Enhanced Amygdala Kindling after Electrical Stimulation of the Ventral Tegmental Area: Implications for Fear and Anxiety

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Electrical kindling refers to the seizure-generating properties of brain stimulation. In addition to producing epilepsy, the reorganization of forebrain neurocircuitry associated with kindling contributes to psychiatric disturbances involving fear and anxiety. The amygdala is a limbic structure that kindles readily and regulates the complex neurocircuitry underlying emotional responding. Dopamine-containing ventral tegmental area (VTA) neurons, known to be activated by threatening environmental stimuli, are an important component of the amygdala-based fear network. Using amygdala kindling as an indicator of sensitization development, we report here that repeated low-current, high-frequency stimulation of the VTA provoked afterdischarge in the central amygdala and enhanced kindling rate. By establishing a fundamental link between VTA activation and neural excitability in the central amygdala, the present results are consistent with the possibility of a common process underlying epileptogenisis and the fear motivational consequences of amygdala and VTA kindling. Considering the established role of the VTA and the amygdala in emotional responding, such a sensitization mechanism might mediate exaggerated fearfulness.

Key words: ventral tegmental area; central amygdala; neural discharge; electrical stimulation; kindling; sensitization; fear and anxiety

Accumulating revelations about the amygdala-based fear system has led to considerable progress in delineating the neural connections and cellular mechanisms that underlie aversive emotionality. The lateral-basolateral amygdala receives sensory input from environmental stimuli and, along with the central amygdala, mediates conditional fear. Through its projections to forebrain, midbrain and hindbrain areas, the central amygdala governs the behavioral, autonomic, and endocrine responses that characterize a central fear state (Davis, 1992; LeDoux, 1996). Although the critical involvement of the amygdala in emotional learning and performance is well documented, the exact neural process involved in the genesis of pathological fear is less clear.

A potential mechanism underlying exaggerated fear is the evolution of neural sensitization provoked by repeated activation of fear-associated neural pathways (Adamec, 1990a; Rosen and Schulkin, 1998). This hypothesis is supported by the observation that fear expression is a prominent consequence of amygdala stimulation and temporal lobe epilepsy in humans (Trimble, 1991; Gloor, 1992). In animal research, electrical kindling refers to the electrophysiological and behavioral effects of the intermittent application of an initially subconvulsant electrical stimulation. Kindling, in the amygdala, is characterized by afterdischarge (AD) activity in the electroencephalogram (EEG) and a progression through five defined seizure stages culminating in generalized seizures (Goddard et al., 1969; Racine, 1972b). In addition to producing epileptogenisis, studies have linked amygdala kindling to enhanced emotionality in laboratory animals (Adamec, 1990a,b; Rosen et al., 1996).

Converging information from neuroanatomical, electrophysiological, behavioral, pharmacological, and neurochemical studies indicate that ventral tegmental area (VTA) dopamine (DA) neurons mediate conditioned fear responding through their ascending projections to the central and basolateral amygdala (Swanson, 1982; Trulson and Preussler, 1984; Deutch et al., 1985; Oades and Halliday, 1987; Borowski and Kokkinidis, 1996; Munro and Kokkinidis, 1997; Waddington Lamont and Kokkinidis, 1998; Guarraci and Kapp 1999; Guarraci et al., 1999). Stevens and Livermore (1978) reported that cats became fearful after kindling DA-containing neurons in the VTA. Given that mesoamygdaloid DA contributes to fear arousal, repeated activation of amygdala neurocircuitry by VTA stimulation might underlie the reported increase in emotionality provoked by VTA neural activation. To determine whether VTA stimulation has an excitatory function on amygdala neurodynamics we electrically kindled the VTA in the present study to induce neural sensitization in the amygdala. The results provide electrophysiological evidence of neural discharge in the central amygdala as a consequence of repeated low-current, high-frequency electrical stimulation of the VTA.

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MATERIALS AND METHODS

Subjects. A total of 36 naive male albino Wistar rats (Charles River, Quebec, Canada) were used as subjects in the present study. Rats weighed between 250 and 300 gm at the beginning of the experiment and were individually housed in galvanized wire mesh cages with free access to food and water. Animals were maintained on a 12 hr light/dark cycle (lights on 8 A.M.) and were tested during the light portion of the cycle.

