Effects of chronic antidepressant drug administration and electroconvulsive shock on activity of dopaminergic neurons in the ventral tegmentum

Charles H. K. West and Jay M. Weiss
Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA

Abstract
Increasing attention is now focused on reduced dopaminergic neurotransmission in the forebrain as participating in depression. The present paper assessed whether effective antidepressant (AD) treatments might counteract, or compensate for, such a change by altering the neuronal activity of dopaminergic neurons in the ventral tegmental area (VTA-DA neurons), the cell bodies of the mesocorticolimbic dopaminergic system. Eight AD drugs or vehicle were administered to rats for 14 d via subcutaneously implanted minipumps, at which time single-unit electrophysiological activity of VTA-DA neurons was recorded under anaesthesia. Further, animals received a series of five electroconvulsive shocks (ECS) or control procedures, after which VTA-DA activity was measured either 3 d or 5 d after the last ECS. Results showed that the chronic administration of all AD drugs tested except for the monoamine oxidase inhibitor increased the spontaneous firing rate of VTA-DA neurons, while effects on ‘burst’ firing activity were found to be considerably less notable or consistent. ECS increased both spontaneous firing rate and burst firing of VTA-DA neurons. It is suggested that the effects observed are consistent with reports of increased dopamine release in regions to which VTA neurons project after effective AD treatment. However, it is further suggested that changes in VTA-DA neuronal activity in response to AD treatment should be most appropriately assessed under conditions associated with depression, such as stressful conditions.

Introduction
Interest in the role of dopamine (DA) in depression has increased substantially in the past decade. Although the monoamines have been a focus of attention in regard to depression for nearly 50 yr, most of this attention was focused first on norepinephrine (NE), deriving from the ‘catecholamine hypothesis of depression’ (Bunney & Davis, 1965; Schildkraut, 1965; Schildkraut & Kety, 1967), and subsequently on serotonin (5-HT), with the introduction of selective serotonin reuptake inhibitors (SSRIs) for treatment of depression (Fuller, 1981; Stark et al. 1985). However, a significant problem for theories that emphasized either NE or 5-HT was that basic research examining effects of manipulating either of these amines has provided little support for their being able to directly impact the types of behavioural changes seen in depression. For example, in experimental animals disruption of NE in the brain was found to affect behaviours such as motor activity (Carey, 1976; Geyer et al. 1972), investigatory behaviour (Delini-Stula, et al. 1984), social interaction (Eison et al. 1977), and sleep (Kaitin et al. 1986), but the resulting changes in these responses caused by profound perturbations in NE were small, variable, and depended upon specific testing conditions (Amaral & Sinnamon, 1977; Carl et al. 1983; Crow et al. 1978, Robbins et al. 1989, Robinson et al. 1977). Similarly, perturbations of 5-HT were observed to affect such responses as sleep, aggressiveness/irritability, and feeding, but such
Manipulations have been described as having only modulatory effects (Blundell, 1992) and not markedly influencing depression-related responses (Delgado et al. 1994; Eriksson & Humble, 1990). In contrast, research carried out across this time period increasingly revealed that DA in the brain was critically involved in responses altered in depression. Studies of the effects of lesions of DA pathways, as well as introduction of DA agonists and antagonists into DA-rich regions of the forebrain, particularly the striatum and nucleus accumbens (NAC), or measurement of DA metabolism in these regions, consistently showed that DA mediated motor activity (Jackson et al. 1975; Kelly et al. 1975; Mogenson & Nielsen, 1984), alimentary behaviour (Stricker & Zigmond, 1984; Ungerstedt, 1971), and also affected reward and hedonic processes (Kiyatkin & Gratton, 1994; Robbins et al. 1989; Stellar & Stellar, 1985). Thus, basic research that has studied the relationship between monoamines in the brain and behavioural responses relevant to depression points to DA as being potentially important in depression.

The first to have clearly suggested the primacy of DA in depression appears to have been Randrup et al. (1975). Beginning in the mid-1980s, Willner advanced a ‘chronic mild stress’ animal model of depression that attempted to highlight ‘anhedonia’ in depression, and this model/approach emphasized DA as the critical monoamine (Willner, 1984; Willner et al. 1992). Within the last few years, the number of formulations suggesting the importance of DA in the brain in depression has grown considerably (Dunlop & Nemeroff, 2007; Montgomery, 2008; Perona et al. 2008).

