The ascending limb of the dose-response curve for cocaine self-administration is an experimental artifact

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Cocaine self-administration is a model of cocaine use disorder and is considered an example of positive reinforcement. Agonist dose-response curves are fundamental to understanding the mechanisms underlying agonist induced responses. According to operant behavior theory, a greater positive reinforcement (higher cocaine unit dose) produced by a stimulus (cocaine injection) would increase the probability of performing the operant behavior (lever press) and result in a higher frequency of lever pressing. Conversely, it is observed that as the cocaine unit dose increases, the rate of cocaine self-administration decreases, particularly at a fixed ratio (FR) 1 schedule, thus creating a paradox. However, at smaller unit doses the rate of cocaine self-administration is reported to increase as the unit dose increases up to a maximum. This ascending limb of the cocaine dose-response curve is considered to represent the positive reinforcing effects of cocaine. FR1 schedule of cocaine self-administration follows the compulsion zone theory which states that cocaine induces lever pressing behavior only when cocaine level is below the satiety threshold and above the remission threshold. This theory explains FR1 and progressive ratio schedules over a range of cocaine unit doses but has not been applied to high FR schedules. We examined the cocaine dose-response relationship through cocaine self-administration on FR1 and FR50 at different unit doses (0.1, 0.3, 0.5, 0.75, 1.5 and 3 μmol/kg). Rats (n=5 completed all phases of the study) were trained to self-administer cocaine on FR1 at different unit doses, and on FR50 at 3 μmol/kg unit dose. Next, they self-administered cocaine in sessions that started with FR1, then proceeded to FR50 across the range of unit doses. Only one dose was used in a session, and three sessions were performed for each dose. Rats completed all injections on FR1 but could not complete all injections on FR50 at doses lower than 1.5 μmol/kg. The ratio of the number of injections completed on FR50 relative to FR1 was 0.03, 0.43, 0.62, 0.72, 1 and 1 at 0.1, 0.3, 0.5, 0.75, 1.5 and 3 μmol/kg cocaine doses respectively. Rats were able to maintain cocaine level at or above the satiety threshold for all unit doses on FR1 as an injection follows one lever press. However, on FR50, they could maintain cocaine level above the satiety threshold only at 1.5 and 3 μmol/kg doses. During cocaine self-administration on FR50 at 0.1, 0.3, 0.5 and 0.75 μmol/kg doses, cocaine levels gradually declined through the compulsion zone while rats completed the 50 required presses. The injection of a small unit dose was not enough to maintain cocaine level within the compulsion zone. This ascending limb of the dose-response curve appears due to rats being unable to complete all injections in the compulsion zone on FR50 before cocaine level falls below the remission threshold. In cocaine self-administration sessions where session time is kept constant, the duration of responding increases with increasing unit doses until responding persists for the entire session. This results in an artifactual increase in the rate of responding as a function of a narrow range of lower unit doses and is exacerbated at FR50. There is no part of the dose-response function that is consistent with the positive reinforcing effects of cocaine.

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