Surgery. Rats were anesthetized with an intraperitoneal injection of sodium pentobarbital (60.0 mg/kg), placed in a Kopf (Tujunga, CA) stereotaxic instrument, and implanted with two bipolar nichrome electrodes (MS-303/1; Plastic One, Roanoke, VA): one directed at the central amygdala [anteroposterior (AP), −0.5 mm from bregma; lateral (L), ±4.5 mm from the midline suture; and ventral (V), −8.5 mm from the skull surface] and the second aimed at the ipsilateral VTA (AP, −2.8 mm from bregma; L, ±1.4 mm from the midline suture; and V, −8.6 mm from the skull surface). Stereotaxic coordinates were taken from the rat brain atlas of Pelligrino et al. (1979). Electrodes were implanted with the rat's skull fixed such that the interaural line was 5 mm below the level of the upper incisor bar. The stimulating and recording electrodes were attached to the skull using jeweler's screws and dental cement.

Apparatus. The kindling chamber was manufactured from clear Plexiglas and measured 20 cm in length, 7 cm in width, and 28 cm in height. The box had an electrically grounded floor made of stainless steel bars spaced 1.0 cm apart. The electrical stimulus originated from a constant-current stimulator and consisted of monophasic square-wave pulses (0.1 msec pulse duration) with a frequency of 100 Hz. Focal electroencephalographic activity (EEG) was recorded on a Grass Instruments (Quincy, MA) model 5D polygraph.

VTA-amygdala stimulation group. Animals in the VTA-amygdala group ($n = 13$) were placed in the Plexiglas chamber and received a train of electrical stimulations of the VTA intended to sensitize amygdaloid neural activity. This was immediately followed by the presentation of a single train of electrical pulses to the central amygdala. VTA activation consisted of 100 electrical stimulations [200 μA (base to peak); 100 Hz; 0.1 msec pulse duration; 0.5 sec train duration] with an interstimulus interval of 10 sec. The current level used to stimulate the VTA was selected because of its behavioral relevance to startle responding. Research from this laboratory has shown that the 200 μA intensity potentiates the amplitude of the acoustic startle reflex (Borowski and Kokkinidis, 1996). Amygdala kindling consisted of a single 200 μA (base to peak) electrical stimulation (100 Hz; 0.1 msec pulse duration) with a 2 sec train duration. This current intensity was selected based on an AD threshold (ADT) test conducted on a separate group of rats. Ten animals were used to determine the current level necessary to induce an AD in the amygdala. Current was initiated at 100 μA and increased in 50 μA steps every 60 sec until an AD was observed in the EEG recording. The mean ± SEM ADT was 680 ± 130 μA in this group of laboratory rats. Our hypothesis that VTA stimulation sensitizes amygdala kindling would be supported by an increase in amygdaloid kindling rate (fewer ADs to a stage 5 seizure). An observation of fewer amygdala stimulations to induce AD would also be consistent with this hypothesis. To investigate the latter possibility we used a subthreshold current intensity to kindle the amygdala. VTA and amygdala focal electrical activity was recorded for 60 sec before VTA stimulation, during the VTA stimulation session, and for 240 sec after amygdala stimulation. The stimulation and recording procedure was conducted once each day until a stage 5 generalized seizure involving loss of postural control was observed (Racine, 1972b).

Amygdala-only and VTA-only stimulation groups. Animals in the amygdala-only group ($n = 10$) were kindled once daily with a 2 sec electrical stimulation (200 μA) until rearing and falling generalized seizures developed. These animals were not stimulated in the VTA. Rats in the VTA-only group ($n = 13$) received 100 electrical stimulations of the VTA each day. The amygdala was not stimulated in these animals. To determine whether long-term activation of VTA neurons would produce excitatory effects on amygdala neural functioning, the daily 100 VTA stimulation schedule was conducted for 50 consecutive days. EEG activity was recorded from the VTA and the amygdala in both the amygdala-only and the VTA-only stimulation groups.

Dependent measures and statistical analysis. The following data were collected: number of ADs to a stage 5 motor seizure, number of stimulations to induce an AD, average duration of AD, latency to clonus, and duration of clonus. When the ADs or convulsions continued past the scheduled end of the test, EEG recording continued until electrophysiological and behavioral changes had terminated. A two-tailed Student's *t* test was used to assess group differences.

