The Influence of Learning on Morphine Analgesia and Tolerance Development in Rats Tested on the Hot Plate

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Abstract. The influence of “learning” on the development of tolerance to the analgesic effect of morphine in rats was examined employing the hot plate procedure. A tested-reinforced (Tr) group and its yoked-control, a tested-non-reinforced (Tnr) group, received identical exposure to the testing procedure; the Tr group was reinforced daily for its behavior on the heated plate whereas the Tnr group was reinforced only on the last day of the experiment. Paired statistical comparisons between these two groups on the last day of the experiment revealed that: 1. pre-morphine control reaction times on the heated plate were significantly lower in Tr than in Tnr animals; and 2. post-morphine increases in reaction time did not differ between Tr and Tnr animals. It was concluded that whereas some “learning” does occur in this testing procedure, “learning” does not influence the “behavioral tolerance” to morphine which develops in this analgesiometric method. An hypothesis which accommodates this “behavioral tolerance” and a mechanistic scheme is offered.

Key-Words: Learning — Morphine Tolerance — Behavioral Tolerance.

It was initially demonstrated by Kayan et al. (1969), and later reaffirmed by Adams et al. (1969), Gebhart and Mitchell (1971a, 1971b) and Gebhart et al. (1971), that experience significantly contributes to the development of tolerance to the analgesic effect of morphine in rats in the hot plate procedure. Ferguson and Mitchell (1969) extended this observation of the contribution of experience in a test procedure to man, employing a submaximum-effort tourniquet technique to measure effect. In addition to these results from our laboratory with respect to the development of tolerance to morphine, investigations employing drugs other than morphine have also demonstrated greater increases in tolerance development when the subjects were confronted with some task to perform or to respond in some manner to terminate a noxious stimulus (Irwin, 1963; Schuster et al., 1966; Wahlstrom, 1968; Le Blanc et al., 1970). In so far as the effect of experience in the hot plate procedure on
the development of tolerance to the analgesic effect of morphine is concerned, Adams et al. (1969) demonstrated that this effect of experience was manifest as a drug-test interaction since it occurred only in animals which had acquired experience on the plate, either heated to 55°C or at ambient temperature (25°C), while under the influence of morphine. Gebhart et al. (1971) examined the influence of stress on tolerance development to morphine in rats tested on the hot plate, which was suggested by Adams et al. (1969) to be the basis of the drug-test interaction, but they were unable to demonstrate any influence of stress on the development of tolerance to morphine as measured by this procedure.

Other workers (Takagi and Iwamoto, 1952; Knoll et al., 1955a, 1955b; Votava et al., 1963; and Jacob, 1963, 1966), while not addressing themselves to the development of tolerance to morphine in the hot plate method, all agree that some learning is involved with respect to the response elicited by this testing method. Jacob (1963) did, however, examine the effect of morphine on adaptive and learning behavior employing a hot plate method. His investigation of the effect of “learning” in this procedure consisted of four total tests on the heated plate (60°C) over a two day period. He concluded that the modification of behavior introduced by re-exposure of the animal to the testing procedure is “a rapid ‘learning’ under stress conditions or a rapid conditioning of the animal where the unconditioned stimulus would be . . . exposure to the hot plate . . . and the conditioned (response) would be an escape reaction which becomes an avoidance reaction after several trials”.

Thus, since stress would appear not to significantly influence the development of tolerance to morphine in the hot plate method (Gebhart et al., 1971) and since adaptive and learning behavior has been reported to play a role with respect to the response elicited in experimental subjects by the heated surface, albeit not necessarily while under the influence of morphine, the contribution of “learning” to the development of tolerance to the analgesic effect of morphine in the hot plate method was investigated. This report details the results of this investigation.

Methods

Animals. Young-adult male Holtzman rats initially weighing 120 to 140 g were used throughout. The rats were maintained in constant environmental conditions with free access to commercial food and water. At least five days were allowed for acclimatization to this environment before use in experiments. On the day of an experiment the animals were transported to a separate room for testing.

Drugs. In all cases, the drug (either saline or morphine sulfate) was administered subcutaneously in the midline of the back in the thoraco-