Our particular interest in dopaminergic systems in depression grew out of experiments utilizing animal models of depression. These experiments, which induced depressive-like responses in rodents by exposing them to stressful events, pointed to depressive behaviour as arising because of increased and hyperresponsive neural activity of the major noradrenergic cell-body region in the brain, the locus coeruleus (LC) (Simson & Weiss, 1988; Weiss et al. 1981). However, this development presented us with the dilemma of having to explain depressive behaviour as resulting from excessive release of NE in the brain, for which there was little support from basic research (see above). The potential resolution of this problem came from an observation reported by Grenhoff and colleagues (1993). They presented data indicating that ‘burst’ firing of LC neurons (i.e. rapid firing of LC) would release galanin (Gal) from terminals on axons of LC that projected to the ventral tegmental area (VTA), and that the hyperpolarizing influence of Gal on DA cell bodies in the VTA would decrease the activity of these DA neurons. This gave rise to the formulation that the hyperactivity of LC neurons observed in conjunction with depression-like behaviour might bring about such behaviour by decreasing the neural activity of dopaminergic cell bodies in the VTA as the result of Gal released from LC-derived terminals in the VTA (Weiss et al. 1996, 1998).

We have tested the formulation described just above in a number of ways. First, Gal microinfused into VTA brought about a reduction in motor activity in both the home cage and a Porsolt-type swim test (Weiss et al. 1998). Second, after depressed motor activity was produced in rats by exposing them to a highly stressful event, blockade of Gal receptors in their VTA by microinfusion of the antagonist galantide into VTA hastened recovery from this stress-induced behavioural depression (Weiss et al. 2005). Third, and of most interest for the research presented here, we have tested the converse of the formulation described above. If depression-related behaviour derives from heightened activity of LC neurons that then leads to decreased activity of VTA-DA neurons, then effective antidepressant (AD) treatments might act by (1) decreasing LC neural activity, and (2) increasing VTA-DA neural activity. Measuring single-unit activity of LC neurons, we have reported that chronic treatment with any of eight AD drugs or a series of electroconvulsive shocks (ECS) all decreased LC activity, both spontaneous firing rate and sensory-evoked ‘burst’ firing (Grant & Weiss, 2001; West et al. 2009). In the present paper, we report the effect of chronic treatment with different AD drugs and also ECS on activity of VTA-DA neurons, assessing whether such drug treatment and ECS might increase neural activity of VTA-DA neurons.

Methods

Animals

Subjects were male albino Sprague–Dawley rats bred and raised in our animal colony, these animals having been derived from original foundation stocks purchased from Charles River Breeding Laboratories (USA). Because the aim of this study was to assess responses to ADs that occur in adult subjects, male rats aged 5–7 months, weighing 550–700 g at the time that the minipump for drug delivery was implanted, were used in all studies. Male rats of this age are considered to be young adult and fully mature (Radon, 2006). Throughout all phases of the experiment, animals were group-housed two per cage in standard rectangular cages (48 × 27 × 20 cm) where they were
maintained on corn cob bedding. The rats were housed in the rat colony on a 12-h light/dark schedule (lights on 07:00 hours), with food (Purina rat chow) and water available ad libitum.

**Drugs**

The following drugs were used: two tricyclic ADs, desipramine HCl (Sigma, USA) and imipramine HCl (Sigma); three SSRIs, fluoxetine HCl (Lilly, USA), paroxetine HCl (prepared by Dr M. Owens as described in McConathy et al. 2007), and sertraline HCl (Pfizer, USA); one dual NE and 5-HT reuptake inhibitor, venlafaxine HCl (Wyeth, USA); one DA reuptake inhibitor, bupropion HCl (Sigma); and one monoamine oxidase inhibitor (MAOI), phenelzine sulfate (Sigma). Because of their lower solubility in water, fluoxetine, sertraline, and paroxetine were dissolved in a vehicle of 50% polyethylene glycol, 25% DMSO, and 25% water; all other drugs were dissolved in a vehicle of distilled water. Doses were based on the salt. For this study, effects of a standard dose of each drug widely used in experiments employing rats was initially assessed; this was followed by testing of additional doses of some drugs to determine if the effect, or lack of effect, for those drugs was seen consistently.

