and they do not develop obesity with age. Three groups of 40 rats each (mature (4 months), middle-aged (18 months) and old (26 months)), were treated with each drug at 14 days interval. Two tests were used: a thermal test (tail immersion in 48°C water and measurement of reaction latency) and a mechanical test (paw pressure and measurement of struggle threshold).

4 Results confirm the increased mechanical sensitivity to pain and no change in thermal sensitivity for old rats compared to mature and middle-aged animals. They show a marked decrease in the effect of morphine with age and no age-related effect for acetaminophen, aspirin or clomipramine. Plasma levels of morphine and metabolites are not different in the three age groups.

5 It is likely that the influence of age on morphine analgesia is linked mainly to pharmacodynamic rather than pharmacokinetic changes.
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Keywords: Age; pain; morphine; acetaminophen; aspirin; clomipramine; Lou/c rat

Abbreviations: 5HT, serotonin; ANOVA, analysis of variance; AUC, area under the curve; M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide; NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitors

Introduction

Changes of pain perception with age and influence of age on the effect of analgesics are still not well known. Pain is however an important problem of public health as it is one of the major causes of diminished quality of life in the elderly, and the International Association for the Study of Pain has identified research on pain in relation to ageing as a priority (Ferrell, 1996). In fact, it is unclear whether age in adult humans influences the sensory processes involved in pain perception (Harkins *et al*., 1994). The effect of drugs on this perception is not clear either: e.g. elderly patients achieve more effective pain relief than do young adults when given equal doses of morphine (Kaiko, 1980; Moore *et al*., 1990). Nor is it clear whether the increase in sensitivity to morphine administration in the elderly is due to pharmacokinetic and/or pharmacodynamic factors.

As regards animals, several teams have investigated the effect of age on nociception and analgesia, and contradictory results have been reported. Various tests using thermal, electrical or mechanical stimulation have been applied to rats aged from 2 to 30 months, and showed either a decrease in pain reactivity (Paré, 1969; Nicak, 1971; Hess *et al*., 1981; Akune & Soliman, 1994), an increase (Gordon *et al*., 1978; Wallace *et al*., 1980; Chan & Lai, 1982; Crisp *et al*., 1994), or no effect (Goicoechea *et al*., 1997). These discrepancies could be interpreted partly by the existence of differences between species or by methodological problems such as the choice of the strain and the pain tests used. More recent studies show that age differences in nociception may be dependent on the test used (Gagliese & Melzack, 2000; Jourdan *et al*., 2000). As regards the influence of the analgesics on experimental pain in animals, older rats are generally less sensitive than younger ones to the antinociceptive effect of opioid agonists (Islam *et al*., 1993; Crisp *et al*., 1994), more sensitive to cholinergic agonists (Pedigo *et al*., 1984; Knisely & Hamm, 1989) and are as sensitive to 5HT agonists as younger ones (Akune & Soliman, 1994).

The present study aims at analysing the impact of ageing on the antinociceptive effect of reference analgesics. We tested various drugs characterised by different structure, site and mode of action: opiate (morphine), non-steroidal-anti-inflammatory drugs (acetaminophen, aspirin) and an antidepressant drug (clomipramine).

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In order to obtain relevant data, the present study was performed on two different tests (mechanical and thermal) because of the differential influence of age on stimulation modalities. In a previous study, we showed that while sensitivity to mechanical nociception increased with age, no changes were observed with thermal stimulations (Jourdan *et al*., 2000). Three age groups were used because important changes occur at mid-life (Gagliese & Melzack, 1999; 2000). Finally the Lou/c strain rat was chosen because this is a relevant model for studying ageing. This strain displays an increased longevity and a lighter body weight than other more common rat strains and does not develop obesity with age, hence providing a model of healthy ageing (Veyrat-Durebex *et al*., 1999).

Methods

Animals

Male Lou/c rats (Harlan France) were used. This strain is an inbred strain of Wistar origin (University of Louvain, Belgium) (Bazin, 1990). The animals were housed in plastic cages and kept in a temperature-controlled room ($22 \pm 1^{\circ}C$) with a 12 h : 12 h light – dark cycle (lights off at 20 : 00 h). They had free access to standard food UAR, A04 (metabolizable energy 2.9 kcal g^{-1}) and water.

Tests

Thermal stimulus: tail immersion test The tail of the rat was immersed (on 5 cm) in a water bath at the noxious temperature of 48°C until the tail was withdrawn or signs of struggle were observed (cut-off time 15 s). Reaction latency (s) was used as a parameter reflecting the intensity of the pain experienced.

