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REVIEW

THE ATTACKED MOUSE: NEUROCHEMICAL, PHYSIOLOGICAL, AND BEHAVIORAL CORRELATES

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RESUMO

O presente trabalho é uma revisão dos dados neuroquímicos fisiológicos e comportamentos mencionados do camundongo agredido. São apresentadas as possíveis relações entre os sistemas de dor, memória e defesa, com especial ênfase no papel dos peptídeos opióides endógenos (EOPs). Nas estruturas do sistema defensivo do cérebro de camundongos agredidos, tem sido encontrado uma diminuição da imunorreatividade semelhante a β - endorfina e modificações nas características de ligações dos opiáceos e benzodiazepínicos. EOPs mediam o aumento da síntese de dopamina no periaqueduto cinzento e cortex frontal no conflito social induzido. A analgesia no conflito social em camundongos agredidos está sob o controle de mecanismos opióide

(**e.g.**, benzodizepina, glutamato) e foi modificado por experiência (**e.g.**, aumento do tempo de reação analgésica, tolerância). EOPs e mecanismos inibidores da dor participam na organização da defesa comportamental, comportamento recuperativo e a memorização da experiência de ataque. Conclui-se que a situação de conflito social entre os murinos, de relevante significado biológico, permite a investigação de mecanismos competidores em vários níveis e constituem uma alternativa aos modelos animais existentes de aversão e defesa.

UNITERMOS: Opióides, conflito social, analgesia, memória, defesa, camundongo.

ABSTRACT

The present work reviews neurochemical, physiological and behavioral data recorded from the attacked mouse. The possible relationships between systems of pain, memory and defense are presented, with special emphasis on the role of endogenous opioid peptides (EOPs). In recipients of attack, decreased β - endorphin-like immunoreativity and changes in opiate and benzodiazepine binding characteristics have been found in structures of the brain defensive system. EOPs mediated the social conflict-induced increase of dopamine synthesis in the periaqueductal grey and frontal cortex. Social conflict analgesia in attacked mice was under the control of central opioid and nonopioid (**e.g.**, benzodiazepine, glutamate) mechanisms, and was modified by experience (e.g., long-term analgesic reaction; tolerance). EOPs and pain-inhibitory mechanisms participated in the organization of behavioral defense, recuperative behavior and the memorization of attack experience. It is concluded that the biologically-meaningful situation of murine social conflict allows investigation of coping mechanisms at various levels and constitutes and alternative to existing animal models of aversion and defense.

KEY WORDS: Opioids, social conflict, analgesia, memory, defense, mice.

INTRODUCTION

In nature, animals are frequently positioned into situations in which they have to defend themselves against aversive events. Typically, such incidences of emergency comprise predator-prey interactions and intraspecific social

conflicts. Successful coping within this framework provides an evolutionary benefit and guarantees the survival of the species. To that end the existence of a defensive system that is triggered by the presence of painful as well as nonpainful danger stimuli is an implicit presupposition. The verification and analysis of a brain defensive system has been made possible by ethoexperimental, operant behavioral and neuropharmacological approaches (for reviews see Adams, 1979; Blanchard and Blanchard, 1988; Graeff, 1981; 1988). For instance, with operant behavioral techniques is has been shown that enhancement of GABAergic, serotonergic and opioid peptidergic neurotransmission in the periaqueductal grey (PAG), an important structure of the brain defensive system, causes antiaversive effects (Graeff, 1988). Antinociception evoked by electrical (Reynolds, 1969) or pharmacological (Jacquet, 1988; Jacquet and Lajtha, 1974) stimulation of the PAG may also be regarded as a component of antiaversion.

Researchers have recently begun to explore the potential significance of intrinsic analgesic systems in the framework of predator-prey interaction (Bolles and Fanselow, 1980; Fanselow, 1986), and during intraspecific social conflict in rodents, mainly in mice (for reviews see Rodgers and Randall, 1987a,b; 1988c). Typically of these latter experimental settings is that of a confrontation between an aggressive resident animal and an intruder. By definition, such a paradigm creates a biased situation in which group-housed nonoggressive intruders are invariably attacked by residents that have been rendered aggressive by a brief period of social isolation, or which represent the dominant individual of a small group of animals. The ensuing agonistic interaction which consists of a well-defined series of acts and postures (Grant and Mackintosh, 1963) is then recorded during the aggressive confrontation, with a preferential focus on the intruder's defensive repertoire. This consists of escape-related behaviors, submissive/defensive postures and

immobility. Following exposure to attack and nociceptive stimulation (bites), nociceptive thresholds are assessed in the intruder by classical pain tests, such as the tail-flick or hot plate assay or the writhing test. The paradigm further allows the study of postconflict recuperative behaviors (**e.g.**, grooming) and of long-term physiological and behavioral adaptations, involving learning and memory mechanisms. Finally, neurochemical changes in the brains of attacked animals may be analyzed.