**Surgery**

To deliver drugs, each animal was implanted subcutaneously with a minipump (Alzet model 2ML2, Durect Corp., USA) to deliver one drug continuously for 14 d. All surgical procedures were conducted under appropriate aseptic conditions and in accord with NIH Guidelines and U.S. Department of Agriculture regulations. Animals were anaesthetized to surgical plane with inhalation of isoflurane, the lower back shaved and disinfected, and a 2–3 cm incision made. A minipump filled with the desired drug was then inserted through the incision and the wound was closed. To ensure adequate delivery of the SSRIs in view of the more viscous vehicle used for dissolving these drugs, a further step was taken by delivering the drug into the peritoneal cavity rather than subcutaneously. To accomplish this, the minipump was again implanted subcutaneously but in these cases a 15-cm length of silastic tubing (0.04 i.d. × 0.085 o.d.) was attached onto the output of the minipump, which was covered at this location by a 10-mm length of tygon tubing (0.02 i.d. × 0.06 o.d.) to ensure a tight juncture between the tubing and the minipump output. At 15 mm from the distal end of the length of silastic tubing, a 3.0-mm piece of larger silastic tubing (0.062 i.d. × 0.095 o.d.) was place onto it forming a bulb at this location. The distal end of the silastic tubing, including the bulb, was then introduced surgically into the peritoneal cavity and the peritoneal wall sutured closed so that the bulb prevented the tubing from being withdrawn back into the subcutaneous space, thereby enabling long-term delivery of drug from the pump into the peritoneal cavity. After surgery, an analgesic was administered. The surgical procedure usually lasted no more than 15 min, after which the animal was returned to its home cage. On the 14th day after the minipump had been implanted, electrophysiological recording for each animal was conducted. In different studies we have confirmed that drugs delivered by the 2ML2 minipump are in circulation at this time after pump implantation (Grant & Weiss, 2001; West et al. 2009).

**ECS**

For each ECS treatment, the animals were anaesthetized with isoflurane for 5 min, after which the ECS was administered to the animal for 500 ms through ear clips moistened with conducting cream. ECS was generated using a 5:1 AC step-up transformer with the primary voltage set to deliver 350 V from the output, which generates a ~50 mA current when administered transcranially via ear clips to the animal (current monitored during application). Animals received the ECS treatment five times, with 72 h intervening between each treatment. Control animals for ECS were anaesthetized and handled in the same manner as were the ECS-treated rats for the five treatment sessions, but were not given ECS. Electrophysiological unit recording was then conducted 3 d or 5 d after the last ECS or control treatment.

**Electrophysiological unit recording**

*Anaesthesia, electrodes, recording equipment, and stereotaxic procedure*

Procedures for single unit recording of dopaminergic neurons given here follow the procedures used by several other major laboratories in this field, as noted below. All animals were anaesthetized with chloral hydrate (400 mg/kg i.p.) and given supplemental doses of anaesthetic as required. After induction of anaesthesia, animals were mounted in a Kopf stereotaxic instrument (Kopf Instruments, USA). Body temperature was monitored and maintained at near 37 °C by a water-circulating heating pad. The skull was opened over the brain area for unit recording, and dura incised and retracted. The brain surface was kept moist throughout the recording session with warm...
saline solution. Micropipette glass electrodes used were pulled from 1.5 mm capillary tubing and filled with 3.6% NaCl. The micropipette tips were broken back to 2–3 μm (2–7 MΩ impedance measured at 135 Hz). The electrical signal from the electrode was led into a preamplifier (Fintronics model WDR-420, Fintronics, USA), and the filtered output from the preamplifier fed into an oscilloscope and audio-monitor and into a computer for analysis, display, and storage by a commercial program (Experimenter’s Workbench, DataWave Technologies, USA). The electrodes were lowered into the brain at the following stereotaxic coordinates for VTA: posterior to bregma 5.0–6.0 mm, lateral 0.6–1.2 mm, ventral from cortical surface 7.5–9.5 mm.

Identification of VTA-DA neurons

Dopaminergic neurons in the VTA were distinguished from non-dopaminergic neurons in this brain region using criteria employed by laboratories with recognized expertise in identification of DA neuronal extracellular recording (Bunney et al. 1973; Chiodo, 1988; Grace & Bunney, 1980, 1983; Guyenet & Aghajanian, 1978; Wang, 1981; White & Wang, 1983). These criteria for identifying putative VTA-DA neurons are: (1) bi- or tri-phasic waveform (positive first), (2) long duration action potential of 2.5–5 ms, (3) an IS-SD break notch on the ascending phase of the action potential, and (4) spontaneous firing rates of 0.1–10.0 spikes/s. Moreover, most but not all VTA-DA neurons show a bursting firing pattern. We used a lower limit to the firing rate criterion (i.e. 0.1 spikes/s) than is typically reported (i.e. 0.5–1.0 spikes/s) because we encountered some very slow firing neurons (although such slow-firing units were rare) with quite distinct dopaminergic neuronal characteristics except for a low spontaneous rate; we did not wish to exclude such units from analysis. Prior to recording of any units included in the data reported here, recording was done from several animals, VTA-DA neurons identified as described above, and the recording site then dye-marked. The brains of these animals were sectioned to establish that recordings were being done exclusively from the VTA region, which was confirmed by this procedure.

