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Variations of Motor Activity Following Intraventricular (D-Pen^2, D-Pen^5)-Enkephalin Administration: Interaction With Acute Uncontrollable Foot-Shock in Mice

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MENDELLA, P. D. AND R. M. ZACHARKO. *Variations of motor activity Following intraventricular (D-Pen^2, D-Pen^5)-enkephalin administration: Interaction with acute uncontrollable foot-shock in mice.* PHARMACOL BIOCHEM BEHAV 53(4) 877–883, 1996. – The effects of intraventricular administration of (D-Pen^2, D-Pen^5)-enkephalin (DPDPE) (0.005, 1.0, and 2.5 μg/μl in a 1-μl vol.) on horizontal activity, rearing, and exploratory head dipping were assessed among CD-1 mice exposed to acute uncontrollable foot-shock 15 min following stressor termination. Foot-shock reduced horizontal activity, rearing, and exploratory head dipping during the immediate 15-min poststressor interval. Mice challenged with 0.005 μg DPDPE were behaviorally indistinguishable from vehicle-treated subjects. The 1.0-μg dose of DPDPE increased horizontal activity in stressed and nonstressed subjects. Intraventricular infusion of 2.5 μg DPDPE potentiated horizontal activity in previously stressed mice but had no effect in nonstressed animals. The suppression of rearing and exploratory head dipping following uncontrollable foot-shock was not ameliorated by the δ-receptor agonist, and DPDPE was without effect on rearing and exploratory head dipping in nonstressed animals. Potential neurochemical mechanisms associated with the expression of these stressor associated behaviors are discussed.

D-Pen^2, D-Pen^5-enkephalin Uncontrollable foot-shock Horizontal activity Rearing
Exploratory head dipping Mouse

CENTRAL administration of opioid peptides provokes alterations of locomotor activity in rats and mice (16,18). The development of selective μ-, δ- and κ-receptor agonists has permitted characterization of the contribution of such receptors to the expression of different aspects of locomotor activity (13,16). Indeed, data derived from these investigations have revealed that selective stimulation of the μ-, δ-, or κ-receptor differentially affects the qualitative and quantitative aspects of motor activity. For example, whereas μ- and δ-receptor agonists dose dependently increase horizontal activity, μ-agonists decrease and δ-receptor agonists may augment or have no effect on rearing in mice (17,18). Moreover, μ-agonists are more effective than δ-agonists in promoting horizontal activity (13). In contrast to the behavioral effects associated with μ- or δ-receptor agonists, selective stimulation of the κ-receptor has been shown to dose dependently decrease general levels of activity in mice (14,26).

The respective locomotor topographies associated with μ- and δ-receptor activation have been attributed, in part, to increased dopamine (DA) turnover within the mesolimbic system. For example, intraventricular or intracerebral administration of D-Ala^2,N-Me-Phe^4-Gly^5-ol-enkephalin (DAMGO) or (D-Pen^2, D-Pen^5)-enkephalin (DPDPE) augments DA turnover within the nucleus accumbens (7,15,25). Conversely, 6-hydroxydopamine (6-OHDA) lesions of the mesolimbic system or pretreatment with DA receptor antagonists attenuates the motor effects ordinarily induced by Try-D-Ala-Gly-NMe-Phe-Gly-ol (DAGO) or DPDPE (12). Taken together, these

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data suggest that the role of the μ- and δ-receptor in the maintenance of motor activity follow from the DA neuromodulatory influence of endogenous opioids within the mesocorticolimbic system.