The present study reviews behavioral, physiological and neurochemical data obtained from the attacked mouse, with special emphasis on the role of endogenous opioid peptides (EOPs).

NEUROCHEMICAL CHANGES IN THE ATTACKED MOUSE

Involvement of EOPs during social conflict has been indicated by various studies. A forty percent reduction of whole brain β-endorphin-like immunoreactivity has been reported in $B6AF_1$ mice after exposure to hundred attack bites by a resident CFW mouse (Miczek and Thompson, 1984). Likewise, levels of β-endorphin were decreased in pituitary (by 27%) and the PAG (by 23%) of C57BL/6 and DBA/2 mice that received fifty bites by an aggressive opponent (Kölling **et al.**, 1988), while exposure of DBA/2 mice to seven attack bites did not, or only to a very moderate degree, decrease β-endorphin levels in the PAG and pituitary, respectively (Kölling et al., 1989). The changes in β-endorphin-like immunoreactivity were interpreted in terms of an increased utilization, **i.e.**, release and subsequent degradation, of brain and pituitary β-endorphin in attacked mice. Opiate binding studies in the medulla-pons region revealed a significant reduction of in vivo [^{3}H] diprenorphine binding in mice subjected to hundred attack bites (Miczek **et al.**, 1986). It may be assumed that this decrement reflects exclusion of the ligand for the opioid receptor by attack-induced release of EOPs. No effect of in

vitro whole brain [^{3}H] etorphine binding was observed in mice that had been bitten thirty times (Siegfried **et al.**, 1989).

Analysis of nonopioid mechanisms in attacked and defeated mice has shown changes in hormonal, monoamine and benzodiazepine systems (for reviews of the older literature see Brain, 1975; Leshner, 1981). Increased in vivo [^{3}H] Ro 15-1788 benzodiazepine binding in cerebral cortex, cerebellum and hypothalamus has been found in defeated mice (Miller **et al.**, 1987). This effect was decreased by lorazepam, a benzodiazepine agonist, but not by Ro 15-1788 or by naloxone. The stress-induced increase in benzodiazepine binding was reduced by adrenalectomy and was restored by corticosterone replacement (Miller **et al.**, 1987). In regard to monoamines, the dopamine metabolites DOPAC and HVA were elevated in the frontal cortex twenty minutes after an attack stress of thirty bites in C57BL/6 and DBA/2 mice (Ornstein **et al.**, 1988). The levels of HVA remained elevated in DBA/2 but not in C57BL/6 mice two hours after the attack stress, pointing to a strain-specific recovery from defeat effects in the frontal cortex. Interestingly, the elevated levels of dopamine, but not those of its metabolites, in the frontal cortex and the PAG of attacked DBA/2 mice were prevented by the opiate antagonist naltrexone (Malnoe **et al.**, 1989), suggesting that EOPs mediated the social conflict-induced increase of dopamine synthesis in these brain structures.

PHYSIOLOGICAL CHANGES IN THE ATTACKED MOUSE: SOCIAL CONFLICT ANALGESIA

Opioid and nonopioid mechanism

In 1982, Miczek and coworkers described for the first time an opioid-mediated antinociception in defeated mice. Since then, the phenomenon of social conflict analgesia has been confirmed by a number of research groups (Rodgers and Hendrie, 1983; Siegfried **et al.**, 1984a; Teskey **et al.**, 1984). Two

