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Differential startle magnitude in mice selected for high and low swim analgesia is not related to difference in nociception

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The acoustic startle response (ASR) elicited by 110 dB 10-ms pulses was studied in relation to pain sensitivity in mouse lines selectively bred for high (HA) and for low (LA) swim analgesia. The magnitudes of ASR, similarly as hot-plate latencies, differed between the lines in the rank order HA > unselected controls (C) > LA. The animals' nociception did not change after the ASR session consisting of a sequence of 20 acoustic stimuli. Morphine hydrochloride (5 and 10 mg/kg IP) increased hot-plate latencies in the order of HA > C > LA, and was not effective on ASR magnitude in HA as well as in C mice. In the LA line, 10 mg/kg of morphine slightly attenuated ASR, but caused only a little analgesia. We conclude that (1) the difference in ASR between the selected lines is inversely correlated with the difference in pain sensitivity; (2) the magnitude of ASR is not altered by morphine analgesia; (3) the procedure of ASR using brief acoustic pulses is not stressful enough to elicit a form of stress analgesia. The lack of a direct relationship between the readiness to startle and pain sensation may be beneficial for an animal's survival in dangerous situations. It is beneficial when the startle to a warning signal precedes defensive behaviours and it often must be effectuated in a state of decreased nociception.

Keywords: acoustic startle, analgesia, nociception, selected mouse lines

INTRODUCTION

The acoustic startle response (ASR) has been widely used for the study of neural mechanisms which process sensory information (Błaszczyk and Tajchert 1997, Błaszczyk 2003), learning, memory, and the control of emotional behavior (Błaszczyk et al. 1999a, b, Błaszczyk and Turlejski 2005). Being a relatively simple oligosynaptic reflex, ASR is subject to modulatory influences of various origins which decrease or augment its magnitude (Koch 1999, Błaszczyk et al. 2010). Such phenomena as potentiation of ASR by a conditioned fear stimulus (Brown et al. 1951, Davis 1986, Davis et al. 1993), habituation, sensitization (Davis 1989, 1974) and inhibition by a nonstartling prepulse (Ison 1978) are believed to reflect the plasticity of the sensory systems involved in the animal's adequate responding to environmental cues. Also, the basal magnitude of ASR tested in the absence of the above intervening factors is not constant. Instead it depends on an animal's early stressful experience (Błaszczyk et al. 1999a), is subject to circadian rhythmicity (Chabot and Taylor 1992) and also differs between strains of mice or rats (Glowa and Hansen 1994, Markou et al. 1994, Bullock et al. 1997, Paylor and Crawley 1997, Kline et al. 1998), which points to its dependence on the genetic makeup of animals.

Recently we reported that the magnitude of the ASR differs between mouse lines selectively bred in our laboratory for divergent magnitudes of analgesia produced by a 3-min swim in 20°C water (Błaszczyk et al. 2000, 2010). Apart from the magnitude of swim stress-induced analgesia (SSIA) (Panocka et al. 1986a), these mouse lines differ in the magnitude of analgesia elicited by electric footshock (Marek et al. 1987), and also in basal pain sensitivity (Panocka et al. 1986a, Sadowski et al. 1996). Unlike what might be expected, the between-line difference in ASR opposes the difference in nociception. That is, the high analgesia (HA) line, exhibits a higher magnitude of SSIA and lower base-

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line pain sensitivity in comparison to the low analgesia (LA) line, which shows a higher magnitude of ASR (Błaszczyk et al. 2000, 2010).

An important feature of the HA/LA mouse lines is the differential expression of opioid-mediated phenomena. Thus, the high SSIA and footshock analgesia in the HA line is partially reversed by naloxone or naltrexone, whereas the low analgesia in the LA line is insensitive to these prototypic antagonists of opioid receptors (Panocka et al. 1986b, Marek et al. 1987, Sadowski et al. 1996). Secondly, HA mice, compared to the LA line, display a fourfold lower ED_{50} of morphine analgesia, as assessed using the tail-flick test (Lutfy et al. 1994). The between-line difference in opiate analgesia is even twenty times greater with respect to specific mu and delta receptor agonists administered intracerebroventricularly (Kest et al. 1999). Thirdly, HA mice manifest a higher density of brain opioid mu and delta receptors, particularly in the nucleus raphe magnus which is a pain inhibitory center (Mogil et al. 1994, Kest et al. 1999). Finally, high SSIA in HA mice is augmented and its duration is prolonged after the administration of D-amino acids, assumed to exert an antienkephalinase action (Panocka and Sadowski 1990).

