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Reversal of Stress-Induced Analgesia by Apomorphine, but not by Amphetamine

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BODNAR, R. J., D. D. KELLY, M. BRUTUS, C. B. GREENMAN AND M. GLUSMAN. *Reversal of stress-induced analgesia by apomorphine, but not by amphetamine*. PHARMAC. BIOCHEM. BEHAV. 13(2) 171–175, 1980.—Acute exposure to severe stressors induce profound analgesia as well as depleting catecholamine levels. The present study examined whether d-amphetamine and apomorphine, agents which increase catecholamine availability, would alter the analgesic effectiveness of cold-water swims (CWS) and 2-deoxy-D-glucose (2-DG) as measured by an operant liminal escape procedure. Two groups of 10 rats each were tested to determine alterations in liminal escape threshold functions following amphetamine at doses of 0.25, 0.5, 1, 2 mg/kg and following apomorphine at doses of 0.025, 0.05, 0.1, 0.2 mg/kg. Half of the amphetamine and half of the apomorphine groups were tested across their respective dose ranges for the drug effects upon CWS analgesia. The remaining animals in each group received 2-DG (600 mg/kg IP) alone followed by 2-DG paired with each stimulant dose. No dose of amphetamine or apomorphine alone altered escape thresholds. While amphetamine produced slight potentiations of 2-DG analgesia at the two low doses, apomorphine at the 0.05 and 0.1 mg/kg doses returned CWS and 2-DG analgesia to within normal placebo values. These results provide indirect evidence for a role for brain norepinephrine and dopamine in stress-induced analgesia, and these data are discussed with respect to catecholamine involvement in pain-inhibitory processes.

Amphetamine Apomorphine Stress Analgesia Pain Cold-water swims 2-Deoxy-D-Glucose Rats

ACUTE exposure to a wide range of severe stressors produces a well-defined series of autonomic, neuroendocrine and behavioral responses [46], including analgesia [1, 2, 14, 15, 19, 27, 35, 39] and depletions in the brain catecholamines, norepinephrine and dopamine [9, 10, 38, 42, 48, 50, 51]. Chronic exposure over 12–14 days to such stressors as cold-water swims and inescapable foot shock results in adaptation to both the analgesic effects [20,39] and the catecholamine depletions [38, 48, 51]. Correspondingly, chronic pretreatment with the glucoprivic agent, 2-deoxy-D-glucose results in adaptation to its analgesic effects [13] and blocks the norepinephrine depletions induced by acute exposure to inescapable foot shock [44].

The present study examined whether the stress-induced alterations in brain catecholamines are responsible for the concomitant analgesic effects by administering pharmacological agents which increase the availability of catecholamines. The catecholaminergic psychomimetic, d-amphetamine [28, 43, 52], and the dopamine receptor agonist, apomorphine [3, 26, 30, 32], were examined for their dose-dependent effects upon analgesia induced by cold-water swims (CWS) and 2-deoxy-D-glucose (2-DG) injections. The analgesimetric measure employed was an operant psychophysical liminal escape procedure which has been shown to reflect both an organism's evaluation of the relative aversiveness of a given stimulus and its motivation to respond, or not, to terminate its presence [36,37]. In addition, the intertrial interval behavior generated by this procedure reliably indicates alterations in the organism's capability to respond and thereby serves to quantify the relative influence of non-specific factors in the determination of the analgesic response.

METHOD

Twenty male albino Holtzman Sprague-Dawley rats (350–500 g) were tested in a standard operant chamber (BRS/LVE) 26.5 cm high with a 30×24 cm grid floor composed of 14 grid bars (0.6 cm diameter) spaced 1.9 cm apart. Initially, each subject was shaped to terminate a train of pulsed foot shocks by pressing a 2-cm wide lever mounted on one wall 7-cm above the grid floor. Each animal was then exposed at the same time every day to a 9-session sequence of increasingly stringent escape contingencies which gradually approached the terminal fixed-ratio liminal escape schedule. The constant current, 200-Hz square-wave foot shock (300 msec on/300 msec off) trains were presented on each trial for 10 sec unless the rat pressed the lever three times to initiate a 20-sec intertrial interval. Responses made during the intertrial interval were recorded, but had no programmed consequences. Each session consisted of 100 trials distributed evenly over five shock intensities: 0.2, 0.4, 0.6, 0.8, 1.0 mA. The programmed shock intensity changed independently of the subject's behavior every four trials, such that every 20 trials the rat was exposed to all five intensities.