qualitatively different profiles of endogenous antinociception have been proposed, depending on whether the intruder was exposed to a mild (5-10 attack bites) or a prolonged (30-100 attack bites) social stress (for review see Rodgers and Randall, 1988c). Involvement of opioid mechanism has mainly been shown after enduring attack, in that this long-lasting (up to 60 min) form of analgesia (high intensity analgesia), was reduced or prevented by the opiate antagonists, naloxone, naltrexone and β-chlornaltrexamine (Miczek **et al.**, 1982; Rodgers and Hendrie, 1983; Rodgers and Randall, 1985; Siegfried and Frischknecht, 1989; Siegfried **et al.**, 1987c; Teskey **et al.**, 1984). Similar antagonism was reported for two putative endogenous opioid antagonists, MIF-1 and FMRF amide (Kavaliers and Hirst, 1985; Teskey and Kavaliers, 1985), while ICI-154, 129, a delta receptor antagonist was ineffective (Teskey and Kavaliers, 1988). Support for a central mediation comes from studies that prevented social conflict analgesia by prior injection of naloxone into the PAG (Miczek **et al.**, 1985; Siegfrid and Nunes de Souza, 1989). In addition, increased nociceptive thresholds after attack have been related to changes in PAG β-endorphin levels, although the strain-dependent difference in the intensity of social conflict analgesia was not linked to the decrease of β-endorphin-like immunoreactivity (Külling **et al.**, 1988). After opioid receptor alkylation by the long-acting antagonist β-chlornaltrexamine (Frischknecht **et al.**, 1983), the blockade of social conflict analgesia was associated with a reduced [^{3}H] etorphine binding to brain homogenates (Lazega **et al.**, 1988). The failure to modify this type of analgesia by various treatments that enhance or block the release of pituitary β-endorphin or the release of enkephalins from the adrenal medulla (Thompson **et al.**, 1988) support a central mediational view. Neverthel less, it should be mentioned that the increased tail-flick latencies observed after increasing number of attack bites (30, 60, 90 bites) were paralleled by increasing plasma corticosterone levels (Thompson **et al.**, 1988) and that α-THDOC, a naturally occurring metabolite of deoxycorticosterone, dose-dependently

attenuated or increased defeat-induced analgesia (Kavaliers, 1988a).

In regard to antinociception elicited after a mild attack stress (low intensity analgesia) the role of nonopioid mechanisms has been emphasized. This view is based on experiments in which naloxone (Rodgers and Bandall, 1986a; Siegfried et al., 1987b) and naltrexone (Siegfried and Frischknecht, 1989) failed to antagonize the short lasting (less than 10 min) analgesia, and on the fact that repeatedly attacked (an average of 6 attack bites per day) animals failed to display cross-tolerance to and from morphine (Rodgers and Randall, 1986a), as it has been reported for animals repeatedly exposed to prolonged attack (Miczek et al., 1982; Rodgers and Randall, 1985). As possible candidates for the nonopioid analgesia, evoked by a mild attack stress, benzodiazepine as well as serotonin receptor-mediated mechanisms have been postulated. Selective neuronal and non-neuronal benzodiazepine recognition site ligands, the competitive benzodiazepine antagonits Ro 15-1788 and Ro 15-3505, and the agonist diazepam prevented this low intensity analgesia (Rodgers and Randall, 1987d; 1988a; 1988b), while these compounds did not affect the high intensity analgesia observed after prolonged attack (Rodgers and Randall, 1987c). Concerning serotonergic mechanisms, the $5HT_{1A}$ receptor agonist, 8-OH-DPAT, while devoid of intrinsic activity, blocked the analgesic consequences of a mild social conflict (Rodgers and Shepherd, 1989), and tryptophan-enriched (4%) diet enhanced conflict analgesia in C57BL/6 but not in DBA/2 mice (Siegfried and Ornstein, unpublished results).

Despite the accentuation on these nonopioid mechanism, it should be mentioned that the long-acting opiate antagonist β-chlornaltrexamine was able to prevent the analgesic response recorded after a mild attack stress (Frischknecht and Sieffried, 1988a; Siegfried et al., 1987b), and that high individual baseline β-endorphin levels in the PAG may be linked to the short-lasting analgesia (Kölling et al., 1989). On the

other hand, it seems very likely that after prolonged attack, social conflict analgesia is not exclusively mediated by endogenous opioids. Only partial opiate antagonism has been found when analgesia was assessed one minute after stress, pointing to a nonopioid component, while antagonism was complete, when the ten minutes values were compared (Siegfried **et al.**, 1987c, experiment 2; Frischknecht and Siegfried, 1988a). Thirty attack bite-induced analgesia was prevented by blockade of either opioid or nonopioid. N-methyl-aspartic-acid (NMDA) receptor sites within the PAG, with the competitive NMDA antagonist AP-7 being more potent than naloxone (Siegfrid and Nunes de Souza, 1989). Finally, peripheral injection of the calcium channel agonist, BAY K 8644, antagonized antinociception in defeated mice (Kavaliers, 1987).

It should be mentioned that the degree of analgesia induced by social conflict not only depends on the intensity of the attack but also on the mouse genotype used. Interestingly, the magnitude of social conflict analgesia correlates well with the sensitivity of different mouse strains to the analgesic affects of morphine. DBA/2 and B6AF$_1$ mice show potent analgesic reactions to attack and morphine, whilst C57BL/6 mice - which preferentially display a 'running fit' response to morphine - as well as the μ-receptor deficient CXBK strain, show only weak social conflict and morphine analgesia (Frischknecht **et al.**, 1988; Miczek **et al.**, 1982; Miczed and Thompson, 1984; Siegfried **et al.**, 1984a). In C55BL/6 mice, the weak social conflict analgesia after prolonged attack was insensitive to naloxone and naltrexone, but sensitive to β-chlornaltrexamine (Külling **et al.**, 1988; Siegfried and Frischknecht, 1989).