The inverse relationship between ASR magnitude and pain sensitivity rules out the possibility that the magnitude of ASR might be directly modulated by a pain-related mechanism. Yet, in our previous study the administration of naltrexone, an opioid receptor antagonist sensitized the ASR in HA mice (Błaszczyk et al. 2000). The results of that study are not consistent with the data showing no effect of naloxone on basal ASR magnitude in rats (Davis 1979). We hypothesized that the expression of ASR in HA mice is possibly attenuated by the upregulated opioid systems. This means that facilitation of ASR by naltrexone can be explained as being due to removal of this 'opioid tone'. Not only SSIA, but also the elevated basal hot-plate thresholds in the HA line were found to be lowered by naltrexone (Sadowski et al. 1996). Accordingly, the increase in ASR magnitude seen in HA mice after a pharmacological blockade of opioid receptors might be attributed, alternatively, to an increased nociceptive value of the startle stimuli.

Based on human judgement, intense acoustic stimuli used to elicit ASR, 110 dB or louder, might be perceived by experimental animals as stressful or even painful. Thus, the repetitive presentation of a potentially aversive sound during a routine ASR session can bear an important 'psychological' load. This possibility seems justified by the data showing that a loud noise, similar to common environmental stressors, activates the hypothalamo-pituitary-adrenocortical axis. This activation causes a release of such stress hormones as the corticotropin releasing hormone, the adrenocorticotropic hormone and corticosterone (Siegel et al. 1980). A loud noise can also produce a decrease in nociception, resembling the phenomenon of stress-induced analgesia (Szikszay et al. 1985). Although these neuroendocrine and analgesic effects are a consequence of prolonged acoustic stimulation lasting several minutes, increased levels of plasma corticosterone (Glowa et al. 1992) and a decrease in nociception (Cranney 1988) were also observed in rats exposed to a series of short acoustic pulses, as those used to elicit ASR.

In the present study we measured pain sensitivity of mice exposed to intense, but brief acoustic pulses eliciting a startle response. We were interested whether this procedure might produce analgesia at least in HA mice with augmented analgesic sensitivity to common environmental stressors. Also, making use of the differential sensitivity of the selected lines to morphine, we compared the magnitudes of ASR against differential magnitudes of morphine analgesia.

METHODS

Animals

Three-month-old Swiss-Webster mice were selectively bred for divergent magnitudes of swim stress-induced analgesia (SSIA). As described in detail elsewhere (Panocka et al. 1986a), mice of an outbred parental stock were given a 3-min swim in 20ºC water, and 2 min afterwards were tested for pain sensitivity on a hot plate (56ºC). Pairs of males and females both displaying longer than 50 s or shorter than 10 s post-swim hot-plate latencies were mated to initiate a high analgesia (HA) and a low analgesia (LA) line, respectively. The same procedure was repeated in consecutive offspring generations, but only long-latency subjects in the HA line, and only short-latency subjects in the LA line were mated. Together with the selected lines, a control (C) unselected line was developed by mating mice at random.

Thirty-six mice of each line and sex, all belonging to the 49th generation, were used in the present study. Their mean body mass ± SD was 38.9±3.3 g (males) and 34.4±3.0 g (females). The animals lived in socially

stable groups of same-sex littermates 4-6 to a cage at 12:12 light/dark photoperiod and ambient temperature of 21±1ºC. Murine chow and tap water were continuously available. All testing occurred in the light phase.

Procedures

Pain sensitivity was measured with the hot-plate method using a metallic plate heated with circulating water to 56ºC. The mouse was confined to a 15-cm wide area in a transparent box to be carefully observed for the latency of a characteristic hind paw flick or lick response; whichever occurred first. The mice were then weighed to the nearest 0.1 g and injected intraperitoneally with 5 or 10 mg/kg of morphine hydrochloride (Polfa, Poland) in 10 ml/kg of saline. Controls obtained the same volume of saline.