Measurement of neuronal activity

The recording electrode was lowered into the brain and VTA-DA units were identified using the criteria described above. Electrode penetrations were made until recording from 10 units in each animal was achieved (in only three animals were 10 units not found). After isolation and stabilization of recording of a VTA-DA unit, baseline spontaneous activity was recorded for 4 min, the last 2 min of which were used for collection of spontaneous firing measurements. For all units, baseline spontaneous firing rate was recorded into 10-s bins for analysis. In addition to spontaneous firing rate, the percentage of spikes occurring as a ‘burst’ was also quantified. The onset of a burst was defined as an inter-spike interval (ISI) of <80 ms, and the termination of a burst is defined as an ISI of >160 ms (Grace & Bunney, 1984). The percentage of burst firing was determined by expressing the number of spikes occurring within bursts during a time period as a percentage of the total number of spikes occurring in that time period.

Data analysis

Statistical analysis was conducted as follows: the activity of each unit was used in the analysis. When VTA-DA activity observed in multiple groups was compared to the activity of a control condition (i.e. several drug and dosage conditions compared to the vehicle condition), a one-way analysis of variance was performed followed by Dunnett’s test comparing each individual condition to the control. When only two groups or conditions were compared to each other, statistical significance was determined by t test.

Results

As noted in the Methods section, drugs were administered using two types of vehicle – for all drugs except the SSRIs, distilled water with the drug delivered subcutaneously, and for the SSRIs, a DMSO, polyethylene glycol, and distilled water vehicle with the drug delivered into the peritoneum via a tube leading from the minipump. Comparison of measures of VTA-DA activity in vehicle-treated animals that received the two different types of vehicle (n = 5 animals for each type of vehicle) revealed no differences that approached significance for any measure, and therefore the results from the vehicle-treated animals were combined to form a single group (n = 10).

Figure 1 shows the effects of 14-d administration of eight different AD drugs, some in different doses, on various measures of the firing of VTA-DA neurons. Figure 1a shows effects on spontaneous firing rate, and Fig. 1b shows effects on the percent of spikes that occurred within a ‘burst.’ The most consistent effects were seen on spontaneous firing rate. As shown in Fig. 1a, all drugs with the exception of phenelzine, the MAOI that was tested, increased spontaneous firing
rate at least at one dose tested. (Only one dose of phenelzine was tested, as this drug was not expected to increase VTA-DA activity, as explained in the Discussion section.) In some cases, the percent of spikes occurring as part of a burst (Fig. 1b) was also increased, but this effect was less consistent than effects on spontaneous firing; only five drugs at one dose of each produced an increase in this measure.

Figure 2 shows the effects of ECS on firing of VTA-DA neurons. Effects on the same measures as shown in Fig. 1 are shown in Fig. 2(a, b). As can be seen in this Figure, a brief series of ECS, with electrophysiological assessment of VTA-DA activity then carried out either 3 d or 5 d after the last ECS, resulted in a marked increase in spontaneous activity (Fig. 2a) and also in the percent of spikes occurring as part of a ‘burst’ (Fig. 2b).
Discussion

When we assessed the effect of chronic administration of a number of AD drugs (i.e. administration for 14 d via subcutaneously implanted minipump) as well as the effect of a series of ECS on the electrophysiological activity of VTA-DA neurons, activity of these cells was found to be altered. With the exception of the MAOI that was tested (phenelzine), all of the drugs examined as well as ECS increased the spontaneous firing rate of VTA-DA neurons. Only at the lowest dose tested for the dual NE and 5-HT reuptake inhibitor (velafaxine) was this effect not observed. We were also interested in the possibility that AD treatment might change the tendency of VTA-DA cells to burst fire, as it has been reported that DA release is considerably increased by burst firing (Cooper, 2002; Floresco et al. 2003; Garris et al. 1994; Gonon 1988). With respect to burst firing, the effects of AD treatment were less pronounced – at one dose five of the drugs tested produced an increase relative to vehicle; ECS also produced a marked increase here. In summary, effective AD treatments (chronic administration of AD drugs or ECS) had a distinct tendency to increase VTA-DA neural activity. The one exception to this was phenelzine, a MAOI. However, insofar as a MAOI will directly increase synaptic and extracellular DA by blocking catabolism of the amine, this type of AD would not be expected to increase firing of DA-containing cell bodies as activity of these neurons will be subject to feedback inhibition. Chenu et al. (2009) have extensively examined effects of chronic administration of MAOIs on VTA-DA cell firing and have not seen any evidence of increased VTA-DA activity.