Experience modifies social conflict analgesia

Several experiments have indicated that experiential factors, (**i.e.**, a memory system), may influence social conflict analgesia. When DBA/2 mice were exposed repeatedly (every second day for nine days) to thirty attack bites they displayed

less and less analgesia, i.e., they became tolerant to the pain-inhibitory effect of the social stress (Siegfried et al., 1989). Similar results have been reported after more drastic defeat experiences (Miczek et al., 1982; 1986; Rodgers and Randall, 1985). The development of tolerance was accompanied by changes in opiate binding characteristics to brain homogenates. While one study reported a reduction of brain opioid receptors and a decrease in receptor affinity (Siegfried et al., 1989), another one found an opioid receptor upregulation without apparent affinity changes (Miczek et al., 1986). Eventually, the differences may be explained on the basis of different ligands([^{3}H] etorphine versus [^{3}H] dihydromorphine), stress regimen (thirty bites every second day during nine days versus hundred daily during five days), and strains of mice (DBA/2 versus B6AF$_1$) used. Significantly elevated in vivo [^{3}H] diprenorphine binding in the brainstem of defeat-tolerant mice was observed when compared to naive mice (Miczek et al., 1986). This indicates that repeated exposure to social conflict may lead to an increase in the number of opioid receptors, or alternatively, that the chronic treatment leads to a depletion of opioid peptides below the levels present in naive mice, thus, providing less competition for receptors following [^{3}H] diprenorphine injection (Miczek et al., 1986). Chronically defeated mice displayed a selective tolerance to the morphine's effect on analgesia, but not on operant behavior (Miczek and Winslow, 1987), and showed a naloxone-precipitated withdrawal jumping (Miczek et al., 1986).

Moreover, it has been shown that the low intensity analgesia elicited by a mild attack stress was modified by a single social confrontation with a nonaggressive or aggressive opponent (Siegfried et al., 1987a; 1987b; 1987c). If the test animal was familiarized with a nonaggressive opponent in the test cage followed, twenty-four hours later, by an exposure to seven attack bites, no social conflict analgesia was recorded (Siegfried et al., 1987b). This suggests an important role for novelty in the elicitation of

low intensity analgesia, and it should be noted that novelty per se, devoid of a nociceptive component, may result in a moderate increase of pain thresholds (Kavaliers and Innes, 1988a; Netto **et al.**, 1987; Siegfried **et al.**, 1987d). If the test animal was subjected to a prolonged attack that resulted in an opioid-mediated high intensity analgesia, the low intensity analgesia after seven attack bites registered twenty-four hours later turned into a long-term analgesic reaction (Siegfried **et al.**, 1987c). The response was characterized by a duration of more than ten minutes, as well as by nonopioid (1 min postattack)/opioid (10 min postattack) mechanisms. This experiment indicates that after a prolonged attack, pain-inhibitory systems remain, at least for twenty-four hours, in a state of increased readiness, similarly as it has been reported after inescapable shock experience (Jackson **et al.**, 1979; Maier **et al.**, 1983). Only after more severe chronic exposure to attack the system may get subsensitive resulting in tolerance (see above). Thus, the two studies characterize low intensity analgesia as an adaptive physiological response that is amenable to plastic changes induced by monaggressive, nonpainful as well as by aggressive, painful experiences. The processing and the consequences of these experiences, **i.e.**, the memory system that modulates the pain-inhibitory output from the defensive system, is likely to be mediated by endogenous opioid receptor stimulation, since naloxone given prior to the aggressive as well as nonaggressive confrontations prevented the effect (Siefried **et al.**, 1987a, Fig. 1); 1987b, Table 2: 1987c, Fig. 2). Nevertheless, a drug-induced state dependency effect could not be excluded on the basis of the experimental evidence. Analogous to tailshock/footshock analgesia (Jackson **et al.**, 1979; Maier **et al.**, 1983), full expression of endogenous opioid analgesia in attacked mice during training was a necessary condition to reinstate analgesia during testing twenty-four hours later (long-term analgesia), while blockade of shock-induced opioid analgesia by naltrexone did not affect the conditioned analgesia

measured twenty-four hours later by the suppression of formalin-induced recuperative behaviors (Helmstetter and Fanselow, 1987).

