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Short communication

THE ALBINO LOCUS PRODUCES ABNORMAL RESPONSES TO OPIATES IN THE MOUSE

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Pedigreed inbred lines of pigmented mice were compared with albino lines differing at either a single locus or by a chromosomal segment of interest, for their responses to morphine. In either of two tests, behavioral activation or reduction in core temperature, albino mice were aberrant in their responses, demonstrating reliably less sensitivity to morphine than closely related pigmented lines. These findings suggest the need for caution in the use of albino lines in opiate research.

Albinism Morphine Opiates Motor activity Temperature

1. Introduction

Because they are readily available, physically robust, genetically and behaviorally well defined, and relatively inexpensive, albino strains of rats and mice are often used in psychobiological and pharmacological research. The albino locus may have effects extending beyond coat color, however. Indeed it is known to also affect behavior (e.g., DeFries, 1969; Van Abeelen and Kroes, 1967; Fuller, 1967; Goodrick, 1973), sensory systems (e.g., Collewijn et al., 1978; Haythorn and Henry, 1975; Guillery, 1974), and possibly, although to a rather limited extent, also to influence pharmacological responsiveness (Fuller, 1967). We present evidence herein that the albino locus may produce greatly reduced responsiveness to opiates, a finding of potential interest given the predominance of albino strains in current research.

2. Materials and methods

The influence of albinism was investigated using two effects of opiates and two genetic techniques. The first opiate effect was stereotyped behavioral activation, which consisted primarily of forward locomotion as measured by remote capacitance sensing upon commercially available monitors (Stoelting, Chicago, IL) and as described below and in greater detail in previous reports (Katz and Schmaltz, 1979; Katz, 1979). Mice were individually placed in 51 × 41 × 22 cm polypropylene containers with fresh wood chip bedding and allowed 4 h to habituate prior to vehicle or drug injection. Activity was then remotely recorded for the test session. The other measure of opiate activity was the lowering of core temperature after systemic opiate injection. The hypothermic response was measured via a Yellow Springs telethermometer with a 1 cm rectal probe. Temperature values were taken after a 20 sec period to allow equilibration.

Coisogenic and congenic lines from the University of Michigan colony were used for genetic analysis (Green, 1966). The coisogenic lines differ at a single locus of interest, based upon an inbred parent line (in the present case C57B1/6J) and a point mutation (for

albinism c). Lines were maintained by back-crossing homozygous male albino mice (57B16J CC) to females heterozygous at the C locus (i.e., C57B16J Cc females). Congenic lines were produced and maintained by repeatedly (based, in the present case, upon 20 generations of back-crosses) mating animals of one strain with a trait of interest (the albino RIII mouse) to a parent stock (pigmented C3H albino mice) to produce a line with a single chromosomal insertion containing a gene of interest but otherwise similar to the parent line. Although congenic lines are widely used in histocompatibility studies, few behavioral studies have made equivalent use of their potential.

The experimental design for both coisogenic and congenic analyses was the same. Each experiment had 3 groups. For the coisogenic study the groups were homozygous pigmented (CC) and albino (cc) lines, and the heterozygous (Cc) pigmented mice. For the congenic study the strains were C3H, RIII and the C3H albino line. Each study utilized 4 (for activity) or 3 (for hypothermia) drug levels (0, 18.3, 37.5, 75.0 mg/kg intraperitoneally) of morphine sulphate with six naive male mice per experimental cell. It should be noted that drug doses for temperature experiments were deliberately chosen to avoid the core temperature elevations typical of lower doses. Mice varied between 25 and 30 g and were maintained in group housing with ad libitum food and water. For activity, data were analyzed as a cumulative 90 min score. For hypothermia 4 blocks each of 15 min were used and a single mean value based upon average reduction across the four measures were used. All experiments were therefore analyzed as two (groups, dosage) factor analyses of variance. Results are presented as means and standard deviations.

