Depressive-Like Effects of the \( \kappa \)-Opioid Receptor Agonist Salvinorin A on Behavior and Neurochemistry in Rats

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ABSTRACT

Endogenous opioids seem to play a critical role in the regulation of mood states. For example, there is accumulating evidence that stimulation of \( \kappa \)-opioid receptors, upon which the endogenous opioid dynorphin acts, can produce depressive-like behaviors in laboratory animals. Here we examined whether systemic administration of salvinorin A (SalvA), a potent and highly selective \( \kappa \)-opioid agonist, would produce depressive-like effects in the forced swim test (FST) and intracranial self-stimulation (ICSS) test, which are behavioral models often used to study depression in rats. We extracted, isolated, and purified SalvA from Salvia divinorum plant leaves and examined its effects on behavior in the FST and ICSS test across a range of doses (0.125–2.0 mg/kg) after systemic (intraperitoneal) administration. SalvA dose dependently increased immobility in the FST, an effect opposite to that of standard antidepressant drugs. Doses of SalvA that produced these effects in the FST did not affect locomotor activity in an open field. Furthermore, SalvA dose dependently elevated ICSS thresholds, an effect similar to that produced by treatments that cause depressive symptoms in humans. At a dose that caused the depressive-like effects in both the FST and ICSS assays, SalvA decreased extracellular concentrations of dopamine (DA) within the nucleus accumbens (NAc), a critical component of brain reward circuitry, without affecting extracellular concentrations of serotonin (5-HT). These data provide additional support for the hypothesis that stimulation of brain \( \kappa \)-opioid receptors triggers depressive-like signs in rats and raise the possibility that decreases in extracellular concentrations of DA within the NAc contribute to these effects.

Although much research on depression has focused on brain norepinephrine and serotonin (5-HT) systems, there is substantial evidence that other systems have important roles in the neurobiology of mood and affective disorders. For example, the mesolimbic dopamine (DA) system—which projects from the ventral tegmental area to the nucleus accumbens (NAc)—contributes importantly to the hedonic (rewarding) effects of food, sexual behavior, and experience reward) (Wise, 1982), a hallmark sign of clinical depression. The mesolimbic DA system is modulated by noradrenergic and serotonergic inputs (Pasquier et al., 1977), as well as endogenous opioid peptides (Devine et al., 1993; Shippenberg and Rea, 1997; Svingos et al., 1999). Agents that selectively affect the function of \( \kappa \)-opioid receptors cause profound alterations in mood in humans (Pfeiffer et al., 1986; Roth et al., 2002) and motivated behaviors in laboratory animals (Shippenberg and Herz, 1987; Todtenkopf et al., 2004), suggesting that manipulations targeting brain \( \kappa \)-opioid systems might be useful in the study and treatment of depressive disorders.