Mechanical stimulus: paw pressure test Nociceptive thresholds, expressed in grams (g), were measured using an Ugo Basil analgesimeter (Apelex, probe tip diameter 1 mm; weight 30 g; cut-off pressure 750 g) by applying increasing pressure to the left hind paw of rats until a struggle occurred.

Drugs

The effect of four reference analgesics has been analysed: morphine chlorhydrate (SIGMA France) 1.25, 2.5, 5, 10 mg kg^{-1}, clomipramine (SIGMA France) 5, 10, 20, 40 mg kg^{-1}, aspirin (Synthelabo France) 50, 100, 200, 400 mg kg^{-1} and acetaminophen (UPSA France) 50, 100, 200, 400 mg kg^{-1}.

Procedure

The animals were divided into three age groups of 40 rats each: mature (4 months), middle-aged (18 months) and old (26 months) rats. During the week preceding day 0, the rats were accustomed to the tests.

In each group, eight rats were treated with a saline solution, the others with analgesics at four different doses ($n = 8$ per group). The animals were successively submitted in random order to mechanical and, 10 min later, to thermal tests, and the age was not known to the experimenters. The rats were tested twice before treatment (control data). These pre-treatment stimulations occurred 30 and 10 min before injection for the mechanical test, 20 min and immediately before injection for the thermal test. The mechanical thresholds were measured 10, 30, 50, 70 and 90 min after the injection of saline or drug, the thermal latencies 20, 40, 60, 80 and 100 min after injection of saline or drug.

This protocol was repeated four times at 14 days interval. Day 0: experiment 1, administration of morphine sc; Day 14: experiment 2, administration of clomipramine sc; Day 28: experiment 3, administration of aspirin sc; Day 42: experiment 4, administration of acetaminophen po.

Plasma concentrations

The origin of potential differences in the effect of a drug could be due to pharmacokinetic modifications across ageing. Plasma concentrations of morphine (10 mg kg^{-1}), its metabolites and acetaminophen (400 mg kg^{-1}) were determined for 10 animals in each age group, 14 days after the end of experiment 4. Blood samplings were performed at the time, corresponding to the maximal effect (30 min after injection) in the retro-orbital sinus after a light anaesthesia with halothane. Morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) determinations in rat serum were performed using liquid chromatography-electrospray mass spectrometry technique (LC-ES-MS). After addition of internal standards (d3-morphine and d3-morphine-3-glucuronide), substances of interest were extracted using Bond Elut certify cartridges (Varian™). After elution of the compounds with methanol and evaporation, the residue was reconstituted with 50 μl of the mobile phase: mixture of 5 mM ammonium formate buffer (pH 3)-acetonitrile (70 : 30, v/v). The chromatographic separation was performed on an Inertsil C_{18}, 5 μm (150×2 mm i.d.) column, using a gradient of the mobile phase, delivered at a flow-rate of 100 μl min^{-1}. The detection was performed using an API 100 mass spectrometer, equipped with an electrospray-type ionisation device (Sciex™). The compounds were detected in the selected ion monitoring mode, using two mass-to-charge ratios (one for quantitation and one for confirmation) for the three analytes: m/z 286.4 and 153.0 for morphine, m/z 462.2 and 286.4 for morphine-3-glucuronide and morphine-6-glucuronide. The limit of quantitation was 2.5 $\mu g\, l^{-1}$ for morphine, morphine-3-glucuronide and 5 $\mu g\, l^{-1}$ for morphine-6-glucuronide. The method was linear from these limits up to 1000 $\mu g\, l^{-1}$ for the three analytes.

Acetaminophen was measured on the Dimension® clinical chemistry system with the Acetaminophen Flex TM reagent cartridge (Dade Behring). The methodology is based on the enzymatic hydrolysis of acetaminophen producing acetate and p-aminophenol. The p-aminophenol is determined colorimetrically by reaction with o-cresol and ammoniacal copper sulphate. The amount of aminophenol produced is proportional to the acetaminophen concentration and is measured using a bichromatic end-point. The assay is specific for the parent compound and does not detect acetaminophen metabolites. Analytical sensitivity of the acetaminophen is 2.0 $\mu g\, ml^{-1}$ and represents the lowest concentration that can be distinguished from zero. The sensitivity is defined as the concentration of two standard deviations above the 0.0 $\mu g\, ml^{-1}$ level.

Statistical analysis

Data are given as mean ± se. The effects of drug and age were determined using analysis of variance (ANOVA) procedures followed by a Fisher PLSD test. Statistical significance was $P<0.05$.