In view of a potential interaction between opioid peptides and mesocorticolimbic DA, considerable emphasis has been devoted to an analysis of neuropeptide involvement in the expression of behavioral pathology. For example, in mice, acute uncontrollable stressors impair performance in a number of paradigms including shuttle escape performance (1), exploration (4), intracranial self-stimulation (28), and conditioned suppression of motility (11). The stressor-induced behavioral disturbances in these tasks have been attributed, in part, to perturbations of central DA activity (3). Indeed, exposure to a mild session of uncontrollable foot-shock elicits conspicuous alterations of DA turnover within the ventral tegmental area (VTA), nucleus accumbens, and medial prefrontal cortex (24). Interestingly, uncontrollable stressor exposure has also been associated with alterations of endogenous enkephalin availability in various central DA sites (10,21). Moreover, central μ- or δ-receptor agonist administration, or inhibition of the enkephalin-degrading enzyme, enkephalinase, has been associated with the alleviation of stressor-induced behavioral disturbances (11,20). Finally, the μ- and δ-receptor-dependent attenuation of behavioral pathology induced by uncontrollable foot-shock is blocked by 6-OHDA lesions as well as low-dose apomorphine or pimozide pretreatment (12). Taken together, these findings suggest that behavioral impairments associated with uncontrollable stressor exposure may be subserved in part, by an interaction between mesolimbic DA and opioid activity.

Previous investigations have described the locomotor profiles associated with central DPDPE administration (17,18), while other laboratories have assessed the effects of δ-receptor agonists on foot-shock-conditioned motoric impairments (11) or the forced swim paradigm (20). Nevertheless, data pertaining to δ-receptor activation and foot-shock-induced alterations in locomotor topography during the immediate post-stressor interval are currently unavailable. The purpose of the present investigation was to evaluate the effects of intraventricular DPDPE administration on stressor-induced changes in horizontal activity, rearing, and exploratory head dipping in the CD-1 mouse. In view of the participation of DA in the promotion of stressor-associated variations of motor activity and the modulatory influence of DPDPE on central DA turnover, the δ-receptor agonist was expected to ameliorate the suppressive influence of uncontrollable foot-shock on behavioral responsivity in the CD-1 mouse.

METHODS

Subjects

Forty-eight naive male CD-1 mice, obtained from the Charles River Laboratory (St. Constant, Quebec, Canada) at 5 wk of age were habituated to the laboratory for 7 wk. Mice were housed in groups of four in polypropylene cages with food and water provided ad lib. Subjects were maintained on a 12 L : 12 D cycle (light on at 0700–1900 h), and all testing was conducted during the light cycle.

Surgery

Mice were anesthetized with sodium pentobarbital (Somnotol) and stereotaxically implanted with a cannula in the lateral ventricle (A.P. +0.8 mm from Bregma, L. +0.7 mm from the midline, and V. −2.8 mm from a flat skull surface), using a David Kopf Micromanipulator (Tujunga, CA). The cannulae, constructed from 23-ga hypodermic needles, were cut to a length of 1.1 cm and fitted with a 30-ga stylette. Following surgery, animals were individually housed on a warm heating pad for at least 3 days and regular diet was supplemented with a Sustagen (Mead Johnson, Evansville, IN) wet mash.

Apparatus

Horizontal activity, rearing, and exploratory head dipping were measured in black aluminum activity tubs (28 cm diam. × 32.5 cm high) (Carleton Technology Centre). Horizontal activity was recorded by the interruption of photobeams mounted 0.5 cm above the tub floor. Rearing was recorded by a separate series of photobeams positioned 7 cm above the tub floor. Head dipping was measured as the number of interruptions of a photoelectric beam placed 0.5 cm below the floor of the activity tub in one of two wells (2 cm diam.). Data were recorded by a Macintosh computer employing a Tub Monitor program (Schnabel Electronics, Saskatoon, Saskatchewan, Canada).

Foot-shock was administered in Plexiglas boxes (30 × 40 × 15 cm), with the floor of each box consisting of 0.32-cm stainless-steel rods spaced 1 cm apart, connected in series by neon bulbs. The end walls of each box were lined with stainless-steel plates connected in series with the grid floor. Foot-shock (150 μA, 60 × 6 s, 59-s intertrial interval) was delivered by a microcomputer-controlled 3000-V source (Carleton Technology Centre).