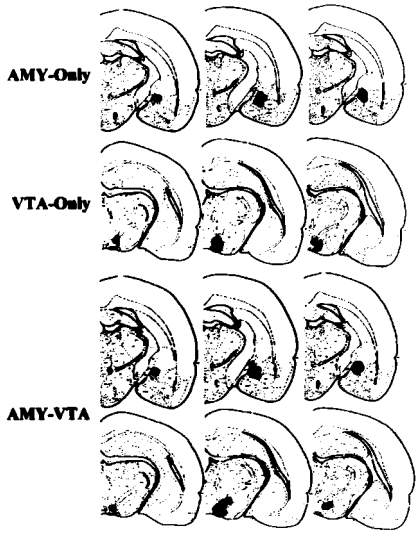

Figure 1. Schematic depiction of electrode placements in the amygdala (−0.4, −0.6, −0.8 mm from bregma) and the VTA (−2.6, 2.8, −3.0 mm from bregma) of the *AMY-Only* and *VTA-Only* stimulation groups. The representative sections were taken from the rat brain atlas of Pelligrino et al. (1979). Electrode placements in the central amygdala (*top*) and in the VTA (*bottom*) of the *AMY-VTA* stimulation group are shown in the *bottom two sections*.

Histology. At the termination of the experiment rats were killed with an overdose of sodium pentobarbital and perfused intracardially with saline followed by 10% formalin. The brains were removed and stored in a formalin solution for several weeks before sectioning. Coronal slices (40 μm) were stained with thionine, and the sections were evaluated under a microscope to determine the location of electrode placements.

RESULTS

Histology

Because electrode accuracy is critical to the hypothesis that VTA stimulation sensitizes neural activity in the amygdala, the data collected from six rats (three from the VTA-amygdala group and three from the VTA-only group) with imprecise electrode placements were excluded from the study. Misplaced amygdala electrodes in the VTA-amygdala group were situated in the caudate putamen. AD and behavioral seizure development were not observed in these subjects. Misplaced electrodes in the VTA-only group were situated in the substantia nigra pars compacta. These animals also did not show EEG or behavioral evidence of seizure activity after 50 d of repeated stimulation. All animals with central amygdala electrodes developed kindled seizures. Likewise, rats with VTA electrodes showed epileptiform events in the amygdala after long-term stimulation. We saw no indication of gliosis or cell loss in either the amygdala or the VTA that would suggest stimulation-induced lesions. Electrode placements in the central amygdala and the VTA are schematically depicted in Figure 1.

Amygdala kindling

The progression of kindled seizures from the amygdala relies on the appearance of an AD and not stimulation-induced changes in AD threshold (Racine, 1972a,b). The numbers of ADs necessary to produce a stage 5 rearing and falling clonic convulsion in the VTA-amygdala and amygdala-only groups are shown in Table 1. Repeated low-current, high-frequency stimulation of the VTA immediately before the daily administration of a single electrical stimulation to the central amygdala significantly accelerated the

Table 1. Effects of VTA stimulation on amygdala kindling

	Amygdala ($n = 10$)[a]	VTA-amygdala ($n = 10$)[a]	Two-tailed t test	Significance (p)
No. of ADs to stage 5 seizure	7.4 ± 0.72	4.9 ± 0.66*	2.43	<0.03
No. of stimulations to AD	18.4 ± 2.6	14.9 ± 3.2	0.82	>0.40
AD duration (sec)	73.4 ± 10.4	79.2 ± 13.5	0.33	>0.74
Latency to clonus (sec)	5.7 ± 1.7	2.8 ± 0.82	1.44	>0.15
Clonus duration (sec)	38.2 ± 4.3	37.4 ± 4.2	0.10	>0.90

[a] Values are mean ± SEM.
*$p < 0.05$.

rate of kindling development. In these groups, AD was not apparent in either the amygdala or the VTA during VTA stimulation. Kindling developed only after AD was initiated in the amygdala by electrically stimulating the central nucleus. There was no indication of epileptiform events in the VTA after stimulating this midbrain region or after amygdala kindling until animals developed stage 3 convulsions (Fig. 2, *top four EEG tracings*). This observation suggests AD spread from the amygdala to the VTA. Stage 1–3 seizure development is thought to involve activation of forebrain neurocircuitry primarily in the amygdala-pyriform region, whereas class 4 and 5 kindling entails the recruitment of hindbrain mechanisms involved in the expression of generalized clonic seizures (Burchfiel and Applegate, 1989).

