Analgesic Potency of Sodium Salicylate, Indomethacin, and Chlordiazepoxide as Measured by the Spatial Preference Technique in the Rat

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Abstract. The analgesic potency of various doses of sodium salicylate (150, 200, 250, 300, 350 mg/kg), indomethacin (1.5, 2.0, 2.5, 3.0, 3.5, 5.0 mg/kg) and chlordiazepoxide (2.5, 5.0, 10.0, 20.0 mg/kg) were measured using the spatial preference technique. All three agents were active in a wide range of doses indicating that this technique is sensitive to the weak analgesics. The chlordiazepoxide data were interpreted to suggest that this tranquilizing agent may be able to impair the appreciation of the emotional (i.e., aversive) qualities of electric shock, thus reducing the animal's motivation to escape the noxious stimulus. A procedure for computing ED₅₀ estimates was also presented along with a summary of the ED₅₀ values for several standard narcotic and narcotic antagonist analgesics. Since this procedure is a reliable and sensitive index of drug-induced analgesia, it should be useful as a screening procedure in evaluating the analgesic potency of a wide variety of chemical agents.

Key words: Analgesia — Spatial Preference Technique — ED₅₀ — Sodium Salicylate — Indomethacin — Chlordiazepoxide.

Previous attempts to design a suitable animal model to predict the analgesic potency of pharmaceutical agents have not been completely successful for a variety of reasons. The major flaws prevalent in the classic pharmacological tests for analgesia are (1) the tests are too specific and thus can detect only one class of analgesics known to be active in man or (2) that the tests lack specificity and thus react to agents that are clinically ineffective. These two basic shortcomings allow one to classify most of the available animal test procedures into two categories depending on whether they can detect only one class of analgesics (too specific) or react to many agents which are not analgesic in man (lack specificity). The tail-flick and hot plate procedures are two popular examples of the first class of tests. In both cases the experimenter measures latency of movement after the application of a painful thermal stimulus. Although these procedures are sensitive and reliable measures of narcotic induced analgesia, their use in analgesic research has
recently been questioned (Dewey, Harris, Howes, and Nuite, 1970) since they fail to detect any of the narcotic antagonist analgesics that are clinically active in man.

The second category of tests, those that can detect nonnarcotic analgesics, include the inhibition of writhing induced by chemicals (Dewey et al., 1970) and complex behavioral schedules (Weiss and Laties, 1961). Although the former procedure is sensitive to the narcotic antagonist analgesics, it lacks specificity and thus many agents which are not clinically analgesic in man show activity in this test (e.g., antihistamines, parasympathomimetics, etc.). The latter procedure which makes use of operant techniques is sensitive to both the narcotic and weak (i.e., aspirin) analgesics, but has been criticized for its complexity in that it involves various cognitive processes (Boren and Malis, 1961) and as such does not strictly reflect the analgesic properties of drugs.

In order to circumvent the flaws prevalent in previous animal models, our laboratory has developed a technique introduced by Campbell and Masterson (1969) which uses a spatial preference cage to determine the aversive threshold in rats. Previous reports have indicated that this technique is sensitive to the narcotic (Houser and Paré, 1972) and narcotic antagonist analgesics (Houser and Paré, 1973) without demonstrating pronounced effects in response to doses of a sedative hypnotic (sodium pentobarbital) which did not block the execution of the escape response. Thus, the spatial preference technique appears to have the advantage of being able to detect several types of analgesic agents known to be clinically active in man without reacting to agents like pentobarbital that are not clinically analgesic in sedative doses. From the initial data it appears that this technique may be reasonably sensitive to the various standard analgesic agents, while remaining relatively selective in detecting activity in only those compounds that are clinically effective in man.

To date, however, no data existed on whether this technique could detect the activity of the weak analgesics. Furthermore, an assessment of other nonanalgesic agents such as the tranquilizers would be of value in determining if the spatial preference technique reflects only the analgesic properties of drugs. Finally, a method for computing ED$_{50}$ estimates for various agents would be of value in comparing this technique to other pharmacological tests used to detect analgesia. The present report is an attempt to supply the necessary data in regard to the above issues. The effects of sodium salicylate and indomethacin upon the aversive threshold were explored using the spatial preference technique. Although these two agents are known to be analgesic in man (Goodman and Gilman, 1970), their potency is relatively weak when compared to narcotic analgesics (e.g., morphine) and thus have posed