Effects of innate and learned danger stimuli on nociception

Concerning the analgesic reaction of mice to innate danger stimuli it has been shown that a short (30 sec) nonvisual exposure of wild white-footed mice to noise and olfactory stimuli of a natural predator, the short-tailed weasel, elicited a brief (15 min) naloxone-insensitive analgesia that was prevented by Ro 15-1788 and by diazepam (Kavaliers, 1988b). Intermediate exposure (5 min) elicited an analgesia of longer duration (15-30 min) that was sensitive to both naloxone and benzodiazepine agonist and antagonist, while prolonged exposure (15 min) induced a high amplitude analgesia of long duration (45 min) that was blocked by naloxone and was insensitive to benzodiazepine manipulations (Kavaliers, 1988b). Similarly, a naloxone-insensitive analgesia was reported after exposing mice to the scent of an isolated potentially threatening male mouse (Kavaliers and Innes, 1988b; Rodgers and Randall, 1986b). Also, the pain-inhibitory response accompanying the cataleptic state after brief pinches at the scruff of mice (Amir **et al.**, 1981) may be viewed as a reaction to an innate danger stimulus. Generally, these data are in accordance with those reported by Fanselow and coworkers in rats (Fanselow, 1985; Fanselow and Sigmundi, 1986; Lester and Fanselow, 1985).

In our hands, learned danger stimuli, **i.e.**, a two or three minutes confrontation of DBA/2 test mice with a nonaggressive C57BL/6 partner mouse in the training box twenty-four hours after a single (1 x 50 bites) or repeated (3 x 50 bites; 50 bites per day) confrontation with a dominant, aggressive C57BL/6 mouse, failed to affect nociceptive thresholds (Külling **et al.**, 1987; Siegfried **et al.**, 1987c; 1989). Speculatively, the absence of conditioned analgesia upon learned stimuli makes insofar sense that during this situation there was no pain and consequently no recuperative behaviors that should have been

suppressed by analgesia to prevent competition with the display of defensive behaviors. Our results were in contrast to the experiments by Fanselow and coworkers (Fanselow, 1984a; 1986; Fanselow and Baackes, 1982; Fanselow and Helmstetter, 1988) in which learned danger stimuli elicited an analgesic response, as defined by the attenuation of formalin-induced recuperative behaviors. It may well be that this discrepancy was based on the different models and approaches used, especially on the use of (a) different species (mice versus rats), (b) different stress procedures during training (attack bites versus footshocks), (c) different learned danger stimuli(nonaggressive opponent versus shock cage in absence of shock) and most importantly, (d) different pain (tail-flick, hot plate versus formalin injection).

BEHAVIORAL CHANGES DURING AND FOLLOWING SOCIAL CONFLICT

Behavioral responses during exposure to nociceptive stimuli and relation to endogenous opioids and analgesia

The specific behaviors displayed by attacked mice (Grant and Mackintosh, 1963) may depend on the stimulus intensity (duration of attack, number of bites received), the previous history of the attacked animal, as well as on the strains of mice used. For example, escape responses displayed in DBA/2 mice during attack without being in contact with the aggressive partner mouse (panic escape), emerged only in the last of three fifteen bite intervale (Frischknecht and Siegfried, 1988a), and experience of being attacked resulted in a changed strategy in subsequent encounters. with the animals showing less escape and more submissive/defensive behaviors (Külling **et al.**, 1987; Roche and Leshner, 1979). Finally, during an initial encounter mice of the DBA/2 strain showed significantly more escape and less defensive upright postures than C57BL/6 mice (Külling **et al.**, 1987; Siegfried **et al.**, 1984a). Thus, in analogy to the concept of species-specific defensive reactions (Bolles, 1970) one might, in the above case, speak of strain-specific

defensive reactions, a suggestion made earlier (Wahlsten, 1972).

An important question which is connected with the function of social conflict analgesia is whether this intrinsic antinociception is associated to specific behavioral changes during attack. The positive correlation found during exposure of DBA/2 mice to a moderate attack (15 bites) indicated that the low intensity, naloxone-insensitive analgesia is related to the frequency of defensive upright postures shown upon contact during the aggressive encounter (Frischknecht and Siegfried, 1988a). Thus, antinociception during initial attack may support coping, in that it favors the display of the defensive upright posture which in turn may reduce the amount of attack bites received (Grimm, 1980). Similarly, this form of antinociception has been related to behavioral defense (Rodgers and Randall, 1986a), and it has been speculated that the function of naloxone-insensitive analgesia, is to prevent the disruption of escape behavior (Rodgers and Randall, 1987a; 1987b). Although this has not been verified experimentally, it should be noted that the defensive upright posture may be regarded as a blocked escape (cutoff) response (Dixon and Kaesermann, 1987). Since increasing frequencies of defensive behavior upon bite or contact can be regarded as an index of learning during attack (Frischknecht **et al.**, 1982; Siegfried **et al.**, 1982; 1984b), the results also suggest that acquisition of submissiveness during attack is associated with the occurrence of analgesia (Frischknecht and Siegfried, 1988a).