Results

Baseline scores

As previously observed in Lou/c/jall rats (Jourdan *et al*., 2000), a clear decrease in mechanical thresholds across ageing was noted ($F(2, 102)=404.1$; $P<0.0001$). For example, the baseline mechanical thresholds in experiment 2 were 210 ± 10 g in the mature group, 138 ± 10 g in the middle-aged group and 116 ± 9 g in the old group. There was no influence of age on the thermal latencies ($F(2, 107)=0.12$; $P=0.88$ NS). For example, the baseline thermal latencies in experiment 2 were 6.7 ± 5 s in the mature group, 6.6 ± 0.3 s in the middle-aged group and 6.6 ± 0.3 s in the old group. The influence of repeated stimulation across time on the baseline scores was also investigated because four experiments were performed successively on the same animals at 14 days interval (Table 1). Concerning the mechanical test, a weak effect of the repetition was observed ($F(3, 306)=3.2$; $P=0.02$). This effect was age-dependent ($F(6, 306)=4.5$; $P=0.0002$); if the pain scores of the mature animals increased with repetition, that of middle-aged and old animals remained stable or slowly decreased. When considering the thermal test, a progressive increase of the latencies was

Table 1 Baseline scores (mean of the two control values) obtained after mechanical (paw pressure test) or thermal stimulation (tail immersion test)

		First measure	*Second measure*	*Third measure*	*Fourth measure*
Paw pressure test (g)	Mature group	191.4 ± 34.4	181.8 ± 23.0	213.6 ± 34.2	199.1 ± 32.1
	Middle-aged group	151.0 ± 22.1	147.8 ± 20.0	145.5 ± 21.8	135.1 ± 19.8
	Old group	115.6 ± 26.4	118.0 ± 26.3	115.4 ± 19.1	110.0 ± 18.9
Tail immersion test (s)	Mature group	6.3 ± 9	6.6 ± 1.1	6.7 ± 1.2	6.5 ± 1.1
	Middle-aged group	6.3 ± 0.8	6.2 ± 0.9	6.6 ± 1.0	6.8 ± 0.9
	Old group	6.3 ± 1.0	6.2 ± 0.9	6.8 ± 0.8	6.7 ± 0.8

The stimulations were repeated four times at 14 days interval. Mechanical data are expressed in grams (g) and thermal ones in seconds (s).