ABBRIVIATIONS: 5-HT, serotonin; NAc, nucleus accumbens; CREB, cAMP-response element-binding protein; E-2078, N-CH\(_2\)-Tyr-Gly-Gly-Phe-Leu-Arg-NH\(_2\); HPLC, high-performance liquid chromatography; ICSS, intracranial self-stimulation; DMSO, dimethyl sulfoxide; FST, forced swim test; UI-50488H, trans-\((-\))\(-\)-3,4-dichloro-N-methyl-N-\([1\)-pyrrolidin][cyclhexyl]benzeneacetamide methane sulfonate salt; U-69593; (\(\alpha\),\(\alpha\),\(\beta\),\(\beta\))-N-methyl-N-\([1\)-pyrrolidin][1-oxaspiro[4,5]dec8-y]-benzenecacetamide; SalvA, salvinorin A; SSRI, selective serotonin reuptake inhibitor; ANOVA, analysis of variance.
Molecular studies in rodents suggest that complex experience-dependent alterations in the function of \( \kappa \)-opioid systems within the NAc contribute to the development and expression of depressive behaviors. For example, stress elevates the activity of the transcription factor CREB within the NAc (Pliakas et al., 2001). Selective elevation of CREB function within the NAc increases immobility behavior in the forced swim test (FST) (Pliakas et al., 2001), a model often used to study depression. This effect is opposite to that caused by standard antidepressants and thus is a potential sign of depressive-like states (Porsolt et al., 1977; Cryan et al., 2002). Elevated expression of CREB in the NAc also reduces the rewarding effects of cocaine, a putative sign of anhedonia (Carlezon et al., 1998; Pliakas et al., 2001). The depressive-like behavioral effects that accompany elevated CREB function within the NAc seem related, at least in part, to CREB-regulated transcription of dynorphin, an endogenous \( \kappa \)-opioid receptor ligand (Carlezon et al., 1998). The \( \kappa \)-antagonist norbinaltorphimine attenuates the behavioral effects of elevated CREB expression within the NAc (Carlezon et al., 1998; Pliakas et al., 2001), suggesting a role for this receptor subtype in the expression of depressive-like behaviors. \( \kappa \)-Antagonists also have antidepressant-like effects in normal rats (Pliakas et al., 2001; Mague et al., 2003; McLaughlin et al., 2003), even when microinjected directly into the NAc (Newton et al., 2002). In contrast, stimulation of \( \kappa \)-receptors in rats produces complex behaviors that might reflect depressant-like or dysphoric-like states. The \( \kappa \)-agonist U-69593 establishes conditioned place aversions (Shippenberg and Herz, 1987), increases immobility in the FST (Mague et al., 2003), and elevates ICSS thresholds (Todtenkopf et al., 2004). These findings are consistent with the observation that \( \kappa \)-agonists produce depressant or dysphoric states in humans (Pfeiffer et al., 1986). The mechanism of these effects likely involves reduced DA function. \( \kappa \)-Agonists decrease extracellular concentrations of DA within the NAc (DiChiara and Imperato, 1988; Spanagel et al., 1992; Devine et al., 1993) through stimulation of \( \kappa \)-receptors that regulate DA release from mesolimbic neurons (Donzanti et al., 1992; Shippenberg and Rea, 1997; Svingos et al., 1999). Considered together, these findings raise the possibility that elevated CREB-mediated transcription of dynorphin within the NAc leads to increased \( \kappa \)-receptor activity, which decreases local DA function and triggers certain signs of depression.

Salvinorin A (SalvA) is a psychoactive compound found in the leaves of *Salvia divinorum*, a plant from the mint family (Roth et al., 2002). Binding and function studies indicate that SalvA is a potent and highly selective \( \kappa \)-agonist, with greater efficacy than that of the synthetic \( \kappa \)-agonists U-50488H and U-69593 (Roth et al., 2002; Chavkin et al., 2004; Munro et al., 2005). SalvA is non-nitrogenous and has no structural similarity with other opioid agonists, making it an ideal agent with which to further examine relationships among dynorphin, \( \kappa \)-opioid receptors, and depressive behavior. The present studies were designed to examine the effects of SalvA in tests (FST, ICSS) that have previously identified the depressive-like effects of U-69593 (Mague et al., 2003; Todtenkopf et al., 2004) and other treatment regimens (e.g., drug withdrawal) that cause depression in humans (Cryan et al., 2002). We also examined the effects of SalvA on locomotor activity to determine whether it causes nonspecific behavioral suppression that might complicate data interpretation. Finally, we examined the effects of SalvA on extracellular concentrations of DA and serotonin within the NAc using in vivo microdialysis in freely moving rats.

### Materials and Methods

**Rats.** A total of 129 male Sprague-Dawley rats (Charles River Laboratories, Boston MA) were used in these studies. Rats used for forced swim testing or locomotor activity testing were housed in groups of four and weighed 250 to 350 g at the time of testing, whereas those used for ICSS testing or brain microdialysis were housed singly and weighed 350 to 400 g at the time of stereotaxic surgery. All rats were maintained on a 12-h light (7:00 AM to 7:00 PM)/12-h dark cycle with free access to food and water, except during testing. Experiments were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication 85-23, 1996) as well as McLean Hospital and National Institute on Drug Abuse-Intramural Research Program policies.