During the prolonged exposure to attack additional behavior-analgesia relationships have been described. As suggested earlier (Miczek **et al.**, 1982). Teskey and coworkers (1984) found a higher level of analgesia in mice that displayed the characteristic defeat posture - defensive upright position, limp forepaws, upward angled head and retracted ears - upon exposure to thirty-five bites than in attacked animals not showing this particular behavior. Data obtained with the C57BL/6 and DBA/2 strains of mice did, however, not favor a

generalization of the above mentioned view (Siegfried **et al.**, 1987a). Rodgers and Hendrie (1983), on the other hand, reported a positive correlation between the degree of analgesia in attacked mice and the duration of the frozen crouch behavior. We have found a link between antinociception and immobility: analgesia after fifteen bites correlated positively with immobility displayed upon contact with the opponent during the subsequent fifteen bite interval (Frischknecht and Siegfried, 1988a). Similarly, pinching of the scruff of the neck - a sensation that may resemble the biting attack of a cat - induced catalepsy and opioid analgesia in mice (Amir **et al.**, 1981: Ornstein **et al.**, 1981), and freezing behavior in rats has been associated with analgesia (Fanselow, 1984a; 1986; Fanselow and Helmstetter, 1988). The panic escape behavior which may be regarded, together with tonic immobility (Rodgers and Randall, 1987a; 1987b), as a terminal defense reaction, was found to be sensitive to opiate antagonists. Naloxone and β-chlornaltrexamine, while suppressing social conflict analgesia, facilitated the occurrence of panic escape; naloxone additionally decreased immobility (Frischknecht and Siegfried, 1988a). In several other cases opioid receptor blockade during agonistic encounter in mice led to a weak shift towards defensive, fearlike behavioral activities (Brain **et al.**, 1985; McAllister **et al.**, 1986; Teskey **et al.**, 1984), while other studies found no effect of naloxone on behavior in reaction to attack (Rodgers and Hendrie, 1983; Siegfried **et al.**, 1982).

It should be mentioned that behavior-analgesia relationships during attack may also, although less acurately, be investigated at another level, in that the behavioral defense strategies and analgesic responses of different mouse genotypes are compared. During a situation without an apparent solution the high analgesic DBA strain engaged in an active searching strategy, **i.e.**, panic escape (Frischknecht and Siegfried, 1988a), while continously attacked mice of the low analgesic C57BL/6 strain engaged in a waiting strategy, **i.e.**,

immobility (Frischknecht **et al.**, 1988; Siegfried **et al.**, 1984a). Thus, viewed from this point, a high analgesic state must not necessarily be associated to immobility during attack, and one might speculate that the DBA/2 strain might afford this active searching pattern since the high analgesic state compensates for the increased damage brought about by the increased movement-induced attraction of the opponent. Increased immobility, frozen crouch, defense and panic escape behaviors may all reflect strain-dependent searching-waiting strategies, and may represent different behavioral manifestations of uncontrollability or helplessness, occuring in the absence of or concomitant to social conflict analgesia.

Together, it may be concluded that - beside pain inhibition - the functional role of EOPs during sustained attack is the reduction of activity, leading to immobility and delaying the emergence of panic escape, as evidenced by the switch from immobility to the precipitation of panic escape reactions during opioid receptor blockade (Frischknecht and Siegfried, 1988a). In accordance with an earlier proposal (Rodgers and Randall, 1987a; 1987b), high intensity opioid analgesia, thus functions to augment behavioral inhibition to eliminate cues which might otherwise provoke further attack. Behavioral responses following exposure to nociceptive stimuli (postconflict recuperative behavior) and relation to endogenous opioids and analgesia.

Little information is yet available on the postconflict behavior of attacked mice. Behavior assessed during the five minutes immediately following the removal of the aggressive opponent which delivered thirty attack bites, revealed, in the low analgesic C57BL/6 strain, increased self-grooming and face washing behavior and a decreased locomotion, while a significantly higher decrement in locomotion and an increase in immobility was found in the high analgesic DBA/2 strain (Frischknecht and Siegfried, 1988b). In the latter strain, postconflict behavior after thirty attack bites was dominated by an immobility response that correlated positively with the

analgesic state (Frischknecht and Siegfried, 1989). Like postshock freezing in the rat (Fanselow and Bolles, 1979b), immobility may be regarded as a defensive fear response which - in the absence of nociceptive stimulation - may be maintained by learned danger stimuli (**e.g.**, smell and place of attack), or by attack-induced EOPs. After exposure of DBA/2 mice to the mild stress of seven attack bites which resulted in a significantly smaller analgesic response than after thirty bites, grooming behavior was significantly elevated (Nunes de Souza and Siegfried, unpublished results). Contrary to that, recuperative autogrooming in DBA/2 mice was associated with the early analgesic and not with the late hyperalgesic postattack period, when the behavior was recorded in the presence of a nonaggressive conspecific (Hendrie, 1989).