The order of shock intensities within successive 20-trial blocks was determined by a Latin Square design in which each intensity occupied a given ordinal position only once and in which no transition was ever repeated. The first 20 trials of each session were recorded separately to allow for behavioral warm-up and these less stable data are not included in the present analysis. From the last 80 trials of each session, the probability to escape and the amount of time spent in shock were recorded separately at each of the five shock intensities. In addition, the persistence of the rat to remain in contact with the lever during the intertrial interval was noted, given its sensitivity to possible disruptions in ongoing motor performance [12, 14, 23, 29, 31, 36, 37].

The first phase of the experimental sequence was designed to ascertain the dose-dependent effects of amphetamine and apomorphine upon liminal escape thresholds, and commenced after stable functions were established. Two matched groups of ten rats each were tested over four pairs of liminal escape sessions at weekly intervals. The first session of each pair was programmed as a control session while the second was programmed as an experimental session. Thirty min prior to the experimental sessions of the first group, intraperitoneal injections of d-amphetamine at doses of either 0.25, 0.5, 1.0, or 2.0 mg (1 ml 0.9% saline solution/kg body weight) were administered according to a Latin Square design. Correspondingly, twenty min prior to the experimental sessions of the second group, subcutaneous injections of apomorphine at doses of either 0.025, 0.05, 0.1 or 0.2 mg (1 ml 0.9% saline solution/kg body weight) were also administered according to a Latin Square design.

The second phase of the experimental sequence examined the dose-dependent effects of amphetamine and apomorphine upon CWS and 2-DG induced alterations in liminal escape thresholds over six sessions. In two sessions, a placebo injection was paired with either one stress condition or its control condition respectively. In the remaining four sessions, each of the doses of either amphetamine or apomorphine was paired with one stress condition. The session sequence was determined according to a Latin Square design. Half of the rats receiving amphetamine in the first phase of the experiment received the same doses of amphetamine paired with a forced 2°C cold-water swim for 3.5 min (AMP-CWS group). The remainder of the amphetamine-test animals received 2-deoxy-D-glucose (600 mg 2-DG/2 ml sterile water/kg body weight, IP) in the stress conditions (AMP-2DG group). All amphetamine injections and swims occurred 30 min before the liminal escape test while 2-DG injections were administered 60 min before testing. Similarly, half of the rats receiving apomorphine in the first phase of the experiment received the same doses of apomorphine paired with CWS (APO-CWS group), while the remaining apomorphine-test animals received 2-DG in the stress conditions (APO-2DG group). All apomorphine injections were administered 20 min before liminal escape testing.

RESULTS

Liminal escape thresholds were not altered significantly by administration of any dose of either amphetamine or apomorphine. However, as summarized in Fig. 1, the stress-induced alterations in liminal escape thresholds were altered by concomitant administration of notably apomorphine, but also amphetamine.

A three-way split-plot analysis of variance analyzing the time spent in shock revealed significant differences across

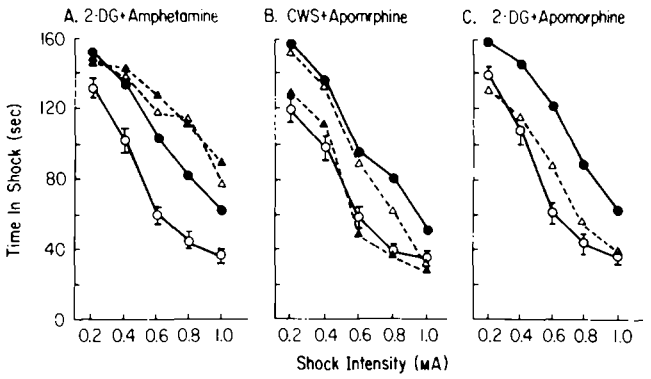

FIG. 1. Alterations in liminal escape thresholds as measured by time spent in shock over placebo (open circles ± SEM) values following acute exposure to: *A*. 2-DG alone (closed circles) or following its pairing with either 0.25 mg/kg (open triangles) or 0.50 mg/kg (closed triangles) of amphetamine. Note that these amphetamine doses potentiated the increased time in shock induced by 2-DG injections. *B*. CWS alone (closed circles) or following its pairing with either 0.05 mg/kg (open triangles) or 0.10 mg/kg (closed triangles) of apomorphine. Note that these apomorphine doses reduced the antinociceptive properties of CWS. *C*. 2-DG alone (closed circles) or following its pairing with 0.05 mg/kg (open triangles) of apomorphine which reduced the 2-DG analgesia.