Procedure

Following a 10-day postoperative recovery period, all subjects were introduced to the locomotor tubs to establish baseline levels of horizontal activity, rearing, and exploratory head dipping. Behavioral measures were recorded at 3-min intervals over a 45-min test session. Animals were tested for 15 min and then removed from the tub and handled in a manner simulating handling during intraventricular drug administration. Subjects were then reintroduced into the tub and behavioral testing proceeded for 30 min. This protocol was followed for 3 days, and the data derived from days 2 and 3 were used in deriving baseline measures.

Using mean horizontal activity levels to match subjects, half of the mice either received uncontrollable foot-shock (n = 24) or were exposed to the shock apparatus for a identical period of time but did not receive foot-shock (n = 24). Following Shock or No-shock treatment, animals in each group were further subdivided (n = 6/cell), placed in the activity chambers, and tested for 15 min. Mice were subsequently removed from the activity tubs and injected intraventricularly with vehicle or DPDPE (0.005, 1.0, or 2.5 μg). Pilot studies revealed that intermediate doses of DPDPE (0.01, 0.05, and 0.1 μg) induced alterations of horizontal activity which were indistinguishable from the data derived with the 1.0-μg dose of the δ-agonist (data not shown). Intraventricular injections were delivered in a 1-μl vol. of sterile saline over a 1-min period employing a Hamilton (Bonaduz, Switzerland) 5-μl syringe connected to a 30-ga injector by polyethylene tubing. Following drug administration, the microinjector was left in place for 1 additional min. At the conclusion of the injection, the stylette was replaced and the animal returned to the locomotor tub and tested for 30 min.

Histology

All subjects were overdosed with sodium pentobarbital and perfused intracardially with physiological saline followed by a 10% formalin solution. The brains were removed from the cranial cavity and stored in formalin for at least 1 wk before histologic assessment. At this time, brains were blocked in a rostral-caudal plane and sectioned on a microtome. Frozen coronal sections (40 μm) were subsequently stained with cresyl violet and examined under a microscope to verify ventricular cannula placement.

Statistical Analyses

Analysis of variance (ANOVA) for repeated measures was conducted on the data corresponding to the 15-min period immediately following the Shock or No-shock conditions to assess the effects of the stressor before DPDPE administration. A separate ANOVA for repeated measures was also performed on the behavioral data corresponding to the 15- to 45-min interval to assess the interaction between Shock and Drug treatment across Time. Newman-Keuls multiple comparisons (α = .05) were conducted where appropriate.

RESULTS

Confirmation of lateral ventricular cannula placement was accomplished for all animals. In cases of tissue displacement, severe tissue necrosis, or evidence of drug diffusion from the lateral ventricle, the animal was excluded from statistical analyses.

Inspection of the exploratory head-dipping scores revealed extremely low operant rates at each of the test intervals. Accordingly, cumulative head dipping was averaged for the two chamber wells for each animal, and Time was excluded from all analyses involving this behavior. Due to equipment malfunction, the rearing data for one mouse in the No-shock/1.0-μg DPDPE group and the exploratory head-dipping data for one subject in the No-shock/0.005-μg DPDPE group were excluded.

Baseline Data

The ANOVA of baseline horizontal activity revealed a significant Time × Shock × Drug interaction [$F(42, 560) = 1.51, p < 0.05$]. Newman-Keuls multiple comparisons associated with this interaction failed to reveal significant differences between mice assigned to the various treatment groups. As such, the significant interaction was attributed to within-group performance deterioration associated with habituation to the testing environment. The ANOVA of baseline rearing [$F(42, 546) = 1.30, p > 0.05$] and exploratory head dipping [$F(3, 39) = 1.50, p > 0.05$] revealed that mice did not differ significantly across these measures.

Immediate Poststressor Behavioral Analysis

The ANOVA revealed a significant main effect of foot-shock on horizontal activity [$F(1, 46) = 33.05, p < 0.01$], rearing [$F(1, 45) = 43.31, p < 0.01$] and cumulative head dipping [$F(1, 45) = 32.18, p < 0.01$] during the 15-min period immediately following termination of the stressor. The stressor-induced performance deficits in horizontal activity (Fig. 1A) and rearing (Fig. 1B) persisted over the course of the test session. Moreover, mice exposed to uncontrollable foot-shock demonstrated a significant decrease in total exploratory head-dipping scores relative to mice in the No-shock condition (Fig. 1C).