Twenty-five minutes after the injection, the mouse was placed in a 140×85×90 mm plastic cage closed with an aluminum grid. Four such cages were simultaneously positioned in a sound-attenuation chamber (Coulbourn Instruments), each on a separate mobile force-sensitive platform. The chamber was illuminated with a 5 W bulb, and the ventilation system produced a continuous background noise that did not exceed 44 dB.

After a 5-min adaptation period the mice were exposed to a sequence of 20 acoustic stimuli delivered at pseudorandom intervals in the range of 5-60 s. Each stimulus was 10-ms wide-band 110 dB SPL pulse with 2 ms rise time. The electric signal produced by the vertical reactive force exerted on the platform by the animal's startle was amplified, rectified, passed through a 40 Hz low-band filter, and digitized at a frequency of 400 Hz. The signal was sampled for 0.2 s with Coulbourn software starting from the onset of the acoustic stimulus. The data were stored for off-line analysis of the peak amplitude of the ASR. Before the experiments the electronic system was calibrated against the 50-gram weight for each platform separately.

Immediately after termination of the ASR session, the mice were tested again on the hot plate. The saline-injected mice were examined prior to those receiving morphine. This order was used so as to conform to the possible occurrence of short-lasting post-ASR analgesia that might be otherwise missed. Whenever no response was emitted within 60 s, the animal was removed from the plate.

Statistics

Statistica 5.0 PL software was used for all statistics. To evaluate the effect of ASR sessions on animal pain sensitivity, post- and pre-ASR hot-plate latencies were compared with a three-way analysis of variance (ANOVA). The hot-plate tests were taken as a repeated measure, and the line and sex as independent measures. The magnitude of morphine analgesia during ASR testing was evaluated by comparing post-ASR hot-plate latencies in morphine- and saline-injected mice with a three-way ANOVA.

ASR amplitudes were first analyzed with a four-way multivariate analysis of variance (MANOVA) taking line, sex and treatment as independent measures, and ASR tests as a repeated measure. Next, appropriate models of analysis of covariance (ANCOVA) were used to compare the startle force in saline- and morphine-injected mice between the lines or within each line. Mean startle magnitude computed from the twenty ASR tests in each session was taken as a dependent variable in these analyses. Animal body mass was included into the analysis as a covariate because of its impact on the startle magnitude. Detailed comparisons, where appropriate, were made with planned contrasts or with the Duncan test.

Bioethics

The protocols of the experiments and of the selection procedure were approved by the Ethics Commission of the Institute for Genetics and Animal Breeding, Polish Academy of Sciences. The rules of intramural humane care of laboratory animals were strictly observed according to the Polish law.

RESULTS

As shown in Fig. 1, hot-plate latencies were longer in the HA than in other lines, $F_{2,67}$=32.39, p<0.0001, two-way ANOVA, and remained unaltered after an ASR session, $F_{1,67}$=1.42, p=0.24. The effect of sex was not significant, $F_{1,67}$=0.51, p=0.48.

Results of the three-way ANOVA showed that the morphine produced a dose-dependent increase in hot-plate latencies, $F_{2,198}$=25.05, p<0.05. This effect was much greater in the HA line than in other lines, $F_{2,198}$=61.34, and $F_{4,198}$=13.60, line x dose interaction (Fig. 2, bottom). A significant effect of sex,

$F_{1,198}$=8.61, p<0.01, together with significant line x sex interaction, $F_{2,198}$=14.20, p<0.0001 reflected higher morphine analgesia in female than in male mice of the HA line.

The startle force did not significantly vary between the twenty individual tests within the ASR sessions, $F_{19,3768}$=1.01, p=0.45. Mean startle magnitudes, averaged for each session, differed between the lines, $F_{1,66}$=4.03, p<0.025 (two-way ANCOVA of saline-injected subgroups), and were significantly higher in HA than in LA mice (p<0.025, Duncan) without regard to sex $F_{1,66}$=1.68, p=0.20 (Fig. 2, top).