Injections of naltrexone before exposure to thirty attack bites dose-dependently antagonized body care and elevated immobility in C57BL/6 mice (Frischknecht and Siegfried, 1988b). A similar increase in shock-elicited freezing has been reported after preshock naloxone application (Fanselow and Bolles, 1989b; Lester and Fanselow, 1986). In DBA/2 mice however, naltrexone diminished postconflict immobility and social conflict analgesia (Frischknecht and Siegfried, 1988b), indicating that the blockade of analgesia, tends to shift behaviors from defense to recuperation. In accordance to that, suppression of pain-induced recuperative behaviors by learned danger stimuli was antagonized by naltrexone (Fanselow, 1984a; 1986; Fanselow and Baackes, 1982). EOPs seem also to participate in postencounter-induced recuperative feeding and drinking activities. Naloxone given prior to attack (35 bites) antagonized the increased consumption of food and water observed during the two (Teskey **et al.**, 1984) or three (Teskey and Kavaliers, 1988) hours following the attack. However, we were unable to replicate these findings. In our experiments, fifty attack bites induced, in C57BL/6 and DBA/2 mice, a naltrexone-reversible reduction in food-intake during the three hours postencounter period (Siegfried and Frischknecht,

unpublished results).

In general, the data suggest that, in the strain C57BL/6, EOPs activated by social stress suppress postencounter immobility and are involved in recuperative grooming behavior, supporting an observation made earlier (Teskey **et al.**, 1984). In the strain DBA/2. EOPs support postencounter immobility in parallel to their analgesic effects. The role of EOPs in postconflict ingestive behaviors is controversial and remains to be further investigated.

Behavioral responses during exposure to learned danger stimuli and relation to endogenous opioids and analgesia

Initially, it has been shown (Frischknecht **et al.**, 1982; Siegfried **et al.**, 1982) that a nonaggressive C57BL/6 partner mouse turned into a learned danger stimulus for an ICR test mouse, twenty-four hours after the test mouse had been attacked and bitten by an aggressive C57BL/6 opponent: Upon contact with the nonaggressive C57BL/6 partner mouse the ICR test mouse displayed submissive postures (crouch, defensive sideways and upright). This was taken as an index of learning since the amount of postures recalled was significantly higher than in nonattacked controls. The experimental set-up allows the analysis of acquisition and especially of extinction processes by assessing the amount of submissive and escape-related behaviors shown between the beginning and the end of the training or testing session, respectively. The paradigm may represent a alternative to traditional aversively motivated learning schemes in that it uses a biologically meaningful situation, including social cues, both as the nociceptive, unconditioned (attack bite by the aggressive opponent), and the conditioned (contact with the nonaggressive opponent) stimulus. Subsequently, the model also included DBA/2, C57BL/6 and C3H/He inbred mice as test animals with socially-isolated DBA/2 and ICR mice as aggressive opponents, in addition to dominant, aggressive C57BL/6 mice. In these studies it was shown that the conditioned recall of submissive

postures and escape was modified by a variety of drugs, and was dependent on the number of bites received during training as well as on the mouse genotype used (Frischknecht **et al.**, 1985; Puglisi-Allegra and Cabib, 1988; Siegfried **et al.**, 1984a; 1984b).

Due to the absence of a conditioned analgesic response by learned danger stimuli in the mouse social conflict model (see above) the assessment of a relationship between conditioned analgesic and behavioral responses is rendered impossible. Nevertheless, the analgesic state during training may influence the encoding and/or recall of the aversive situation. For instance, individual correlational analysis in attacked DBA/2 mice revealed a negative relationship between the magnitude of analgesia immediately after training and the avoidance of attack place during testing (Siegfried and Frischknecht,1989). It has also been speculated that the decreased retention observed in DBA/2 mice, twenty-four hours after exposure to fifty attack bites, in comparison to ten bites, may have been due to the higher antinociception induced by fifty attack bites. The unchanged low analgesic state upon increasing number of bites in the C57BL/6 strain in turn may have favored the increased retention after fifty when compared to ten bites. (Siegfried **et al.**, 1984a; 1986; 1987a). These data may eventually be explained by the concept of endogenous state dependency (Izquierdo, 1984) which says that the more the endogenous state during testing resembles that during training, the better the information is retrieved. Thus, with the absence of conditioned analgesic responses in C57BL/6 and DBA/2 mice during testing (Külling **et al.**, 1987; Siegfried **et al.**, 1987c) it follows that the higher was the analgesic response during training the higher was the difference between the states during training and testing, and thus the less efficient was the recall. Alternatively, a high analgesic response before or during training may lead to a faster extinction of defensive upright postures (Siegfried **et al.**, 1987a) or avoidance responses (Galina and Amit, 1986a). The analgesic