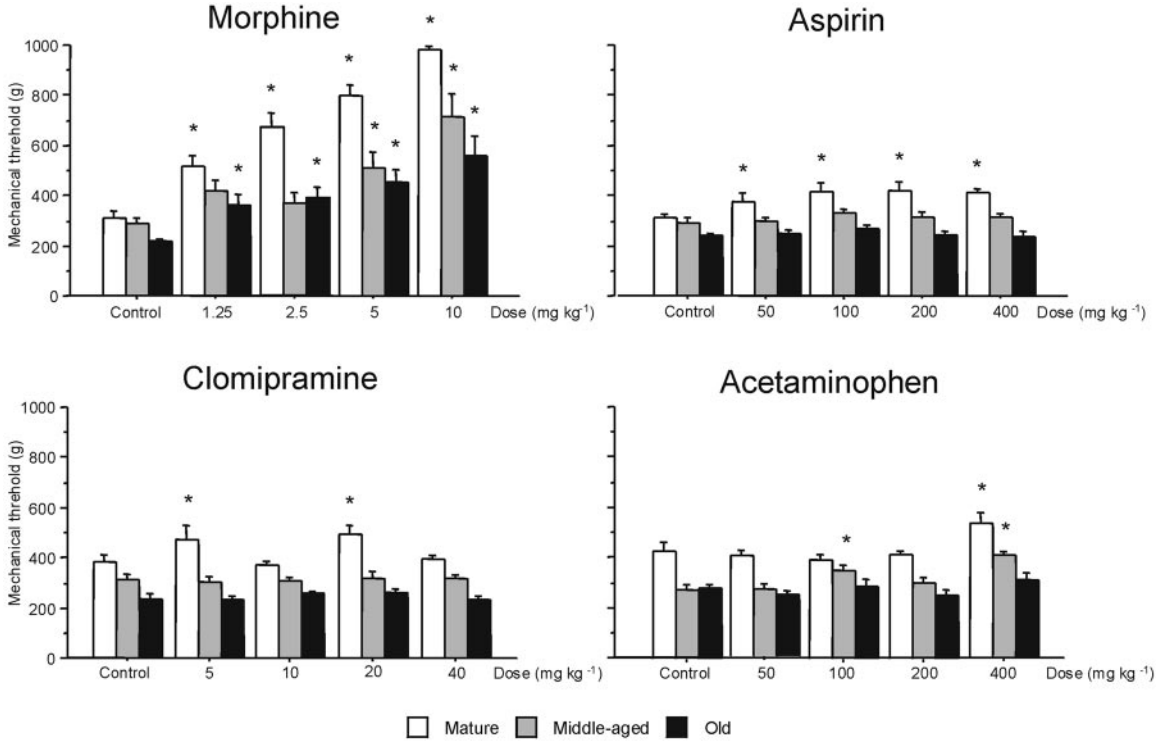

Figure 1 Influence of age on the effect of reference analgesics on the paw pressure test in three groups of rats of different age (4, 18 and 26 months). Values correspond to the AUC (area under the curve) calculated by trapezoidal rules from t + 30 to t + 50 min after injection. Morphine 1.25, 2.5, 5, 10 mg kg^{-1} (sc) induced a dose and age-related increase in thresholds, aspirin 50, 100, 200, 400 mg kg^{-1} (sc) induced an increase in thresholds, acetaminophen 50, 100, 200, 400 mg kg^{-1} (po) induced a dose-related increase in thresholds and clomipramine 5, 10, 20, 40 mg kg^{-1} (sc) had no significant effect. *Different from controls, $P<0.05$.

observed ($F(3, 321) = 6.1$; $P = 0.0005$), but this effect was not age-related ($F(6, 321) = 0.9$; $P = 0.5$ NS). The statistical analyses were performed on the mean of the two control data (before injection).

Effect of analgesics on mechanical thresholds

Whatever the age-group considered, morphine induced a dose-dependent ($F(4, 99) = 42.1$; $P = 0.0001$) increase in mechanical thresholds (Figure 1). This effect was all the more marked as the rats were young ($F(2, 99) = 9.3$; $P = 0.0002$). The duration of the effect was longer in old animals (interaction age × time $F(8, 316) = 2.5$; $P = 0.0012$) (Figure 2 and 5A). No effect of clomipramine was found on thresholds ($F(4, 104) = 1.7$; $P = 0.15$ NS). Aspirin induced an increase in mechanical thresholds ($F(4, 101) = 6.1$; $P = 0.0002$) and this effect was not age dependent (interaction age × dose $F(8, 101) = 1.4$; $P = 0.2$NS). Acetaminophen induced a dose dependent increase in mechanical thresholds ($F(4, 91) = 6.1$; $P = 0.0002$), this effect was not age dependent (interaction age × dose $F(8, 91) = 0.9$; $P = 0.5$ NS).

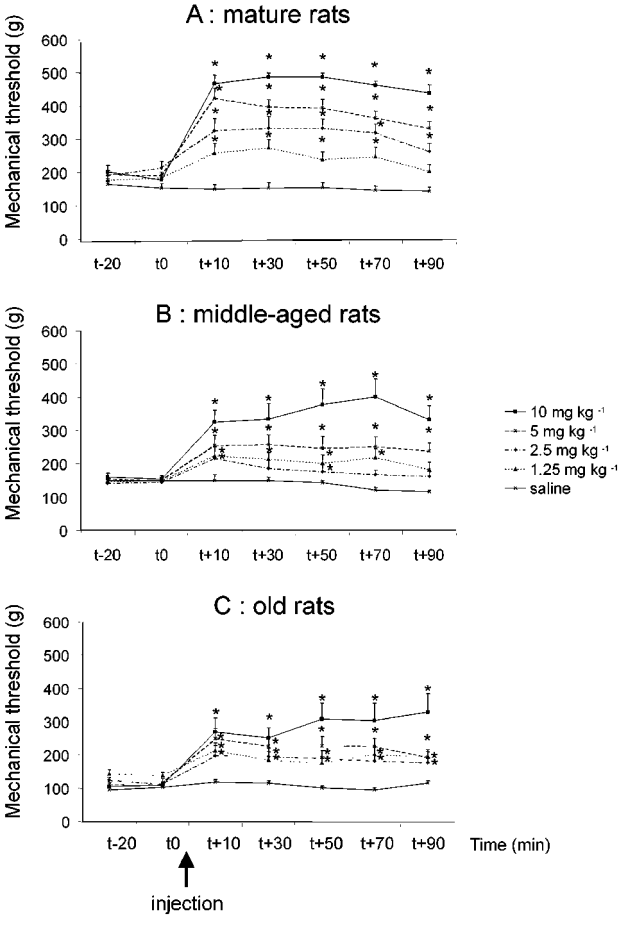

Figure 2 Analgesic effect of morphine (paw pressure test) in three groups of rats of different age ((**a**) mature 4 months, (**b**) middle-aged 18 months and (**c**) old 26 months). For the three groups a dose-dependent effect of morphine was observed but this effect was all the more important as the animals were young. *Different from controls, $P < 0.05$.