the four groups, $F(3,80)=5.41$, $p<0.002$, across the five shock intensities, $F(4,80)=89.19$, $p<0.001$, and across the six experimental sessions, $F(5,720)=38.88$, $p<0.001$. A significant group by session interaction was also observed, $F(15,720)=3.77$, $p<0.01$. Similarly, a three-way split-plot analysis of variance analyzing escape probability revealed significant differences across the four groups, $F=4.87$, $p<0.004$, across the five shock intensities, $F=80.17$, $p<0.001$, and across the six experimental sessions, $F=29.73$, $p<0.001$. Again, a significant group by session interaction was also observed, $F=3.24$, $p<0.01$. Since the effects upon the two behavioral measures paralleled each other, all Post-hoc, paired Tukey comparisons will report only alterations in time spent in shock.

The catecholaminergic stimulants had the following effects upon CWS and 2-DG analgesia. First, no amphetamine dose was effective in altering significantly the increases noted in the time spent in shock following CWS. Second, no amphetamine dose lowered 2-DG analgesia. Indeed, 2-DG analgesia was significantly potentiated at moderate (0.6 mA) shock intensities when paired with the two lower amphetamine doses: 0.25 mg/kg: $t(4)=2.81$, $p<0.05$; 0.50 mg/kg: $t=3.15$, $p<0.05$. Third, apomorphine attenuated CWS analgesia in a dose-dependent U-shaped function. While the lowest (0.025 mg/kg) and highest (0.2 mg/kg) apomorphine doses failed to affect CWS analgesia, the 0.05 mg/kg and particularly the 0.1 mg/kg dose returned the liminal escape thresholds of CWS-stressed rats to within normal values at moderate (0.6 mA: $t(4)=3.71$, $p<0.05$) and high (0.8 mA: $t=3.94$, $p<0.05$; 1.0 mA: $t=2.54$, $0.10>p>0.05$) shock intensities such that these thresholds did not differ significantly from placebo values. Finally, no dose of apomorphine was capable of completely eliminating 2-DG analgesia, although the 0.05 mg/kg dose of apomorphine lowered the time spent in shock of 2-DG treated rats to within normal limits of placebo values (0.6 mA: $t=1.79$; 0.8 mA: $t=1.52$; 1.0 mA: $t=1.14$).

Inter-trial escape behaviors, as measured by the amount of bar-holding were altered significantly from placebo values following 2-DG, $F(9,90)=3.83$, $p<0.01$, but not CWS ($F=1.22$) treatments. Post-hoc Scheffé comparisons revealed that in the 2-DG Groups, both 2-DG alone and 2-DG paired with each and every dose of amphetamine lowered significantly bar-holding behavior. Thus, amphetamine failed to alter the decrements in operant escape behavior and inter-trial bar-holding induced by 2-DG alone. By contrast, each and every dose of apomorphine returned the 2-DG induced decrement in bar-holding back to within normal limits. Since only the 0.05 mg/kg dose eliminated 2-DG analgesia, apomorphine's effects upon pain thresholds and inter-trial behaviors were dissociable. Though CWS did not alter significantly bar-holding behavior, the decrements resemble the analgesic effects. While amphetamine paired with CWS yielded bar-holding decrements similar to CWS itself, the lower three doses of apomorphine paired with CWS produced inter-trial behavior indicative of placebo. Only the high, escape-disruptive dose of apomorphine paired with CWS ceded values similar to CWS.

DISCUSSION

The present study yielded five novel findings: (1) a wide dose range of the catecholamine stimulants, amphetamine and apomorphine, does not alter operant liminal escape thresholds; (2) amphetamine when paired with CWS does not alter CWS analgesia; (3) amphetamine when paired with 2-DG is capable of potentiating 2-DG analgesia at moderate doses; (4) moderate (0.05 and 0.1 mg/kg) doses of apomorphine reverse CWS analgesia to near placebo values; and (5) moderate (0.05 mg/kg) doses of apomorphine reverse 2-DG analgesia to near placebo values. Therefore, it seems that apomorphine, but not amphetamine has the ability to decrease the analgesic effectiveness of the CWS and 2-DG stressors.