Morphine was ineffective on ASR magnitudes in HA, $F_{2,68}$=0.43, p=0.65, and in C mice, $F_{2,65}$=0.36, p=0.70, but attenuated the ASR in LA mice, $F_{2,68}$=3.20, p<0.05, separate one-way ANCOVAs. Post-hoc comparison confirmed this attenuation only at the dose of 10 mg/kg (p<0.02, Duncan). Animal body mass as a covariate did not reach statistical significance in all the analyses.

DISCUSSION

A sequence of 20 intense brief tones which elicited a vigorous startle failed to modify nociceptive thresholds in the selected mice. This observation is particularly important with respect to the HA line, known to respond with marked analgesia even to a mild stress, such as a 3-min swimming in 25ºC water (Sadowski et al. 1996). It is then justified to conclude that acoustic startle stimuli, at least at parameters used in the present study, are not stressful enough to elicit an analogue of stress-induced analgesia in mice. Our results also indicate an inverse relationship between nociceptive sensitivity and the magnitude of acoustic startle in our mouse lines, since as in pre- and post-ASR hot-plate latencies, the ASR magnitudes differed between the mouse lines in the order of HA > C > LA.

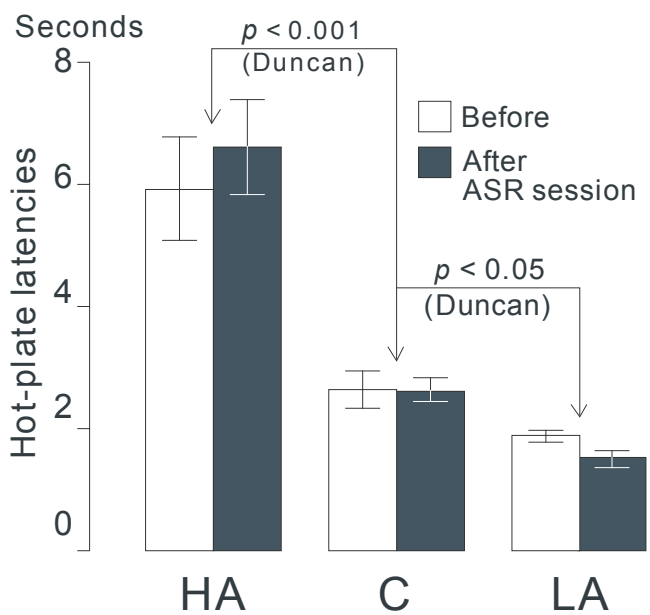

Fig. 1. Mean latencies ± SE of hind-paw flicking or licking on a hot plate (56°C) in mice of the high analgesia (HA), low analgesia (LA) and unselected control (C) lines, assessed 30 min before and immediately after testing the acoustic startle response.

It is known that not the duration, but a steep onset of the acoustic stimulus is important for the elicitation of ASR (Pilz et al. 1987). Parametric studies with varying pulse durations demonstrated that stimuli which are even shorter than 2 ms are already able to elicit an ASR in the rat, and the magnitude of the response attains asymptote at about 8-ms width of the pulse (Marsh et al. 1973). Based on the concept of dual organization of the auditory pathways (Gersuni 1965), the startle-eliciting pulses are thought to activate a short time-constant system (Ebert and Koch 1992). This system responds to an abrupt initial increase of intensity, and not to the ongoing action of the tone (Dykman and Ison 1979).

Electrographic recordings show that excitation produced by a startle stimulus already attains after 4 ms or less, the caudal pontine reticular nucleus regarded as a sensorimotor interface in the ASR circuitry (Lingelhöhl and Friauf 1992, 1994). It appears that the middle ear reflex, due to 5-ms or longer latency (Pilz et al. 1997), cannot efficiently protect the ear against intense though brief startle stimuli. But the lack of such protection is perhaps not deleterious, because the exposure of mice to a sequence of twenty 10-ms ASR pulses, as inferred from the absence of analgesia, did not appear stressful. On the other hand, ASR stimuli of longer duration than necessary to elicit the ASR, and adequate to invade the long time-constant auditory system, may become aversive and produce an analgesic or an endocrine stress response. Accordingly, we assume that because of using 10-ms instead of longer acoustic pulses we did not replicate, even in the stress-sensitive HA line, the conspicuous analgesia induced in rats by a sequence of ten 50-ms startle-eliciting stimuli (Cranney 1988). This reasoning is justified by the

fact that 115 dB 30-ms long acoustic stimuli were found to elevate plasma corticosterone levels in Fischer (F344/N), and albeit to a lesser extent, also in outbred Harlan Sprague-Dawley rats (Glowa et al. 1992). Another possibility is that 70 dB background noise used in (Cranney 1988), but not by us, might have added to the stressful conditions of that study.