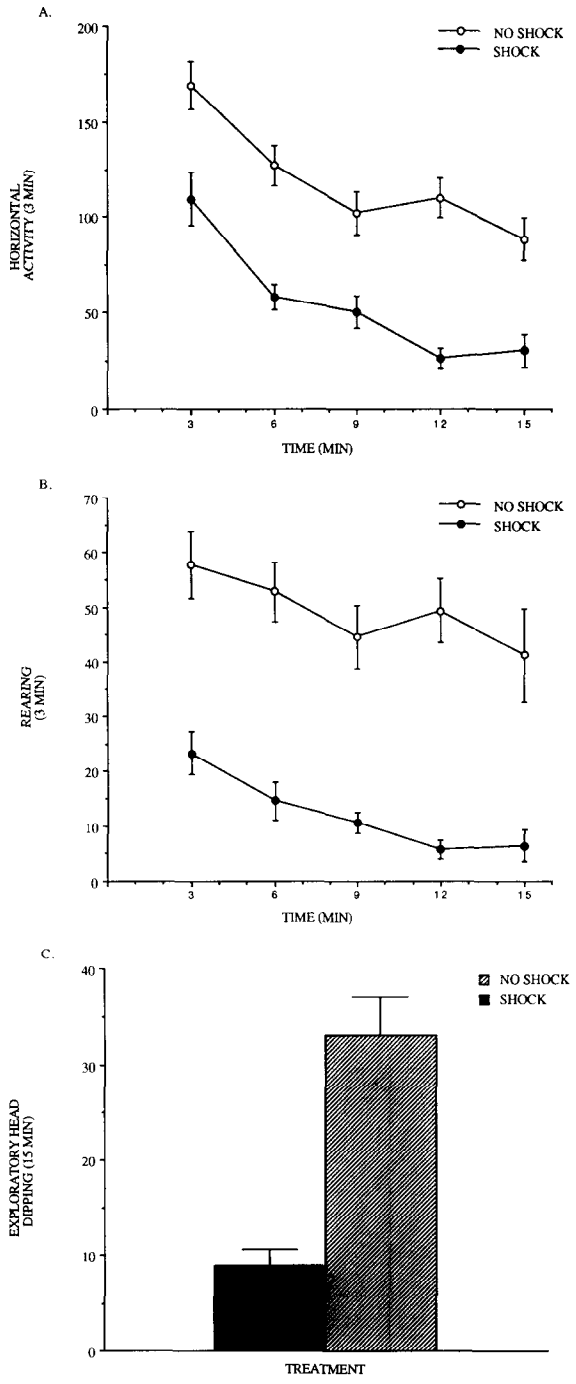

FIG. 1. Mean levels (± SEM) of horizontal activity (A), rearing (B), and exploratory head dipping (C) among CD-1 mice exposed to acute uncontrollable foot-shock or no shock. Locomotor activity and rearing were assessed at 3-min intervals during the immediate 15-min poststressor interval; exploratory head dipping was evaluated over the entire 15-min test session.

Postintraventricular DPDPE Behavioral Analysis

The ANOVA of horizontal activity, rearing, and exploratory head-dipping scores of mice exposed to foot-shock and intraventricular DPDPE administration revealed a significant

Shock × Drug [$F(3, 40) = 4.63$, $p < 0.01$] interaction for horizontal activity (Fig. 2A and 2B). In contrast, a significant interaction between the stressor and drug treatment was not apparent with respect to rearing [$F(3, 39) = 0.16$, $p > 0.05$] (Fig. 3A and 3B) or exploratory head dipping [$F(3, 39) = 0.76$, $p > 0.05$) (Fig. 4A and 4B).