Effect of analgesics on thermal latencies

Whatever the age-group considered, morphine induced a dose-dependent ($F(4, 99) = 9.5$; $P = 0.0001$) increase in thermal latencies (Figure 3). This effect was all the more marked as the rats were young ($F(2, 99) = 3.4$; $P = 0.0037$). The duration of the effect was longer in old animals (interaction age × time $F(8, 312) = 3.4$; $P = 0.0009$) (Figure 4 and 5B). No effect of clomipramine ($F(4, 104) = 1.1$; $P = 0.38$ NS) or aspirin ($F(4, 104) = 0.6$; $P = 0.64$ NS) was found on thermal latencies. Acetaminophen induced a dose dependent increase in thermal thresholds ($F(4, 98) = 10.0$; $P = 0.0001$); this effect was not age dependent (interaction age × dose $F(8, 98) = 0.8$; $P = 0.6$ NS).

Drug plasma concentrations

Morphine plasma concentrations after 10 mg kg^{-1} injections slightly decreased with age, but this drop was not significant ($F(2, 21) = 1.4$; $P = 0.2$ NS). No significant modifications were observed in morphine metabolite concentrations (M3G $F(2, 21) = 0.28$; $P = 0.9$ NS) and M6G $F(2.20) = 0.13$; $P = 0.9$ NS) between the different groups (Table 2). Plasma acetaminophen levels were not different between groups: the plasma concentrations were 67 ± 13 μg in the mature group, 85 ± 7 μg in the middle-aged group and 78 ± 13 μg in the old group ($F(2, 19) = 0.3$; $P = 0.7$ NS).

Discussion

Results obtained in this study confirm previous research (Jourdan *et al*., 2000) on the changes of nociceptive thresholds with ageing in the Lou/c/jall rat: a decrease of thresholds in the paw pressure test that corresponds to an increase of nociceptive mechanical sensitivity, and no changes in thermal latencies. Age differences were observed in the efficiency of the opioid agonist since a decrease in provided analgesia with equal doses of the drug was noted across ageing.

Compared to literature reports, thresholds obtained with the paw pressure test in mature adult male Lou/c rats are close to those obtained in common strains (Bardin *et al*., 1997). With the exception of our previous study (Jourdan *et al*., 2000), only one report, (Akune & Soliman, 1994), investigating the influence of age on mechanical thresholds, found that aged Fischer-344 rats were less sensitive to pain using the paw pressure test than younger rats. However this study was performed on only two age groups (3 and 24 months). The paucity of published data using mechanical tests complicates the interpretation of reported differences. In our study, no effect of age on tail withdrawal latency after a thermal stimulus was observed. This result is in line with the review by Gagliese & Melzack (2000) which suggests that there is no change in reflexive responses to nociceptive thermal stimulus, even though some studies show an increase (Hess *et al*., 1981) or a decrease (Crisp *et al*., 1994) in reaction latency with age. Methodological differences including strains, parameters, stimuli intensities and age of the animals may explain these discrepancies.

Results concerning the effect of age on opioid analgesia differ from one study to another: ageing is accompanied with