Our observation that HA mice displayed high magnitude ASR together with pronounced morphine analgesia is not only consistent with the report showing no effect of morphine on basal ASR magnitude in rats (Davis 1979). Our observation also argues for no positive correlation between animal pain sensitivity and the readiness to startle. However, the little, but significant suppression of ASR by 10 mg/kg of morphine in LA mice seems to contradict the above claim. Morphine was found to markedly decrease the startle response to electric tail shock in rats, but to a lesser degree and only at high doses also to an acoustic stimulus. This difference was interpreted as reflecting a primary action of morphine on the aversive, and not on the sensory component of startle-eliciting stimuli (Warren and Ison 1982). Since LA mice are more sensitive to pain than HA mice, it would be reasonable to assume that they perceive intense acoustic pulses as aversive. This is why it would also be reasonable to assume that the aversiveness of this sensation might be reduced by morphine.

There are, however, two objections against this interpretation. First, morphine had only a marginal effect on nociception in LA mice, so that hot-plate latencies in morphine-injected LA mice did not even equalize with the latencies seen in saline-injected HA mice. Secondly, in contrast to LA mice, HA mice exhibit greater emotionality in various behavioral tests. In particular, they are less active in an open field (Błaszczyk et al. 2000). When exposed to forced swimming at certain temporal/temperature parameters, they display a depressive-like behavior sensitive to antidepressant treatment (Panocka et al. 2001). In addition to these observations, we recently found that a conditioned fear stimulus potentiates an ASR in the HA, and not in the LA line. In view of these observations, morphine would be expected to reduce ASR in the emotionally sensitive HA, rather than in the less fearful or anxious LA mice.

The above discrepancy can be explained based on the assumption that ASR in the HA line is tonically suppressed by an upregulated endogenous opioid system, whereas this modulatory mechanism does not function in the LA line. Therefore, even a large dose of morphine that reduced ASR in LA mice, could not further augment the opioid inhibition of the ASR in HA mice. This interpretation is consistent with the earlier found facilitation of ASR in HA mice by naltrexone, supposed to attenuate the enhanced 'opioid tone' in this line (Błaszczyk et al. 2000, Sacharczuk et al. 2009).