The study reported here derived from the view that dopaminergic activity arising from VTA-DA neurons may play a role in depression, with decreased VTA-DA activity and decreased forebrain DA release possibly involved in producing depression, and, conversely, increased VTA-DA activity possibly resulting from AD treatment. As noted in the Introduction, the number of investigators calling attention to the potential role of forebrain dopaminergic activity in depression is increasing (see references cited in Introduction). Additionally, one can point to experimental findings that are consistent with this view. For example, lesioning of the VTA, which will decrease release of DA in the forebrain, results in depression-like behaviour in the rat (Pioli et al. 2008; Winter et al. 2007). Conversely, Mizoguchi et al. (2008) observed that when rats were made to show depressive-like behaviour by being exposed to chronic stress, these rats also showed decreased DA release in the prefrontal cortex (PFC), where DA arises, although not exclusively, from activity of VTA-DA neurons. We also reported that exposure of rats to a highly stressful event (inescapable electric shock) that gives rise to depressive-like behaviour (called ‘stress-induced behaviour depression’) results in evidence of decreased DA release in the NAc, a projection field of VTA-DA neurons (Weiss et al. 2000). Further, Friedman et al. (2008, 2009) report that rats of the Flinders sensitive rat line, which show depression-related behavioural responses and are thought to be a rodent model of depression (Overstreet, 1993), show reduced ‘burst’ firing of VTA neurons.

Despite the possible significance of the VTA-DA neuronal activity in depression, there have been relatively few studies that have examined the effect of chronic administration of AD drugs, which is their therapeutic regimen, on the electrophysiological activity of VTA-DA neurons. As discussed earlier, there is reason to suspect that effective AD treatments would increase activity of VTA-DA neurons. Chiodo & Bunney (1983) reported that 21-d administration of desipramine (averaging 11.4 mg/kg.d intake in drinking water) increased the number of spontaneously activity DA neurons in the VTA as well as the substantia nigra. Sekine and colleagues (2007) reported a similar effect (increased number of active VTA-DA neurons per track) following 21-d administration of fluoxetine (2.5 and 5.0 mg/kg i.p.), paroxetine (1.0 mg/kg i.p.), and citalopram (1.0 mg/kg i.p.). Prisco & Esposito (1995) reported that 21-d administration of fluoxetine (10 mg/kg i.p.) eliminated the inhibitory effect of acute fluoxetine and mCPP on VTA-DA neuronal activity that typically occurs in naive (non-drug) rats. In the legends to figures 6 and 7 in their paper showing these data, they also report that the chronic administration of fluoxetine increased the spontaneous firing rate of the VTA-DA neurons. Chiodo & Antelman (1980a, b) have similarly reported that repeated administration of tricyclic ADs or ECS reduces the sensitivity of DA somatodendritic autoreceptors, thereby reducing an inhibitory influence; however, their studies largely focused on substantia nigra neurons. Finally, there have been two exceptions to finding of excitatory effects of chronic administration of AD drugs on VTA-DA neuronal activity. Dremencov et al. (2009) reported that 14-d administration (via minipump) of escitalopram decreased firing rate and burst firing of VTA-DA neurons, and similar administration of citalopram decreased burst firing. These investigators also did not replicate the findings of Sekine et al. (2007) reporting that these drugs had no effect on number of active cells per track.
Additionally, Mansari et al. (2008) reported that 14-d administration of bupropion via minipump did not affect the spontaneous firing rate of VTA-DA neurons. In both of these exceptions, however, the dose of drug used may have been an important factor. We report here an increase in firing rate with 14-d administration of bupropion at two lower doses (10 and 20 mg/kg.d) than the dose used by Mansari et al. (30 mg/kg.d); additionally, our lower dose was somewhat more effective than the higher dose. Moreover, Sekine et al. used a much lower dose of citalopram (1.0 mg/kg.d) than were used by Dremencov et al. (10.0 and 20 mg/kg.d). Thus, the higher doses used by Mansari et al. and Dremencov et al. might explain the differences in their findings in relation to those of others. Such results, as well as other findings shown in Fig. 1, suggest that lower doses of some drugs may be more effective in elevating VTA-DA neuronal activity than are higher doses.