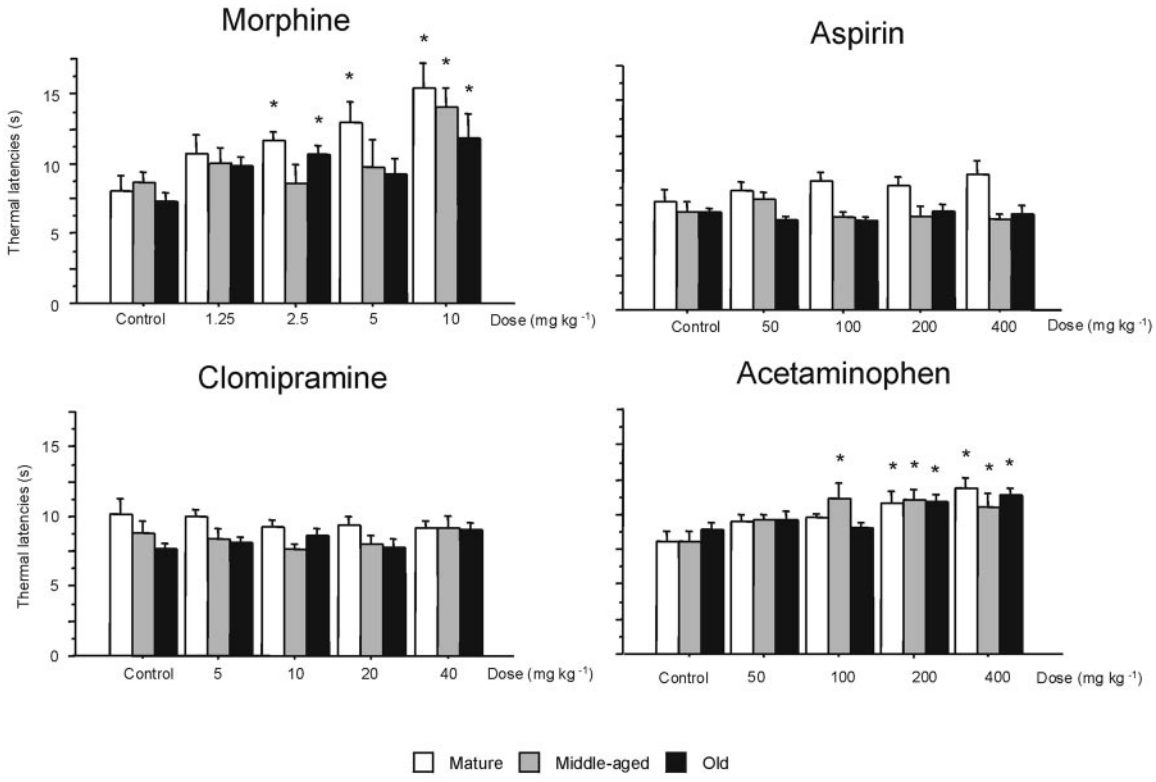

Figure 3 Influence of age on the effect of reference analgesics on the tail immersion test in three groups of different ages (4, 18 and 26 months). Values correspond to the AUC calculated by trapezoidal rules from t+30 to t+50 min after injection. Morphine 1.25, 2.5, 5, 10 mg kg^{-1} (sc) induced a dose and age-related increase in thresholds, acetaminophen 50, 100, 200, 400 mg kg^{-1} (po) induced a dose-related increase in thresholds, aspirin 50, 100, 200, 400 mg kg^{-1} (sc) and clomipramine 5, 10, 20, 40 mg kg^{-1} (sc) had no significant effect. *Different from controls, $P<0.05$.

either a reduction (Wallace *et al*., 1980; Chan & Lai, 1982; Kavaliers *et al*., 1983; Islam *et al*., 1993) or an increase (Saunders *et al*., 1974) in morphine effect. A cautious reading of the available data suggests however that advancing age may be associated with a decreased sensitivity to opioid agonists (Gagliese & Melzack, 2000). Various hypotheses, associated particularly with pharmacokinetic and pharmacodynamic factors, have been suggested to explain age-related differences.

From a pharmacokinetic point of view, the present study shows modifications in the effect of morphine without any differences in plasma levels at the time of maximum effect. Likewise, a study performed on 3–6 and 24 months old Wistar rats (Van Crugten *et al*., 1997) showed no differences in plasma morphine and metabolite concentration curves. This study also showed that plasma levels of the drug and its metabolites remained higher during a longer period in old rats than in young ones. This fact could explain the longer duration in the effect of morphine in the old group in our study.

On the other hand, some data suggest there may be pharmacodynamic changes with age. Indeed, a general decline in the opioid system with age was described (Amenta *et al*., 1991), with a decrease of opiate receptor in the CNS (Hess *et al*., 1981) and in the level of met-enkephalin in the cervical and thoracic segments of the spinal cord (Missale *et al*., 1983) throughout ageing. Nevertheless, the influence of these neurochemical modifications on pain sensitivity remains to be determined. Authors also suggested that this difference in the effect of the opioid agonists could be attributed to the degeneration of the endogenous pain-inhibition systems (Kramer & Bodnar, 1986; Crisp *et al*., 1994). It has been suggested that opioids exert their antinociceptive effects, at least partly, via descending inhibitory serotonergic fibres at spinal level (Basbaum & Fields, 1984), and the 5-HT system seems to be affected by ageing. With advancing age, the concentration of 5HT and the binding affinity and number of 5HT receptors decrease in several brain regions (Goicoechea *et al*., 1997) and in the spinal cord (Ko *et al*., 1997). In addition, it has been shown by electrophysiological methods that the descending inhibitory system acting on the dorsal spinal neuronal activity was depressed in old rats (Iwata *et al*., 1999).