**Salvinorin A.** Dried *S. divinorum* leaves were purchased from Salvia Space (Lawrence, KS). SalvA (Fig. 1) was extracted, isolated, and purified using published methods with minor modifications (see Lee et al., 2005 and references therein). In brief, the leaves were treated sequentially with hexane and acetone. The acetone extract was purified by chromatography on activated carbon, and SalvA was crystallized from acetone and methanol to yield a white crystalline solid. Spectroscopic analyses confirmed that the SalvA obtained with these methods is chemically identical to that described in other reports (Roth et al., 2002). The samples used for testing were determined by HPLC to be >99% pure. SalvA was dissolved in a vehicle of 75% dimethyl sulfoxide (DMSO), 25% distilled water and was administered by i.p. injection in a volume of 1 ml/kg.

**Forced Swim Test.** Forty rats were used to study the effects of SalvA in the FST. The FST is a two-day procedure in which rats swim under conditions where escape is not possible. On the first day, the rats are forced to swim for 5 min. The rats initially struggle to escape from the water, but eventually they adopt a posture of immobility in which they make only the movements necessary to keep their heads above water. When the rats are retested 24 h later, immobility is increased. Treatment with standard antidepressant drugs within the 24-h period between the first exposure to forced swimming and retesting can block facilitated immobility, an effect correlated with antidepressant efficacy in humans (Porsolt et al., 1977; Detke et al., 1995).

On the first day of the FST, rats were placed in clear 65-cm tall, 25-cm diameter Plexiglas cylinders filled to 48 cm with 25°C water.

![Fig. 1. Chemical structure of salvinorin A, a potent, efficacious, and highly selective non-nitrogenous \( \kappa \)-opioid receptor agonist.](image-url)
After 15 min of forced swimming, the rats were removed from the water, dried with towels, and placed in a warmed enclosure for 30 min. The cylinders were emptied and cleaned between rats. Rats (6–8 per treatment condition) received three separate injections of Salva (0.125–2.0 mg/kg, i.p.) at 1, 19, and 23 h after the first exposure to forced swimming. This is a commonly used treatment regimen (Porsolt et al., 1977; Detke et al., 1995) that we followed to enable qualitative comparisons with previous studies of agents with antidepressant-like and prodepressant-like effects (Mage et al., 2003). At 24 h after the first forced swim, rats were retested for 5 min (300 s) under identical swim conditions. Retest sessions were videotaped from the side of the cylinders and scored using a behavioral sampling method (Detke et al., 1995; Mage et al., 2003) by raters unaware of the treatment condition. Rats were rated at 5-s intervals throughout the duration of the retest session; at each 5-s interval, the predominant behavior was assigned to one of four categories: immobility, swimming, climbing, or diving. A rat was judged to be immobile if it was making only movements necessary to keep its head above water, climbing if it was making forceful thrashing movements with its forelimbs directed against the walls of the cylinder, swimming if it was actively making swimming movements that caused it to move within the center of the cylinder, and diving if it swam below the water toward the bottom of the cylinder. (Data quantifying diving behavior is not shown in the present report because it rarely occurred, and it was not affected by any of the treatments tested.) This behavioral sampling method differentiates certain classes of antidepressant drugs. For example, tricyclic antidepressants decrease immobility and increase climbing without affecting swimming, whereas selective serotonin reuptake inhibitors (SSRIs) decrease immobility and increase swimming without affecting climbing (Detke et al., 1995). It is also sensitive to treatments that cause depressive effects in humans, including antimanic agents and drug withdrawal (Carlezon et al., 2002; Cryan et al., 2002).

The number of occurrences (to a maximum of 60) of each category of behavior was analyzed using separate one-way (treatment) analyses of variance (ANOVA). Significant effects were analyzed using post hoc Newman-Keuls tests.

**Locomotor Activity.** Fifty-eight rats were used to determine whether the doses of Salva examined in the FST studies altered locomotor activity. These studies were conducted exactly as the FST studies had been conducted until the point of re-testing; i.e., all rats (8–11/group) underwent the first day of the FST and were treated with Salva at the normal pretreatment times (1, 19, and 23 h after swimming). At 24 h after the first exposure to forced swimming, the rats were placed for 1 h in automated E × 3.2 × 32.5 cm L × W × H activity chambers (MED Associates, St. Albans, VT) instead of being retested in the FST. The total number of activity counts (photocell beam breaks) during the 30-min test session was quantified in 5-min bins, and differences among the treatment groups were analyzed using a one-way ANOVA (for total counts) and a two-way (treatment × time) ANOVA with repeated measures.