The other dependent measures are also shown in Table 1. The two amygdala-kindled groups required a similar number of electrical stimulations to produce an AD, suggesting that preactivation of the VTA before each amygdala stimulation did not affect neural events that underlie AD development. Additionally, no differences were seen between groups with respect to AD durations, suggesting that VTA stimulation specifically enhanced kindling evolution without altering the other characteristics of AD development and expression. VTA activation also did not modify behavioral seizure activity, as indicated by the absence of group differences for the latency to clonus and clonus durations.

VTA kindling

After continued daily repeated stimulation of the VTA, all animals in the VTA stimulation-alone group progressed to various stages of the kindling process. After 50 d of stimulation, 7 of the 10 subjects exhibited stage 5 clonic convulsions. AD in the amygdala was apparent in some animals after 35 d of stimulation, and AD activity was seen in all animals after 50 d of electrical VTA stimulation. In those rats that developed stage 5 seizures the mean ± SEM number of amygdala ADs to a generalized seizure was 3.28 ± 0.6. Figure 2, *bottom two tracings*, shows the EEG recorded from the amygdala of one subject that displayed stage 1 (oral and facial movements) kindling behaviors on the 40th day of repeated low-current stimulation of the VTA. AD was induced in the amygdala during the first 12 VTA stimulations (Figure 2, *tracing A*). Electrical stimulation of the VTA was delivered every 10 sec, and there was an inhibition of amygdala AD activity during the remainder of the recording until the last (100th) stimulation after which AD reappeared in the central amygdala (Figure 2, *tracing B*).

DISCUSSION

Main findings

We report here that electrical stimulation of VTA neurons immediately before stimulation of the central amygdala enhances kindling rate. This likely involves the effects of VTA stimulation on mechanisms that mediate kindling genesis. Faster AD development and a decrease in AD threshold cannot explain this effect, because VTA neural excitation did not significantly reduce the number of amygdala stimulations necessary to induce an AD in this limbic structure. It would appear from the present results that repeated stimulation of VTA neurons has short- and long-term consequences on the neural dynamics of amygdaloid functioning. Over the short term (5 d), VTA stimulation facilitated kindling evolution, an effect that contrasts with the inhibitory actions of substantia nigra activation previously shown to retard amygdala kindling (Morimoto and Goddard, 1987). Equally important, long-term stimulation of the VTA, in the absence of amygdala stimulation, was observed to induce neural discharge in the amygdala. Animals in the VTA stimulation-only group subsequently progressed to various seizure stages after 50 d of stimulation. Unlike the results of Burnham et al. (1981), showing that high-intensity electrical stimulation of the mesencephalic reticular formation elicits convulsive activity without evoking AD in the forebrain, the VTA-related seizures in the present study were produced by low-intensity stimulation and appeared to be time-

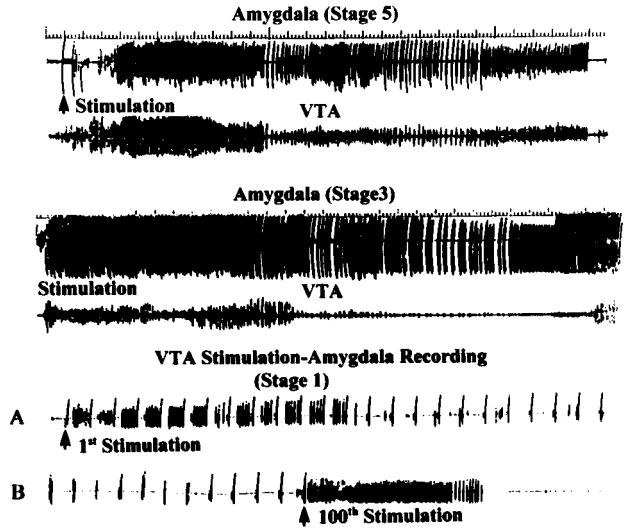

Figure 2. The *top four EEG tracings* are from the amygdala and the VTA and show AD spread to the VTA in one animal with a stage 5 seizure and a second animal with a stage 3 seizure after amygdala stimulation. The *bottom two EEG tracings* (*VTA Stimulation-Amygdala Recording*) are from the central amygdala on the 40th day of electrically stimulating (100 stimulations) the VTA. Stimulations 1–24 are shown in *tracing A*, and *tracing B* depicts stimulations 89–100. The rat exhibited a stage 1 seizure (oral and facial movements). Afterdischarge was evident in the recording after each of the first 12 electrical stimulations and after the last (100th) stimulation.