state may have been responsible for the stable behavioral pattern observed during repeated aggressive confrontations in the high analgesic DBA/2, but not in the low analgesic C57BL/6 strain (Kölling **et al.**, 1987). Pointing in the same direction, Castellano and Puglisi-Allegra (1983) have shown that a posttraining sixty minute immobilization stress which results in pain inhibition in the DBA/2 strain (Publisi-Allegra and Oliverio, 1983), impaired passive avoidance learning in DBA/2 mice and led to a facilitation in C57BL/6 mice. Galina and Amit (1986b) reported a deficit of learned escape responses during repetitive hot plate testing, due to coldwater swin stress-induced analgesia, and antinociception induced by learned danger stimuli was shown to reduce a nociceptive unconditional stimulus' ability to support Pavlovian conditioning (Fanselow and Bolles, 1979a).

Prevention of the analgesic state and of the action of EOPs by opiate antagonist treatment before training resulted in an increased retention of submissive postures and escape behavior during testing (Siegfried **et al.**, 1982; 1987a). This is in accordance with the enhanced nociceptive learning found on the hot plate (Messing **et al.**, 1983; Ramabadran **et al.**, 1979) and the increased conditioned freezing (Lester and Fanselow, 1986) seen after pretraining administration of opiate antagonists. Contrary to that, pretraining naltrexone blocked social conflict analgesia and reversed the aversively motivated place avoidance learning in attacked DBA/2 mice (Siegfried and Frischknecht, 1989). Since this effect was not due to drug-induced state dependency, it was suggested that EOPs released during stress may - in parallel to a pain-inhibitory system - directly facilitate place memory. Previous studies have shown "amnesia" after pretraining opiate antagonists (for reviews see Messing, 1988; Siefried and Frischknecht, 1989), and it is suggested that the incongruous effect of pretraining antagonists on memory may be explained by the drug's ability to increase the perceived intensity of the aversive unconditioned stimulus. This is strengthened by the fact that the effects of naloxone

pretreatment parallel those of increasing shock intensity (Fanselow, 1984b). Thus, opiate antagonists may induce memory facilitation in cases where they shift the perception of electric footshocks (Lester and Fanselow, 1986) or attack bites (Siegfried et al., 1982; 1987) towards optimal levels of arousal, and memory may be impaired when the aversiveness of the situation is enhanced to a degree that is incompatible with processing of information, e.g., overarousal, as may have been the case in the place avoidance study (Siegfried and Frischknecht, 1989). Nevertheless, it cannot be excluded that the different effects obtained with pretrial opiate antagonists on defensive (Siegfried et al., 1982; 1987) versus place avoidance learning (Siegfried and Frischknecht, 1989) of attacked mice were due to the drug's different action on the memorization of environmental (place of attack) versus social (characteristics of opponent) cues.

In summary, it is proposed that EOPs released during the stress of being attacked may modulate memory by their analgesic effects, as well as by mechanisms independent of pain-inhibitory systems.

CONCLUSIONS

The murine social conflict model represents a biologically-meaningful situation which allows investigation, at various levels, of coping mechanisms during a naturalistic stress. More specifically, the model may especially be useful to elucidate basic mechanisms of intrinsic analgesia and its relation to defense and recuperation. Within this framework new drugs may be tested and their potential efficacy can be interpreted on the basis of their specific and unspecific effects on defensive and recuperative behaviors, changes in pain sensitivity and memory processes. The social conflict model constitutes an alternative to existing animal models of aversion and defense (for reviews see Blanchard and Blanchard, 1988; Fanselow, 1986;

Graeff, 1988), and hopefully, the present model may have a heuristic value in that it will generate further questions for research and stimulate new experiments so that the present assumptions and hypotheses may be verified or rejected. Knowledge of the neuroanatomical, neurochemical, neurophysiological and neuropharmacological substrate of the defensive and pain motivational systems and their modulation by memory may lead to a better understanding and therapeutic management of the pathological responses in humans given to dangerous, threatening, and stressful situations, such as hypo- or hyperdefensiveness, panic attack, chronic pain and maladaptive avoidances.

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