Newman-Keuls multiple comparisons associated with the Shock × Drug interaction for horizontal activity revealed that vehicle or 0.005 μg DPDPE did not influence horizontal activity of stressed or nonstressed mice. In contrast, the 1.0-μg dose of DPDPE elevated horizontal activity scores of both stressed and nonstressed mice relative to mice within the respective vehicle or 0.005-μg DPDPE groups. Finally, although 2.5 μg DPDPE did not exert a significant influence on horizontal activity of nonstressed mice, the identical dose of DPDPE potentiated horizontal activity among mice subjected to foot-shock relative to stressed mice in the remaining drug treatment groups. Moreover, stressed mice receiving 2.5 μg DPDPE exhibited significantly elevated horizontal activity scores compared to nonstressed subjects receiving the identical dose of DPDPE.

The ANOVA of the behavioral scores corresponding to the postintraventricular drug administration period also revealed

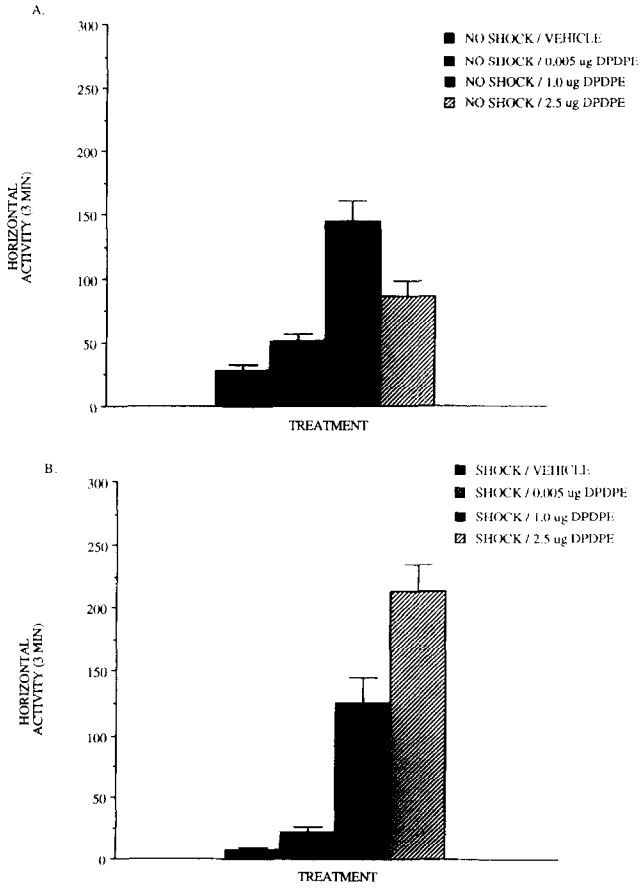

FIG. 2. Mean cumulative horizontal activity scores (± SEM) of nonshocked (A) and shocked (B) mice challenged intraventricularly with vehicle (0.0 μg) or 0.005, 1.0, or 2.5 μg of DPDPE. Horizontal activity was assessed for a 30-min period, at 3-min intervals, immediately following intraventricular injection with vehicle or DPDPE.