locked to AD in the amygdala. Once amygdala-induced seizures developed, AD spread to the VTA during stage 3–5 convulsions (Wada and Sato, 1974). These observations, coupled with the absence of differences in the seizure-related dependent measures, are not consistent with the possibility that activation of midbrain and hindbrain structures involved in the propagation of convulsive activity mediate VTA kindling. Rather, it is likely, as is the case with the substantia nigra, that the VTA is recruited into a seizure-propagating network involving midbrain and brainstem regions during the advancement of amygdala epileptogenisis (Bonhaus et al., 1991).

VTA stimulation-only animals displayed the various seizure stages typically seen with limbic system kindling (Racine, 1972b), and the finding that VTA kindling was associated with AD development in the amygdala suggests that VTA stimulation excites forebrain kindling mechanisms. Efferent VTA projections innervate several nuclei in the amygdala, including the central amygdala (Swanson, 1982; Oades and Halliday, 1987). On the basis of this neuroanatomical connection, and the rapid kindling observed in the VTA-amygdala stimulation group, it can be reasonably assumed that the positive transfer observed in the present study involves the direct neural link between the VTA and the amygdala. However, we cannot rule out the potential involvement of shared connections with other forebrain systems. Although additional research is necessary to establish the role of monosynaptic and polysynaptic pathways in the enhancement of amygdala kindling and in the production of VTA kindling, the ventral striatum appears to be resistant to the epileptiform effects of VTA stimulation, as indicated by the absence of kindled seizures, although spike activity can be elicited (Stevens and Livermore, 1978). Furthermore, VTA DA neurons are thought to mediate the development of amphetamine sensitization (Kalivas and Stewart, 1991). It is noteworthy, in this regard, that whereas long-term amphetamine treatment enhances amygdala kindling rate, kindling of the dorsal and ventral hippocampus was unaffected by amphetamine preexposure (Kirkby and Kokkinidis, 1987; Kirkby et al., 1991).

Behavioral implications

By virtue of the sensitivity of VTA DA neurons to threatening environmental stimuli and the known role of the VTA and the amygdala in mediating emotional responding (Davis, 1992; Borowski and Kokkinidis 1996), the finding of positive transfer in the present study may have explanatory value with respect to the relationship between temporal lobe seizure excitability and exaggerated fearfulness (Trimble, 1991). Electrical stimulation of the human amygdala produces fear as does temporal lobe neural discharge in epileptics (Trimble, 1991; Gloor, 1992). Comparing the human studies with animal research reveals some interesting parallels. For example, potentiated startle, a widely used indicator of emotionality in animals, is readily elicited by electrically stimulating the central amygdala and the VTA (Borowski and Kokkinidis, 1996). Moreover, VTA DA neurons are activated by fear-arousing stimuli (Trulson and Preussler, 1984; Deutch et al., 1985; Guarraci and Kapp, 1999); mesoamygdaloid DA activity mediates conditioned fear responding (Coco et al., 1992; Borowski and Kokkinidis, 1996; Munro and Kokkinidis, 1997; Waddington Lamont and Kokkinidis, 1998; Guarraci et al., 1999); and high-frequency stimulation of DA neurons in the VTA produces a behavioral profile characterized by intense fear (Stevens and Livermore, 1978). Although future research will delineate the common neural substrates that govern electrical kindling and DA-based fear, it is interesting to note that long-term-potentiation (LTP) in the amygdala is associated with fear learning (Rogan et al., 1997); DA receptors in the amygdala contribute to LTP (Huang and Kandel, 1996); and the function of the amygdala in emotionality is enhanced by electrical kindling possibly through an LTP process (Adamec, 1993).