The functional significance a change in VTA-DA neuronal activity arising from AD treatment would most likely derive form a change in the release of DA in the terminal regions to which VTA-DA neurons project. Indeed, apparent increases in DA release in these projection regions have been reported to result from AD treatment. Administration of AD drugs has been found to increase extracellular DA and dopaminergic metabolites in the PFC and NAc, with chronic administration producing this type of change much more efficaciously than acute administration of AD drugs (Kihara & Ikeda, 1995; Mousseau & Greenshaw, 1989; Page & Lucki, 2002; Tanda et al. 1996). However, increased DA release in the PFC can also derive from increased release of amine from noradrenergic terminals, with the DA being co-released with NE (Devoto et al. 2004; Hertel et al. 1999); consequently, increased DA in PFC is not necessarily the result of increased activity of VTA-DA neurons. With respect to a functional effect of a change in VTA-DA activity, reports of changes in DA release in NAc are more clearly indicative of this. For NAc, we have found nine reports in which extracellular DA and/or metabolites were measured by microdialysis, or where the presence of DA metabolites (HVA and DOPAC), indicators of release, were assessed post-mortem in response to chronic administration of AD drugs. In regard to evidence of DA release under basal, or unstimulated, conditions as a consequence of chronic administration of AD drugs, four studies found no differences from saline-treated controls (Nomikos et al. 1991; Pallis et al. 2001; Rossetti et al. 1991; See et al. 1992), four studies found either increased extracellular DA or increased dopaminergic metabolites (HVA and/or DOPAC) (Ichikawa et al. 1998; Juorio et al. 1990; Nomikos et al. 1992; Stewart & Rajabi, 1996), and one study reported a tendency for extracellular DA to be elevated but without elevation of HVA or DOPAC (Clark et al. 1996). Many of the above-cited studies also reported effects on DA release in response to DA-releasing drugs, such as amphetamine, cocaine, and somatostatin, as well as release in response to an additional injection of the AD drug. Eight out of eight studies reported that chronic administration of an AD drug augmented the release of DA in NAc produced by such DA-releasing drugs (Clark et al. 1996; Ichikawa et al. 1998; Nomikos et al. 1991, 1992; Pallis et al. 2001; Rossetti et al. 1991; See et al. 1992; Stewart & Rajabi, 1996). In summary, following chronic treatment with AD drugs, approximately half of the studies conducted have reported an increase in release of DA in the NAc under ‘resting’ or baseline conditions, and all studies reported an increase in release of DA in NAc when DA release was stimulated.

The extent to which the changes in VTA-DA activity reported in the present study after chronic administration of AD drugs and ECS may have contributed to the effects on DA release in NAc reported in earlier papers remains a question, but the tendency for DA release to be increased appears to be congruent with the electrophysiological observations we report here. It seems noteworthy that the most consistent effects of chronic AD treatment on DA release in NAc were seen when DA release was stimulated or provoked. In this regard, investigators have postulated that chronic AD treatment biases VTA-DA neurons to respond more vigorously to stimulatory events (Linnér et al. 2001; Nomikos et al. 1991). In contrast to such conditions, electrophysiological activity reported in the present paper was recorded under perhaps the ultimate conditions of non-stimulation, i.e., in anaesthetized animals; thus, the extent to which VTA-DA activity might have been altered under excitatory conditions (such as stressful conditions) seems to be an important question unansweredy by the findings described here. Particularly in relation to depression, the influence of effective AD treatments on VTA-DA activity in the context of stressful events would seem to be a highly significant issue that awaits further study.

Acknowledgements

This research was supported by Public Health Service grants MH65737 and MH79794.

Statement of Interest

None.
References


Mousseau DD, Greenshaw AJ (1989). Chronic effects of clomipramine and clorgyline on regional levels of brain amines and acid metabolites in rats [Short Note]. *Journal of Neural Transmission* 75, 73–79.


Stewart J, Rajabi H (1996). Initial increases in extracellular dopamine in the ventral tegmental area provide a mechanism for the development of desipramine-induced sensitization within the midbrain dopamine system. Synapse 23, 258–264.