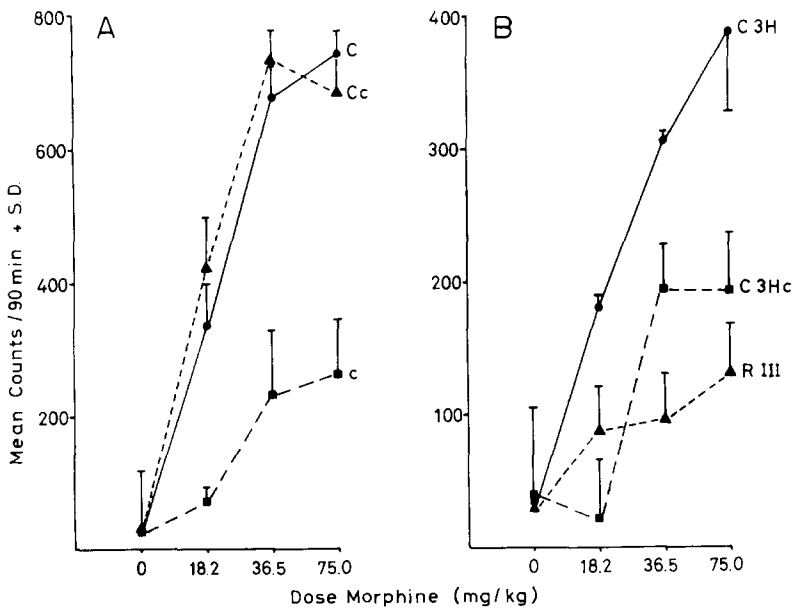

Fig. 1. Influence of the albino locus upon behavioral activation to intraperitoneal morphine. Panel A presents an analysis based upon coisogenic lines and Panel B a similar analysis upon congenic lines. In Panel A, C = homozygous pigmented; Cc is heterozygous pigmented and c = albino point mutation. In Panel B, C3H is pigmented parent line, C3Hc is albino line congenic with C3H, and RIII is the albino line serving as the normally albino parent stock. Four hours habituation preceded injection with 0.9% sodium chloride vehicle or one of three doses of morphine.

3. Results

Results across all measures and techniques were consistent in demonstrating that albinism was associated with significantly reduced opiate sensitivity. Findings are presented in figs. 1 and 2. Fig. 1 presents data based upon motor activity. As may be seen, morphine increased activity in all groups in comparison with vehicle, but this increase was less in lines coisogenic (Panel A) or congenic (Panel B) for albinism. The effects were statistically reliable beyond chance, with reliable main effects of groups (F 2, 60 = 37.5, 18.4), dosage (F 3,60 = 68.5, 18.6) and significant interaction (F 6,60 = 6.4, 5.8 respectively for coisogenic and congenic analyses; all results were reliable at $P \leqslant 0.0001$. Similar findings were also present for the second dependent variable, reduction of core temperature. Findings are presented in fig. 2 and also were confirmed statistically. Main effects for groups (F 2,45 = 9.3, 11.6), dose (F 2,45 = 4.8, 12.1) and interaction (F 4, 45 = 12.3, 5.1) again were significant respectively for coisogenic and congenic lines ($P <$ 0.02 in all cases).

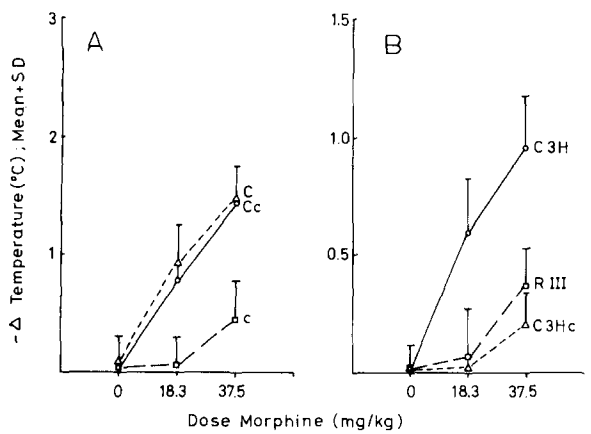

Fig. 2. Influence of the albino locus upon reductions of core temperature after intraperitoneal morphine in coisogenic (Panel A) or congenic (Panel B) lines genetic of mice. Description of lines as presented in fig. 1 and text.

4. Discussion

The findings of the present study are that albino mice are relatively insensitive to morphine by either of two independent tests of genetic influence, and by either of two measures of opiate activity. Therefore, the effects of albinism upon morphine responses may be assumed to be reasonably general. This establishes a novel pleiotropic effect, and a caveat for future research. The cellular mechanisms underlying these reduced effects are not known. It is possible the present results reflect altered receptor number, or perhaps and yet more problematically reduced individual opiate receptor sensitivity. Altered sensitivity of other systems (e.g., monoamine systems), which might modulate or be modulated by opiate systems also cannot be ruled out at present. Finally, altered rates of drug metabolism and/or secretion must be considered. Regardless of this, however, given the present findings it may be argued that special consideration should be given to the use of albino mice in the future, particularly in the investigation of opiates.

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