In addition to electrical stimulation, activation of central fear pathways by psychomotor stimulant drugs such as amphetamine and cocaine can provoke exaggerated fearfulness. Amygdala DA D_1 receptors mediate conditioned fear responding (Waddington Lamont and Kokkinidis, 1998; Guarraci et al., 1999), and it has been suggested that the pathological expression of fear and anxiety after psychomotor stimulant administration may entail amplified mesoamygdaloid DA activity (Borowski and Kokkinidis, 1998). Cocaine paranoia in male drug addicts is enhanced in terms of frequency and severity with repeated drug use and is blocked by neuroleptic treatment (Gawin, 1986; Satel et al., 1991). Research with laboratory rats has shown that chronic administration of psychomotor stimulant drugs has an excitatory influence on conditioned fear responding (Borowski and Kokkinidis. 1994; Willick and Kokkinidis, 1995) and, as mentioned earlier, long-term amphetamine administration enhances amygdala kindling (Kirkby and Kokkinidis, 1987, 1991; Kirkby et al., 1991). Additionally, amygdala and VTA kindling was reported to sensitize DA-mediated behaviors (Kokkinidis and Borowski, 1991; Gelowitz and Kokkinidis, 1993; Ben-Shahar and Ettenberg, 1994). The behavioral and electrophysiological results of the present study demonstrate VTA kindling and raise the interesting possibility that VTA neural sensitization provoked by intrusive stimuli and by other means (e.g., psychomotor stimulant drugs) may have the potential to produce hyperexcitability of amygdala-associated fear neurocircuitry.

REFERENCES

Adamec R (1990a) Does kindling model anything clinically relevant? Biol Psychiatry 27:249–279.

Adamec R (1990b) Amygdala kindling and anxiety in the rat. NeuroReport 1:255–258.

Adamec R (1993) Partial limbic kindling—brain, behavior, and the benzodiazepine receptor. Physiol Behav 54:531–545.

Ben-Shahar O, Ettenberg A (1994) Repeated stimulation of the ventral tegmental area sensitizes the locomotor response to amphetamine. Pharmacol Biochem Behav 48:1005–1009.

Bonhaus DW, Russell RD, McNamara JO (1991) Activation of the substantia nigra pars reticulata neurons: role in the initiation and behavioral expression of kindled seizures. Brain Res 545:41–48.

Borowski TB, Kokkinidis L (1994) Cocaine preexposure sensitizes conditioned fear in a potentiated acoustic startle paradigm. Pharmacol Biochem Behav 49:935–942.

Borowski TB, Kokkinidis L (1996) Contribution of ventral tegmental dopamine neurons to expression of conditional fear: effects of electrical stimulation, excitotoxin lesions, and quinpirole infusion on potentiated startle in rats. Behav Neurosci 110:1349–1364.

Borowski TB, Kokkinidis L (1998) The effects of cocaine, amphetamine, and the dopamine D_1 receptor agonist SKF 38393 on fear extinction as measured with potentiated startle: implications for psychomotor stimulant psychosis. Behav Neurosci 112:952–965.

Burchfiel JL, Applegate CD (1989) Stepwise progression of kindling: perspectives from the kindling antagonism model. Neurosci Biobehav Rev 13:289–299.

Burnham WN, Albright P, Schneiderman J, Chiu P, Ninchoji T (1981) Centrencephalic mechanisms in the kindling model. In: Kindling 2 (Wada JA, ed), pp 161–178. New York: Raven.

Coco ML, Kuhn CM, Ely TD, Kilts CD (1992) Selective activation of mesoamygdaloid neurons by conditioned stress: attenuation by diazepam. Brain Res 590:39–47.