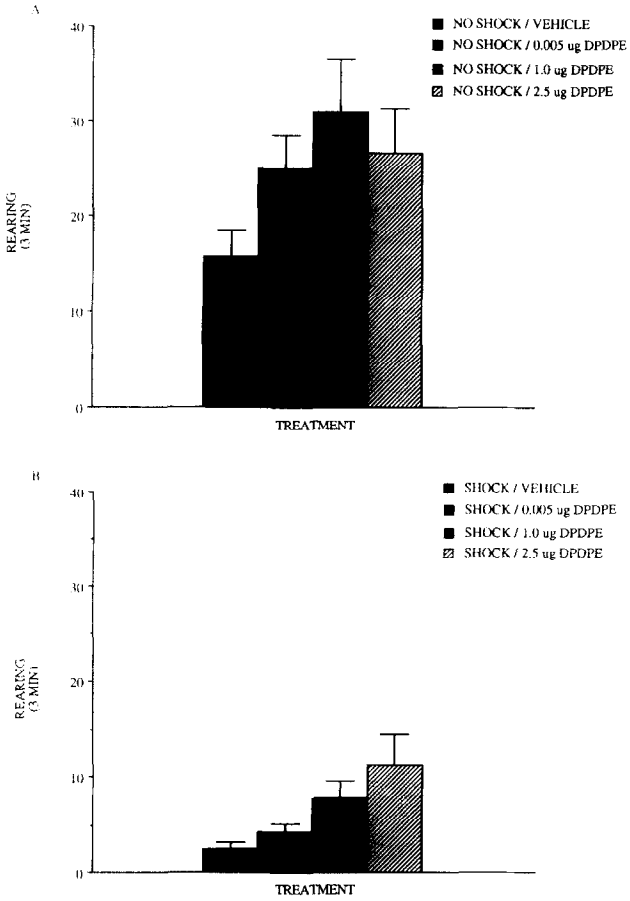

FIG. 3. Mean cumulative rearing scores (± SEM) of nonshocked (A) and shocked (B) mice challenged intraventricularly with vehicle (0.0 μg) or 0.005, 1.0, or 2.5 μg of DPDPE. Rearing was assessed for a 30-min period, at 3-min intervals, immediately following intraventricular injection with vehicle or DPDPE.

a significant Time × Drug interaction for both horizontal activity [$F(27, 360) = 1.70$, $p < 0.05$] and rearing [$F(27, 351) = 2.21$, $p < 0.01$]. Newman-Keuls multiple comparisons of the significant Time × Drug interaction for horizontal activity revealed that the performance of vehicle and 0.005-μg DPDPE-treated mice were comparable. Mice treated with either the 1.0- or 2.5-μg dose of DPDPE exhibited increased horizontal activity relative to vehicle or 0.005 μg DPDPE-treated mice at six and seven of the 10 3-min test intervals examined, respectively. In contrast, posthoc comparisons pertaining to the Time × Drug interaction for rearing revealed that 1.0 μg DPDPE induced an increase in rearing scores compared to vehicle-treated mice only at the 30-min test interval, whereas the 2.5-μg dose of DPDPE was without effect at any of the test intervals examined (data not shown).

DISCUSSION

Exposure to uncontrollable foot-shock provokes behavioral deficits in shuttle escape performance (1) and exploratory behavior (4), and induces conditioned suppression of motility (11). Consistent with such observations, mice exposed to acute uncontrollable foot-shock in the present investigation exhibited significant decreases in horizontal activity, rearing, and