**ICSS.** Each of seven rats was anesthetized with a mixture of ketamine plus xylazine (80 mg/kg plus 12 mg/kg i.p.; Sigma-Aldrich, St. Louis, MO), and given subcutaneous atropine sulfate (0.25 mg/kg) to reduce bronchial secretions. Each rat was then implanted with a monopolar stainless steel electrode (0.250-mm diameter; Plastics One, Roanoke, VA) aimed at the left medial forebrain bundle at the level of the lateral hypothalamus (2.8 mm posterior to bregma, 1.7 mm lateral from the midsagittal suture, and 7.8 mm below dura; Paxinos and Watson, 1986). The electrodes were coated with polyamide insulation, except at the flattened tip. Skull screws (one of which served as the ground) and the electrode were secured to the skull with dental acrylic.

After at least one week of recovery, the rats were trained on a continuous reinforcement schedule (FR1) to respond for brain stimulation using procedures described previously (Toltenkopf et al., 2004). Each lever-press earned a 0.5-s train of square-wave cathodal pulses (0.1-ms pulse duration) at a set frequency of 141 Hz. The delivery of the stimulation was accompanied by the illumination of a 2-watt house light. Responses during the 0.5-s stimulation period did not earn additional stimulation. The stimulation current (100–300 μA) was adjusted gradually to the lowest value that would sustain a reliable rate of responding (at least 40 rewards/min). Once the minimal effective current was found for each rat, it was held constant for all subsequent phases of training and testing.

Each rat was then adapted to brief tests at its minimal effective current with each of the descending series of 15 stimulation frequencies. Each series comprised 1-min test trials at each frequency. For each frequency tested, there was an initial 5-s “priming” phase during which noncontingent stimulation was given followed by a 50-s test phase during which the number of responses was counted. Following the test phase, there was a 5-s time-out period during which no stimulation was available. The stimulation frequency was then lowered by approximately 10% (0.05 log10 units), and another trial was started. After responding had been evaluated at each of the 15 frequencies, the procedure was repeated such that each rat was given six such series per day (90 min of training). During the training procedure, the range of frequencies was adjusted for each rat so that only the highest seven to eight frequencies would sustain responding. To characterize the functions relating response strength to reward magnitude, a least-squares line of best fit was plotted across the frequencies that sustained responding at 20, 30, 40, 50, and 60% of the maximum rate of responding on the water level using custom-designed analysis software. ICSS thresholds were defined as the frequency at which the mean threshold magnitude was reduced to 75% of the initial value (6–8 per treatment condition) to enable administration of anesthetic during insertion of the microdialysis probes (see below). The rat was then placed in a stereotaxic instrument. A plastic intracerebral guide cannula (CMA 12; CMA/Microdialysis, Solna, Sweden) was implanted above the NAc (1.6 mm anterior to bregma, 1.6 mm lateral from the midsagittal suture, and 6.2 mm below dura; Paxinos and Watson, 1986) according to published methods (Baumann et al., 2001). The guide cannula was fixed to the skull using stainless steel screws and dental acrylic. Animals were singly housed postoperatively and were allowed 7 to 10 days to recover. On the evening before an experiment, rats were moved to the testing room and lightly anesthetized with an intravenous injection of 10 mg/kg methohexital, an ultra-rapid short-acting anesthesia. A microdialysis probe
with a 2 × 0.5-mm exchange surface (CMA/12) was lowered into the guide cannula, and an extension tube (PE-50; Becton Dickinson, Sparks, MD) was attached to the jugular catheter. Each rat was placed into its own plastic container and was connected to a tethering system that allowed unrestricted movement within the container. The microdialysis inflow and outflow tubing, as well as the catheter extension tubing, were connected to a fluid swivel (Instech Laboratories, Plymouth Meeting, PA). Artificial Ringers’ solution containing 147.0 mM NaCl, 4.0 mM KCl, and 1.5 mM CaCl2 was pumped through the probe overnight at 0.5 μl/min. On the next morning, 10-μl dialysate samples were collected at 20-min intervals. Samples were immediately assayed for DA and 5-HT by HPLC with electrochemical detection as described below. When three stable baseline samples were obtained, drug treatments were administered; rats received an i.p. injection of 1.0 mg/kg SalvA, 0.125 mg/kg SalvA, or vehicle (75% DMSO). Sampling continued for 2 h after treatment.