Hence, in our study, observed age-related differences could be accounted for by a pharmacodynamic effect (modification in the reactivity of the endogenous opiate system after an exogenous stimulation of the mu receptors) mainly because no differences were observed in morphine plasma concentrations. This was also due to the fact that age differences differ with the behaviour considered. Indeed, a study performed in our laboratory on the same strain (Boghossian *et al*., 2001) showed that the anorexigenic effect of morphine increases with age.

Gagliese & Melzack (2000) suggested that age differences in morphine analgesia could be a bias due to differences in body temperature which alter tail flick latencies (Berge *et al*., 1988).

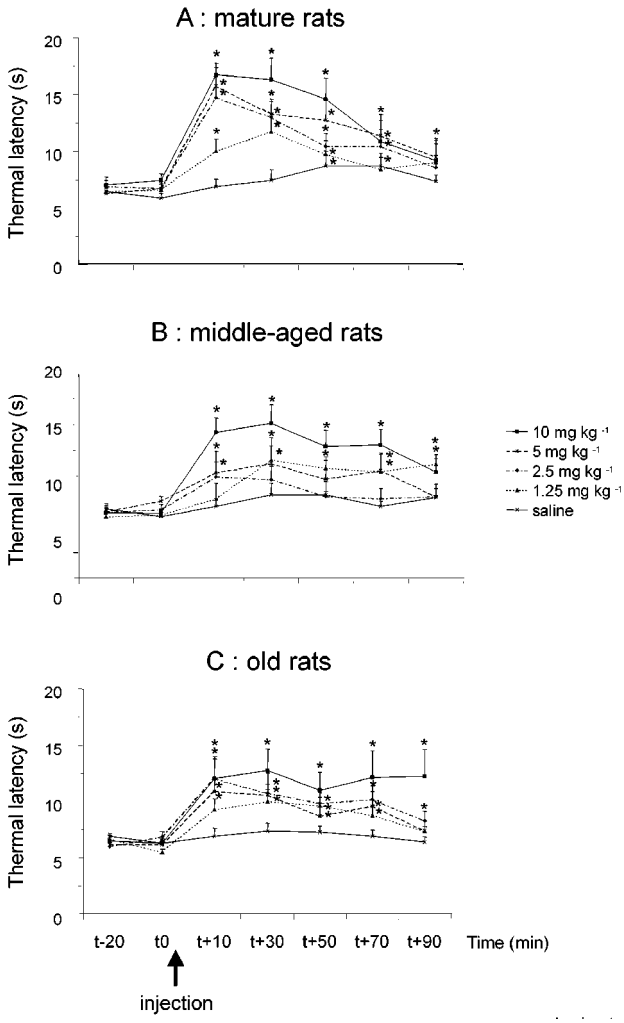

Figure 4 Analgesic effect of morphine (tail immersion) in three groups of rats of different age ((**a**) mature 4 months, (**b**) middle-aged 18 months and (**c**) old rats 26 months). For the three groups a dose-dependent effect of morphine was observed, but this effect was all the more marked as the animals were young. *Different from controls, $P<0.05$.

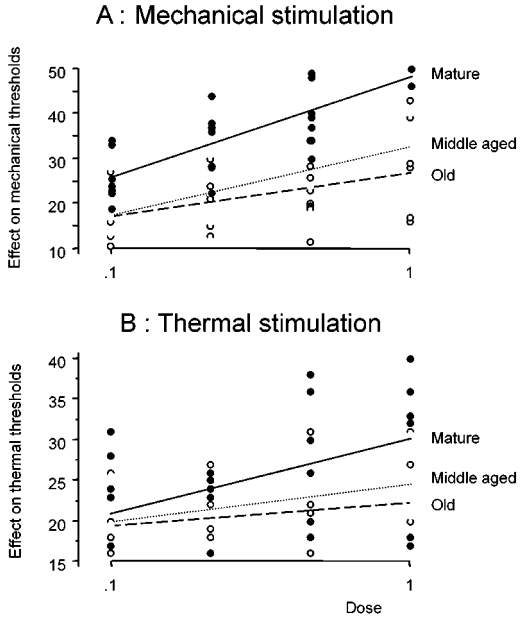

Figure 5 Mechanical thresholds (**a**) and thermal latencies (**b**) dose-response relationship after sc administration of morphine 1.25, 2.5, 5, 10 mg kg^{-1} (sc) in rats of three age groups (4, 18 and 26 months). Data are expressed as AUC calculated by trapezoidal rules from t+30 to t+50 min after injection. The slope of the curve was all the steeper as the rats were young. Mechanical test : mature ($y=23.2\pm24.9x$; $r2=0.703$), middle-age ($y=15.7\pm17.1x$; $r2=0.3$) and old rats ($y=15.9\pm10.9x$ $r2=0.207$). Thermal test : mature ($y=19.8\pm10.2x$; $r2=0.195$), middle-age ($y=19.5\pm5.1x$; $r2=0.044$) and old rats ($y=19.1\pm3.1x$ $r2=0.029$).