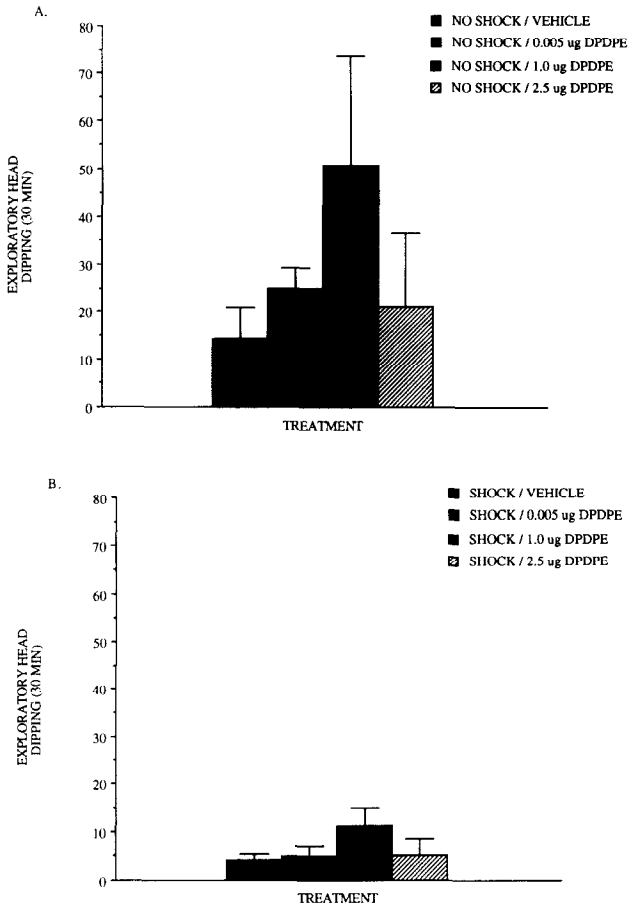

FIG. 4. Mean cumulative exploratory head-dipping scores (± SEM) of nonshocked (A) and shocked (B) mice challenged intraventricularly with vehicle (0.0 μg) or 0.005, 1.0, or 2.5 μg of DPDPE. Rearing was assessed for a 30-min period immediately following intraventricular injection with vehicle or DPDPE.

exploratory head dipping. Although stressor-induced disruptions of motor activity have ordinarily been attributed to perturbations of central norepinephrine, DA, and/or serotonin activity (2,7), uncontrollable foot-shock also alters met- and leu-enkephalin concentrations in discrete regions of the mouse and rat brain (10,21). Indeed, such neuropeptide alterations have been implicated in the expression of behavioral pathology (27).

Uncontrollable stressors typically evoke increased DA release and promote accumulation of DA metabolites in the medial prefrontal cortex (24) and nucleus accumbens (23). In view of the role of mesocorticolimbic DA in the expression of locomotor activity (5), it is tempting to suggest that the stressor-associated deficits in horizontal activity, rearing, and exploratory head dipping in the present investigation follow from variations of mesocorticolimbic DA activity. Moreover, stressor-induced disruption of central enkephalinergic activity may potentiate DA alterations and exacerbate behavioral pathology.

Intraventricular administration of 1.0 μg DPDPE increased horizontal activity among mice exposed to either the uncontrollable foot-shock or no-shock treatment conditions. In contrast, the 2.5-μg dose of DPDPE reversed the deleterious effects of uncontrollable foot-shock on horizontal activity but had no effect in nonstressed animals. Such findings are commensurate with previous reports that activation of the δ-opioid receptor is associated with a potentiation of horizontal activity over a range of doses in rats (13) and mice (17). In addition, these data are consistent with the finding that deficits in motor activity in mice resulting from exposure to the cues associated with uncontrollable foot-shock presentation are prevented by pretreatment with the δ-receptor agonist (D-Ala^2, D-Leu^5)-enkephalin (DADLE) (11).

The potentiating effects of the 1.0- and 2.5-μg doses of DPDPE on horizontal activity noted in the present investigation may have been occasioned, in part, by the influence of DPDPE on DA cell bodies within the VTA. Indeed, intraventricular administration of DPDPE has been shown to increase DA synthesis and enhance DA metabolism in the nucleus accumbens but not the striatum (15). Interestingly, both intra-VTA as well as intraaccumbens opioid administration have been associated with elevated levels of horizontal activity, but only intra-VTA opioids effected increased DA activity in the nucleus accumbens (9). Moreover, the locomotor potentiating effects of intra-VTA opioid peptides, as well as the reversal of stressor-induced motoric impairments by an intraventricularly administered δ-agonist, are abolished by DA antagonist pretreatment or destruction of mesolimbic DA neurons following 6-OHDA administration (9,12). These data suggest that in some instances, the motoric effects induced by opiate peptides in general and δ-receptor agonists in particular are mediated by mesolimbic DA activity. It should be emphasized nevertheless that central opiate peptide administration potentiates locomotor activity in sites other than the mesolimbic system, including the globus pallidus and substantia nigra, and these behavioral effects are DA independent (9). Taken together, these findings suggest that the activating effects of 1.0 μg DPDPE as well as the reversal of foot-shock-induced decrements in horizontal activity by 2.5 μg DPDPE may be accounted for in part by a DA-dependent or DA-independent interface within the mesotelencephalic system.