Aliquots of the dialysate were injected into a microbore HPLC column (5 μm, C18, 100 × 1 mm, Unijet; BAS Bioanalytical Systems, West Lafayette, IN) that was coupled to an amperometric detector (Model LC-4C; BAS Bioanalytical Systems). A glassy carbon electrode was set at a potential of +650 mV relative to an Ag/AgCl reference. Mobile phase consisting of 150 mM monochloroacetic acid, 150 mM NaOH, 2.5 mM sodium octanesulfonic acid, and 250 μM disodium EDTA with 1 ml of triethylamine, 6% MeOH, and 6% CH3CN per liter of water (final pH = 5) was pumped (model 260D; ISCO, Lincoln, NE) at a rate of 60 μl/min. Chromatographic data were acquired on-line and exported to a Millennium software system (Waters, Milford, MA) for peak amplification, integration, and analysis. Standards of DA and 5-HT were run daily before dialysate samples, and standard curves were linear over a wide range of concentrations (0.1–100 pg). A monoamine standard mixture containing DA, 5-HT, and their respective acid metabolites was injected before and after the experiment to ensure validity of the constituent retention times. Peak heights of unknowns were compared with peak heights of standards and the lower limit of assay sensitivity (3× baseline noise) was 50 fg/5-μl sample.

Extracellular concentrations of DA and 5-HT were expressed as percentage of baseline, and the data for each neurotransmitter were analyzed separately. Differences among the treatment groups were analyzed using two-way (treatment × time) ANOVA with repeated measures on the time factor. Significant effects were analyzed further using post hoc Newman-Keuls tests.

**Histology.** Rats that had undergone stereotaxic surgery to implant ICSS electrodes or microdialysis probes were overdosed with pentobarbital (130 mg/kg i.p.) and perfused with 4% paraformaldehyde. The fixed brains were sliced in 40-μm sections for cresyl violet staining to confirm placements.

**Results**

In the FST, SalvA produced effects on behavior (Fig. 2a) that were opposite to those typically seen after administration of selective serotonin reuptake inhibitors (see Detke et al., 1995; Mague et al., 2003). Specifically, SalvA dose dependently increased occurrences of immobility (F5,34 = 5.98, P < 0.01) and decreased occurrences of swimming behavior (F5,34 = 6.07, P < 0.01). There was no effect on climbing or diving behaviors (data not shown). Post hoc analyses revealed that SalvA significantly increased immobility at 0.25 mg/kg (P < 0.05, Newman-Keuls test), 0.5 mg/kg (P < 0.05), 1.0 mg/kg (P < 0.01), and 2.0 mg/kg (P < 0.01). Similarly, SalvA significantly decreased swimming behavior at all doses from 0.25 to 2.0 mg/kg (P < 0.01). In contrast, SalvA caused no treatment-related differences in locomotor activity in an open field at any of the doses tested, regardless of whether the data were analyzed as 5-min bins (Fig. 2b) or as total activity over the 30-min test period (data not shown). As would be expected, activity levels decreased significantly in all groups over the course of the 30-min test period (F5,260 = 350.5, P < 0.01).

In the ICSS assay, there was no effect of repeated testing with SalvA on thresholds or maximal rates at any of the doses tested (data not shown). Because there were no effects of repeated testing, data from the first and second test sessions were combined into single means for each condition. The effects of SalvA on ICSS thresholds depended upon treat-
ment ($F_{6,42} = 19.0, P < 0.01$); the drug produced effects on behavior (Fig. 3a) that were opposite to those typically seen after administration of psychomotor stimulant drugs such as cocaine (see Mague et al., 2003). Treatment with vehicle tended to cause small nonsignificant increases in ICSS thresholds and decreases in maximum response rates in comparison with saline, suggesting nonspecific effects of DMSO. In comparison with vehicle, SalvA significantly increased ICSS thresholds within the same range of doses that had behavioral effects in the FST: 0.5 mg/kg ($P < 0.05$), 1.0 mg/kg ($P < 0.01$), and 2.0 mg/kg ($P < 0.01$). SalvA also appeared to affect maximal response rates ($F_{6,42} = 3.72, P < 0.01$). However, post hoc analyses revealed that this effect was due to differences between saline treatment and SalvA at 1.0 and 2.0 mg/kg. There were no differences between maximum rates after vehicle and any dose of SalvA, again suggesting nonspecific effects of DMSO on behavior in this assay.