It is important to emphasize, that neither morphine

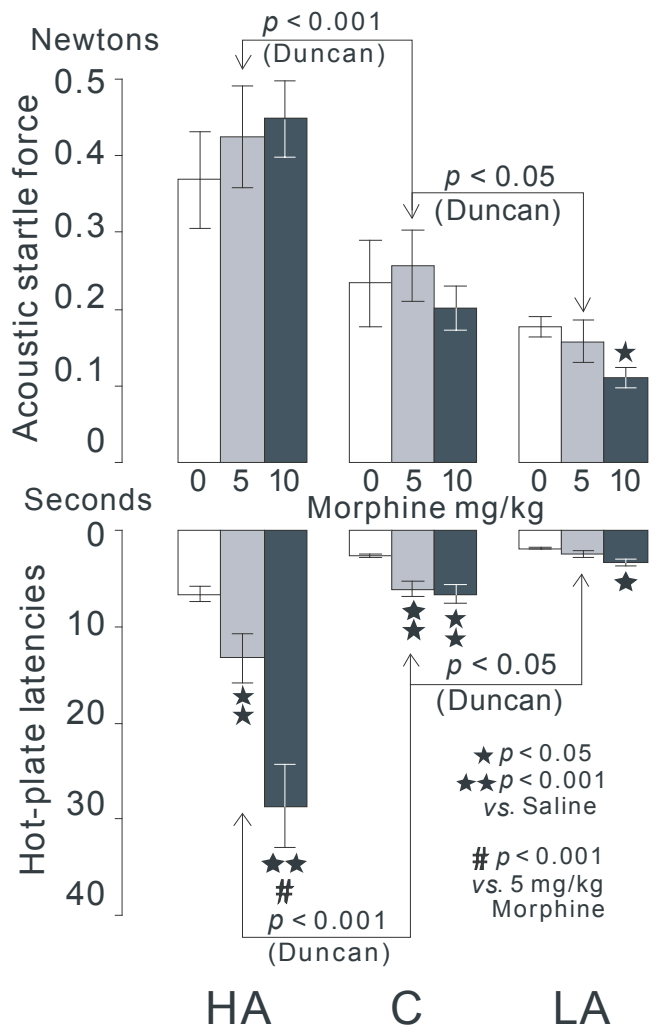

Fig. 2. Mean magnitude (± SE) of the acoustic startle response elicited by a 110 dB acoustic stimulus (top), and mean hot-plate latencies ± SE assessed after the ASR session. Morphine hydrochloride (5 or 10 mg/kg) or saline (0 mg of morphine) was injected 30 min prior to ASR testing. HA – high analgesia, LA – low analgesia, C – unselected control line.

in the present nor naltrexone in the previous study (Błaszczyk et al. 2000) modified ASR magnitude in the unselected control (C) mice. One might infer that insensitivity of the startle to pharmacological modulation of opiate receptors in either direction is the feature of mouse populations with moderate expression of endogenous opioid systems activity. However, opposite to the selected lines, the randomly mated C mice often vary across generations with respect to analgesic or other phenomena. Thus, the ASR magnitude in C mice, previously found to be close to that of HA mice (Błaszczyk et al. 2000) in the present study assumed an intermediate value between the two selected lines, and was closer to the LA line. The genetic variability of C mice can also account for their present lower morphine analgesia as compared to previous generations (Panocka et al. 1986b, Sadowski et al. 1996, Błaszczyk et al. 2010). Therefore, any extrapolation of the results obtained from the unselected mouse line over heterozygotic populations of this species in general should be undertaken with caution.

In conclusion, the procedure of eliciting ASR, at least with short pulse duration, is not stressful enough to induce analgesia in mice. Also, the magnitude of ASR does not appear to depend on the pain sensitivity of the animal. This feature of ASR may be relevant for better understanding the biological role of the startle in the natural environment where it is elicited by sudden warning signals, and often precedes freezing or flight. Experimental forms of these defense behaviors were found to be accompanied by transient loss of pain sensation – a phenomenon termed defeat analgesia (Miczek et al. 1986). Therefore, the ability to perform an efficient startle against lessened nociception may be beneficial for the animal's survival in dangerous circumstances. These circumstances include a predator's attack or intraspecies competition.

There were several observations suggesting that the magnitude of the ASR is positively correlated with the level of anxiety (Koch 1999, Davis and File 1984). On the other hand the relationships between a level of fear or anxiety and nociception have still not been well recognized. There were several clinical and experimental observations showing that fear and anxiety can either increase (Cornwall and Donderi 1988, Jones and Zachariae 2002) or decrease pain reactivity (Bolles and Fanselow 1980, Gameiro et al. 2006). Obviously, the type of stressor, its intensity and duration affect the potency of the analgesic or hyperalgesic effect, as well as the neuronal mechanisms responsible for them (Werka 1997, for review see Herman and Cullinan 1997). Considering that the level of fear or anxiety in the HA animals was higher than in the C and LA mice it might be supposed that the magnitude of the startle reflex is a more efficient index of anxiety level than the level of pain sensitivity in the animal.

CONCLUSIONS

We conclude that (1) the difference in ASR between the selected lines is inversely correlated with the difference in pain sensitivity; (2) the magnitude of ASR is not altered by morphine analgesia; (3) the procedure of ASR using brief acoustic pulses is not stressful enough to elicit a form of stress analgesia. The lack of a direct relationship between the readiness to startle and pain sensation may be beneficial for an animal's survival in dangerous situations. It is beneficial when the startle to a warning signal precedes defensive behaviours and it often must be effectuated in a state of decreased nociception.

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