If it is assumed that the decrements in horizontal activity exhibited by stressed mice are attributable in part to stressor-induced decreases in mesocorticolimbic DA availability, the 2.5-μg dose of DPDPE may have induced horizontal activity by "reactivating" DA neurons. In fact, a recent investigation employing microdialysis revealed that among rats exhibiting decreased levels of mesolimbic DA, DOPAC, and HVA during a protracted session of restraint stress, release from restraint effected a significant increase in mesolimbic DA release and metabolite concentrations (22). The sudden elevation in mesolimbic DA activity was attributed to emotional arousal, triggered by environmental change (release from restraint). These findings suggest that mesolimbic DA is not invariably depleted following exposure to an uncontrollable stressor, but rather that availability is decreased. As such, it is conceivable that pharmacological manipulations which augment DA activity may reverse stressor-induced locomotor deficits associated with DA hypoactivity.

It will be recalled that 1.0 μg of DPDPE elicited hyperactivity to a comparable degree among stressed and nonstressed mice, whereas the 2.5-μg dose of DPDPE was without effect in nonstressed mice. Such data are not incompatible with the proposition that 2.5 μg of DPDPE elicits hyperactivity in stressed mice by reactivating DA neurons in the mesolimbic system. It is conceivable that among mice exposed to foot-shock, 2.5 μg of DPDPE is sufficient to "reactivate" mesolimbic neurons and promote horizontal activity. However, among

nonstressed presumably neurochemically intact (i.e., DA) mice, the increase in mesolimbic DA induced by the 2.5-μg dose of DPDPE may promote DA autoregulatory activity, precluding the appearance of behavioral hyperactivity. It may be noted parenthetically that behavioral hyperactivity induced by 2.5 μg DPDPE has been detected in C57BL/6J mice, although systematic increases of hyperactivity were not evident at higher doses of the δ-agonist (i.e., 30 μg) (18). Although interstrain variability in the behavioral responsivity to δ-receptor stimulation is conceivable (C57BL/6J cf. CD-1 strain), the 2.5-μg dose of DPDPE just failed to provide a statistically acceptable level of significance in the present investigation.

Stimulation of different opioid receptor subtypes qualitatively affects the locomotor topographies exhibited by mice. In contrast to the activating effects of DPDPE on horizontal activity, DPDPE had no effect on rearing or exploratory head dipping. These data suggest that the mechanisms subserving expression of the latter behaviors may be independent of those underlying horizontal activity, or may not be affected by DPDPE in the dose range employed in the present experiment. Although these data appear to be inconsistent with the demonstration of a DPDPE-induced increase in rearing in CD-1 Swiss albino mice (17), the microinjection volume employed and the deployment of intraventricular administration in conscious noncannulated animals compromise data interpretation in the comparison study. Interestingly, whereas failure to detect an influence of DPDPE on rearing has been reported, these effects appeared in C57BL/6J mice, which raises the issue of drug-dependent interstrain variability (18). There are, however, no data to date which assess the effects of δ-receptor stimulation on exploratory head dipping in either stressed or nonstressed mice. Taken together, there is a relative paucity of data to permit a conclusion regarding the effects of intraventricular DPDPE administration in mice on either rearing or exploratory head dipping in the CD-1 mouse strain.

In summary, the data of the present investigation suggest that the selective δ-receptor agonist DPDPE dose-dependently reverses the effects of uncontrollable foot-shock on horizontal activity. In contrast, DPDPE failed to influence rearing or exploratory head dipping among nonstressed mice and failed to attenuate the suppressive effects of uncontrollable foot-shock on these latter behaviors. These data support the notion that neuropeptides in general and leu-enkephalin in particular are activated in response to aversive stimulation and may modulate behavioral responsivity to a stressor (8). However, the diverse neurochemical profiles associated with stressor-induced pathology preclude expectation that the entire repertoire of stressor associated behavioral change would be ameliorated following δ-receptor activation. These findings underscore the importance of employing a multidimensional analysis of behavior in the assessment of the relative contribution of specific neuropeptides to the alleviation of pathology following stressor exposure.

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