In the in vivo microdialysis studies, systemic administration of SalvA produced effects on extracellular concentrations of DA in the NAc that depended upon an interaction between dose and time ($F_{9,168} = 9.47, P < 0.01$) (Fig. 4a). Injection of 1.0 mg/kg SalvA produced rapid decreases in DA that were detectable for the entire 2-h test period ($P < 0.01$ for 0–100 min; $P < 0.05$ for 100–120 min), whereas DMSO or 0.125 mg/kg SalvA had no effect at any time point. In contrast, none of the treatments affected extracellular concentrations of 5-HT at any of the time points tested (Fig. 4b).

All ICSS electrodes were located within the medial forebrain bundle at the level of the lateral hypothalamus. The placements were indistinguishable from those depicted previously (Todtenkopf et al., 2004). Similarly, all microdialysis probes were located within the NAc (Fig. 5). As such, data from all rats were included in the analyses.
Discussion

Systemic administration of SalvA—a potent, efficacious, and highly selective κ-opioid receptor agonist (Roth et al., 2002; Chavkin et al., 2004)—has profound behavioral effects in rats. SalvA increased the occurrences of immobility behavior in the FST, an assay often used in the study of depression (Cryan et al., 2002). This general effect is opposite to that seen with SSRIs, which decrease immobility and increase swimming behaviors (Detke et al., 1995). Although an increase in swimming behaviors is associated with the serotonergic actions of SSRIs, the significance of a decrease in swimming behaviors is unknown. This pattern of results might be an early indicator that the effects of SalvA on behavior in the FST involve 5-HT systems in critical brain regions. Moreover, SalvA increased ICSS thresholds, suggesting that it reduced the rewarding impact of medial forebrain bundle stimulation. Considering that reduced sensitivity to rewarding stimuli in rodents reflects anhedonia—a hallmark sign of clinical depression—these ICSS data provide additional evidence that SalvA produces depressive-like effects. We have reported previously that U-69593 produces the same pattern of results in these tests (Mague et al., 2003; Todtenkopf et al., 2004), suggesting a general effect of κ-agonists rather than a specific effect of SalvA. The potency and efficacy of SalvA in these tests are approximately equivalent to those seen with U-69593, although the present studies were designed to enable qualitative rather than quantitative comparisons between these agents. Considering that SalvA binds to few (if any) other types of receptors in the brain (Roth et al., 2002), these data suggest that selective stimulation of κ-receptors can produce depressive signs, at least in rats.

One concern when using the FST is that nonspecific treatment effects on activity levels could complicate data interpretation. We conducted locomotion studies in parallel with the FST studies to identify potentially confounding effects. To facilitate comparisons between the assays, the locomotion studies were conducted under conditions identical to those used in the FST studies, except during the second day of testing the rats were placed in activity chambers rather than being re-exposed to forced swimming. SalvA did not alter activity at any of the doses tested. Additionally, the methods we use to conduct the ICSS test also enable analyses of whether SalvA affects the performance capabilities of the rats. Although there were nominal decreases in response rates over the 1-h ICSS test session, this was a general effect of the 75% DMSO vehicle rather than a specific effect of SalvA. Thus it seems unlikely that nonspecific effects of SalvA on performance capabilities can explain the prodepressant-like effects of the drug in the FST or ICSS tests at the doses tested here.