These data provide further evidence that the analgesic properties of 2-DG and CWS share common characteristics. That these two stressors are subserved by similar pain-inhibitory processes is supported by the observations that 2-DG and CWS analgesia develop full and reciprocal cross-tolerance [47] and that high doses of naloxone are unable to eliminate their analgesic effects [16,18]. This is not to say that they possess identical modes of action. While 2-DG and morphine analgesia develop cross-tolerance and synergy effects [16,47], CWS analgesia does not exhibit any cross-tolerance with opiates [21]. Moreover, while 2-DG and morphine analgesia are potentiated in hypophysectomized animals [17], CWS analgesia is attenuated by this procedure [12]. Finally, CWS, but not morphine, analgesia is eliminated in rats either with diabetes insipidus [22] or medial-basal hypothalamic damage [11].

While one pharmacological effect of amphetamine is to stimulate release of transmitter from both norepinephrine and dopamine neurons, it also acts to inhibit reuptake of dopamine into the pre-synaptic cleft [28, 43, 52]. By contrast, apomorphine acts as a dopamine receptor stimulant [3, 26, 30, 52]. Administration of either apomorphine at doses as low as 0.1 mg/kg or amphetamine at doses as low as 0.25 mg/kg results in a profound depression in the firing rates of dopaminergic neurons with cells in the pars compacta of the substantia nigra recovering faster than cells in the midbrain ventral tegmental area [25]. However, mechanisms causing the depression in firing of dopaminergic neurons appear to differ for the two drugs. While amphetamine-induced depressions are eliminated by either diencephalic transections or lesions placed in the crus cerebri, apomorphine-induced depressions persist following these manipulations [24]. This suggests that while amphetamine-induced depressions may be mediated through a negative striato-nigral feedback loop as described by Groves and co-workers [34], apomorphine-induced depressions appear to be mediated by either pre-synaptic dopamine autoreceptors or post-synaptic dopamine receptors on dopamine neurons [24,30]. Such mediation has been used to explain the paradoxical effects of low apomorphine doses causing hypomotility and sedation and high apomorphine doses causing stereotypies and hypermotility [30,49] in that the former effects are presumed to be pre-synaptic and the latter post-synaptic. The present data appear to exhibit similar properties since low doses (0.05 and 0.1 mg/kg) of apomorphine decrease CWS and 2-DG analgesia, while a higher dose (0.2 mg/kg) slightly increases the analgesic effects. However, it is too premature to imply that these apomorphine effects are indeed mediated through such dopaminergic processes.

That the analgesic response to stress appears to be impervious to increased catecholamine availability induced by amphetamine or high doses of apomorphine differentiates this property of the stress response from the well-known deficits in avoidance and escape behavior induced by uncontrollable shock (see reviews: [4, 45, 54]). Although one explanation of these latter interference effects has been the "learned helplessness" hypothesis [40, 41, 45], alternative explanations have emphasized the importance of norepinephrine as well as other neurochemical depletions [5, 33, 53, 55]. Therefore, pharmacological approaches which vary neurochemical availability have been employed to evaluate these deficits. Administration of l-DOPA, which, like amphetamine, increases the availability of catecholamines, antagonizes the disruptive effects of inescapable foot shock [6,7]. By contrast, administration of apomorphine induced biphasic effects upon escape deficits. At a dose (0.3 mg/kg) comparable to that which reversed cold-water swim and 2-DG analgesia, shock-induced escape deficits were increased. Yet apomorphine at doses of 1.5 or 3 mg/kg reduced shock-induced escape deficits [7]. These data suggest that the mechanisms underlying the escape deficits and the analgesic responses induced by stress may differ despite the facts that: (a) the same CWS stressor exhibits adaptation to both analgesia [20] and escape deficits [55] following repeated exposure; and (b) that CWS pretreatment eliminates the development of shock-induced escape deficits. Further work is necessary to characterize the mechanisms involved in each of these consequences following acute exposure to severe stressors.

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