Davis M (1992) The role of the amygdala in conditioned fear. In: The Amygdala: neurobiological aspects of emotion, memory, and mental dysfunction (Aggleton JP, ed), pp 255–305. New York: Wiley.
Deutch AY, Tam SY, Roth RH (1985) Footshock and conditioned stress increase 3,4 dihydroxyphenylacetic acid (DOPAC) in the ventral tegmental area but not the substantia nigra. Brain Res 333:143–146.
Gawin FH (1986) Neuroleptic reduction of cocaine-induced paranoia but not euphoria? Psychopharmacology 90:142–143.
Gelowitz DL, Kokkinidis L (1993) The effects of amygdaloid stimulation on amphetamine-elicited locomotor sensitization. Brain Res Bull 32:561–565.
Gloor P (1992) Role of the amygdala in temporal lobe epilepsy. In: The amygdala: neurobiological aspects of emotion, memory, and mental dysfunction (Aggleton JP, ed) pp 505–538. New York: Wiley.
Goddard GV, McIntyre DC, Leech CK (1969) A permanent change in brain function resulting from daily electrical stimulation. Exp Neurol 25:294–330.
Guarraci FA, Kapp BS (1999) An electrophysiological characterization of ventral tegmental dopaminergic neurons during differential pavlovian fear conditioning in the awake rabbit. Behav Brain Res 99:169–179.
Guarraci FA, Frohardt RJ, SL, Kapp BS (1999) Amygdaloid D1 receptor involvement in Pavlovian fear conditioning, Brain Res. 827:28–40.
Huang Y-Y, Kandel ER (1996) D1/D5 receptors mediate a protein synthesis-dependent late phase of LTP in the amygdala. Soc Neurosci Abstr 22:332.
Kalivas PW, Stewart J (1991) Dopamine neurotransmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. Brain Res Rev. 16:223–244.
Kirkby RD, Kokkinidis L (1987) Evidence for a relationship between amphetamine sensitization and electrical kindling of the amygdala. Exp Neurol 97:270–279.
Kirkby RD, Kokkinidis L (1991) Amphetamine sensitization and amygdala kindling: pharmacological evaluation of catecholaminergic and cholinergic mechanisms. Brain Res Bull 26:357–364.
Kirkby RD, Gelowitz DL, Kokkinidis L (1991) The effects of amphetamine preexposure on electrical kindling of the hippocampus and related transfer phenomena. Brain Res 550:161–164.
Kokkinidis L, Borowski TB (1991) Sensitization of mesolimbic brain stimulation reward after electrical kindling of the amygdala. Brain Res Bull 27:791–796.
LeDoux JE (1996) The emotional brain. New York: Simon & Schuster.
Morimoto K, Goddard GV (1987) The substantia nigra is an important site for the containment of seizure generalization in the kindling model of epilepsy. Epilepsia 28:1–10.
Munro LJ, Kokkinidis L (1997) Infusion of quinpirole and muscimol into the ventral tegmental area inhibits fear-potentiated startle: implications for the role of dopamine in fear expression. Brain Res 746:231–238.
Oades RD, Halliday GM (1987) Ventral tegmental area (A10) system: neurobiology. I: anatomy and connectivity. Brain Res Rev 12:117–165.
Pelligrino LJ, Pelligrino AS, Cushman AJ (1979) A stereotaxic atlas of the rat brain. New York: Plenum.
Racine RJ (1972a) Modification of seizure activity by electrical stimulation: I. after-discharge threshold. Electroencephalogr Clin Neurophysiol 32:269–279.
Racine RJ (1972b) Modification of seizure activity by electrical stimulation: II. motor seizure. Electroencephalogr Clin Neurophysiol 32:281–294.
Rogan MT, Staubli UV, LeDoux JE (1997) Fear conditioning induces associative long-term potentiation in the amygdala. Nature 390:604–607.
Rosen JB, Schulkin J (1998) From normal fear to pathological anxiety. Psychol Rev 105:325–350.
Rosen JB, Hamerman E, Sitcoske M, Glowa JR, Schulkin J (1996) Hyperexcitability: exaggerated fear-potentiated startle produced by partial amygdala kindling. Behav Neurosci 110:43–50.
Satel SL, Southwick SM, Gawin FH (1991) Clinical features of cocaine-induced paranoia. Am J Psychiatry 148:495–498.
Stevens JR, Livermore A (1978) Kindling of the mesolimbic dopamine system: animal model of psychosis. Neurology 28:36–46.
Swanson LW (1982) The projections of the ventral tegmental area and adjacent regions: a combined fluorescence retrograde tracer and immunofluorescence study in the rat. Brain Res Bull 9:321–353.
Trimble MR (1991) The psychoses of epilepsy. New York: Raven.
Trulson ME, Preussler DW (1984) Dopamine-containing ventral tegmental area neurons in freely-moving cats: activity during sleep-waking cycle and effects of stress. Exp Neurol 83:367–377.
Wada JA, Sato M (1974) Generalized convulsive seizures induced by daily electrical stimulation of the amygdala in cats. Neurology 24:565–574.
Waddington Lamont E, Kokkinidis L (1998) Infusion of the dopamine D_1 receptor antagonist SCH 23390 into the amygdala blocks fear expression in a potentiated startle paradigm. Brain Res 795:128–1136.
Willick ML, Kokkinidis L (1995) Cocaine enhances the expression of fear-potentiated startle: evaluation of state-dependent extinction and the shock-sensitization of acoustic startle. Behav Neurosci 109: 929–938.