The mechanisms that mediate these putative prodepressant actions of SalvA are not known. One possibility is that SalvA, through selective actions at κ-receptors, affects the function of DA systems. Indeed, previous reports in rodents indicate that systemic or intracerebroventricular administration of κ-agonists (e.g., U-50488H or the dynorphin analog E-2078) decreases extracellular concentrations of DA within the NAc (DiChiara and Imperato, 1988; Spanagel et al., 1992; Devine et al., 1993; Maisonneuve et al., 1994). These effects may be mediated, at least in part, within the NAc itself (Donzanti et al., 1992). Within the NAc, κ-receptors are located on the terminals of DA neurons (Shippenberg and Rea, 1997; Svingos et al., 1999), where they are in a position to regulate DA release. In addition, inhibitory actions within the midbrain may also contribute to decreased extracellular concentrations of DA within the NAc (Margolis et al., 2003). Regardless, our microdialysis data confirm previous observations that κ-agonists reduce activation of the mesolimbic DA

Fig. 5. Histological reconstruction of the areas sampled in the microdialysis studies. All probes were located in the NAc; the active portions of the membranes are depicted by the black lines.
system and extend them to SalvA, which is more selective and efficacious than the other agents. In contrast to the effects of SalvA on extracellular DA in the NAc, the drug had no effects on 5-HT concentrations in this region. These data provide early evidence that the decreases in swimming activity in the FST do not reflect reductions in 5-HT activity within the NAc, although different effects in other brain regions (e.g., raphe nucleus) cannot be ruled out. Considered together, our data raise the possibility that decreases in DA in the NAc contribute to the depressive-like behaviors that were observed in the present studies. Indeed, it has been proposed previously (Wise, 1982) that decreased DA function in the NAc produces anhedonia.

Interestingly, a recent report in which in vivo microdialysis was performed in mice suggests that SalvA reduces extracellular concentrations of DA within the caudate putamen, but not within the NAc (Zhang et al., 2005). It is not clear why stimulation of k-receptors in mice would produce a different pattern of results than those seen here with SalvA, or in previous studies with other k-agonists (DiChiara and Imperato, 1988; Spanagel et al., 1992; Donzanti et al., 1992; Devine et al., 1993; Maisonneuve et al., 1994). This discrepancy raises the possibility that rats and mice have different k-receptor distributions or different sensitivities to k-agonist modulation of mesolimbic DA function, or that the small size of the striatum in mice makes it difficult to resolve the caudate putamen from the NAc in microdialysis studies.

Alterations in the function of k-opioid systems may be part of a complex process that leads to the development and expression of depression or other mood disorders. Factors that can trigger depression in humans and depressives-like behaviors in laboratory animals—including stress and drug withdrawal—increase the activity of CREB in the NAc (Pliakas et al., 2001; Barrot et al., 2002; Shaw-Lutchman et al., 2002; Chartoff et al., 2003). Increased CREB activity in the NAc in turn, leads to expression of the gene for dynorphin (Carlezon et al., 1998). The possibility that increased stimulation of k-receptors causes depressive-like behaviors is supported by the finding that selective k-agonists produce antidepressant-like effects in models used to study depression (Pliakas et al., 2001; Newton et al., 2002; Mague et al., 2003; McLaughlin et al., 2003). These findings, together with other evidence, have raised the possibility that selective k-agonists might have clinical utility as antidepressants (Pliakas et al., 2001; Mague et al., 2003) or treatments for drug addiction (Rothman et al., 2000). Under some circumstances, the ability of k-agonists to decrease DA function in the basal forebrain might also have clinical utility. For example, antipsychotic drugs—which are frequently used to treat mania—activate dopaminergic neurons (Ma et al., 2003). Although SalvA produces hallucinogenic effects under some conditions (e.g., when smoked) (Roth et al., 2002; Chavkin et al., 2004; Bucheler et al., 2005), it is conceivable that administration of a derivative or related compound under more carefully controlled conditions might be useful for the treatment of disorders characterized by hyperfunction of dopamine systems (e.g., mania). Less selective k-agonists (e.g., endanoline, spiradoline) can produce measures of sedation and decrease the frequencies of tics in individuals with Tourette’s Syndrome (Chappell et al., 1993; Walsh et al., 2001).

Regardless, the present studies confirm and extend the idea that k-opioid receptors may play a key role in regulating complex mood states.

References


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