Table 2 Influence of age on the plasma levels: The plasma concentrations of morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) drugs have been determined at the time corresponding to the maximal effect (30 min after injection) after morphine (10 mg mg^{-1}) for 10 animals in each age group

	Morphine ($\mu g\ L^{-1}$)	*M3G* ($\mu g\ L^{-1}$)	*M6G* ($\mu g\ L^{-1}$)	*M3G/ Mor*	*M6G/ Mor*
Young rats	2492 ± 725	7207 ± 3213	18 ± 9	3.0	0.008
Mature rats	2101 ± 447	7138 ± 3520	16 ± 8	3.8	0.009
Old rats	2145 ± 267	7501 ± 3027	19 ± 10	3.6	0.009

The ratio metabolite/morphine are also indicated.

Our results show that this hypothesis could be rejected because the influence of age on morphine analgesia was found with thermal as well as with mechanical tests.

Nevertheless, the inconsistency of the influence of age on the effect of morphine in humans and in rats remains. Elderly patients achieve more effective pain relief than do young adult patients given equal doses of morphine (Kaiko, 1980; Moore *et al*., 1990). This difference may be due to differences between species in the metabolism of morphine. An important difference exists between humans and rats concerning the metabolism of morphine. In humans, morphine is strongly metabolised to M6G (Milne *et al*, 1996), but in rats the formation of M6G is negligible (Kuo *et al*., 1991). M6G is a potent analgesic (Abbot & Palmour, 1988) with opioid receptor subtype binding affinities similar to those of morphine (Chen *et al*., 1991). After systemic administration in rodents, it is more potent than morphine (Frances *et al*., 1992). The differences in the formation of M3G are less important, but this metabolite does not have significant analgesic properties (Pasternak *et al*., 1987). Differences between species may be due to differences in the pharmacokinetics of morphine and the increased sensitivity to morphine seen in elderly humans may be due to age-related elevations in plasma M6G. It could be suggested that if ageing is accompanied with a decrease in the pharmacodynamic sensibility of the opiate system, whatever the species considered, this decrease in humans is masked by the pharmacokinetic accumulation of M6G due to the deterioration of renal function.

The antinociceptive effect of the two NSAIDs (nonsteroidal anti-inflammatory drugs) differs. While the effect of aspirin was weak and only observed in the mechanical test, that of acetaminophen was marked in the two tests. This difference has been already observed (Piletta *et al*., 1991). It could be interpreted by the fact that the antinociceptive

effect of acetaminophen differs from that of the other NSAID in that it is essentially centrally-mediated (Alloui *et al*., 1996; Pelissier *et al*., 1996). We showed that there was no influence of age on the antinociceptive effect of the NSAID. To our knowledge, there are no published studies on this subject.

In our study acute clomipramine had no effect on pain behaviour. This result is not surprising as a single injection of antidepressant in normal rats does not generally induce any modification in nociceptive thresholds (Ardid *et al*., 2001). On the contrary, acute clomipramine is known to induce analgesia in chronic pain models, particularly models of neuropathy (Ardid & Guilbaud, 1992). Our hypothesis was that if the increase in mechanical thresholds in old rats was due to alterations in nervous physiology with age, perhaps close to phenomena observed in neuropathies, the effect of clomipramine could be more marked in old rats. Our findings however, like the trial carried out by Akune & Soliman (1994) with a SSRI, fluoxetine, showed a lack of impact of age on the effect of antidepressant drugs.

Conclusion

Results obtained in this study confirm previous research on the changes of nociceptive thresholds with ageing in the Lou/c rat: a decrease of thresholds that corresponds to an increase of nociceptive mechanical sensitivity. The effect of the injection of morphine, acetaminophen, aspirin and clomipramine in mature animals is rather similar to the one obtained in other strains. The influence of age appears in the effect of morphine with a lessening of the analgesic effect with ageing. This influence of age, as reported in the literature, is probably linked mainly to pharmacodynamic rather than pharmacokinetic changes. The physiological basis of these differences remains unknown and further studies are needed to achieve a better understanding of this interesting observation.

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