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Influence of chronic administration of antidepressant drugs on mRNA for galanin, galanin receptors, and tyrosine hydroxylase in catecholaminergic and serotonergic cell-body regions in rat brain

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ABSTRACT

Activity of locus coeruleus (LC) neurons and release of the peptide galanin (GAL), which is colocalized with norepinephrine (NE) in LC neurons, has been implicated in depression and, conversely, in antidepressant action. The present study examined the influence of chronic administration (for 14 days, via subcutaneously-implanted minipump) of antidepressant (AD) drugs representing three different classes (tricyclic [desipramine], selective serotonin reuptake inhibitor [SSRI] [paroxetine], and monoamine oxidase inhibitor [MAOI] [phenelzine]) on mRNA for GAL, GAL receptors (GalR1, GalR2, and GalR3), and tyrosine hydroxylase (TH), the rate-limiting enzyme for NE synthesis, in four brain regions – LC, A1/C1, dorsal raphe (DRN), and ventral tegmentum (VTA) of rats. Consistent with previous findings that chronic administration of AD drugs decreases activity of LC neurons, administration of AD drugs reduced mRNA for both GAL and TH in LC neurons. GAL and TH mRNA in LC neurons was highly correlated. AD drugs also reduced GAL and TH mRNA in A1/C1 and VTA but effects were smaller than in LC. The largest change in mRNA for GAL receptors produced by AD administration was to decrease mRNA for GalR2 receptors in the VTA region. Also, mRNA for GalR2 and GalR3 receptors was significantly (positively) correlated in all three predominantly catecholaminergic brain regions (LC, A1/C1, and VTA). Relative to these three brain regions, unique effects were seen in the DRN region, with the SSRI elevating GAL mRNA and with mRNA for GalR1 and GalR3 being highly correlated in this brain region. The findings show that chronic administration of AD drugs, which produces effective antidepressant action, results in changes in mRNA for GAL, GAL receptors, and TH in brain regions that likely participate in depression and antidepressant effects.

1. Introduction

The locus coeruleus (LC), the principal noradrenergic cell group in the brain, has been implicated in the pathophysiology of depression since the catecholamine hypothesis of depression was proposed in the 1960s (Bunney and Davis, 1965; Schildkraut, 1965; Schildkraut and Kety, 1967). Research suggests that activity of LC neurons is elevated in depression; evidence supporting this has been observed in clinical studies (e.g., Ordway et al., 1994; Wong et al., 2000; Ehnvall et al., 2003) as well as in preclinical investigations that have examined neurobiological changes in animal models of depression (Weiss et al., 1981; Simson and Weiss, 1988; Stone et al., 2009, 2011). Consistent with this, the converse also appears to be the case – namely, that LC activity is reduced when effective antidepressant (AD) therapy is applied. The data supporting this similarly derives from preclinical studies with animals (for a summary of effects of antidepressant treatments on electrophysiological measurement of LC activity, see Table 1 in West et al., 2009; also Nestler et al., 1990) as well as clinical studies that have observed reductions in the noradrenergic metabolite 3-methoxy-6-hydroxyphenylglycol (MHPG) in cerebrospinal fluid of patients undergoing AD treatment (for summary, see Table 4 in Grant and Weiss, 2001).

However, a notable inconsistency in relating heightened activity of LC neurons to depression (and, by extension, diminution of LC activity to recovery from depression) is that the most apparent consequence of heightened LC activity would be increased release

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of norepinephrine (NE) in the brain, and the evidence linking the behavioral changes seen in depression to perturbations of NE in the brain is tenuous. Reviewing basic research relating symptoms of depression to changes in noradrenergic activity in the brain reveals that experimental alterations in brain NE can affect behaviors such as motor activity, investigatory behavior, social interaction, and sleep (e.g., Stone and Mendlinger, 1974; Carey, 1976; Delini-Stula et al., 1984; Eison et al., 1977; Kaitin et al., 1986), but the changes in these behaviors resulting from profound perturbations of NE are often small, variable, and depend upon specific testing conditions for changes to be seen (e.g., Amaral and Sinnamon, 1977; Carli et al., 1983; Crow et al., 1978; Robbins et al., 1977, 1989). In contrast, alteration of brain dopamine (DA) appears to have much more impact on behaviors related to depression. Lesions of DA pathways in the brain and/or introduction of DA agonists and antagonists into DA-rich regions of the forebrain (i.e., striatum and nucleus accumbens), as well as measurement of DA metabolism in these brain regions, consistently shows that changes in DA have major effects on motor activity, alimentary behavior, and reward/hedonic processes (e.g., Pijnenburg and van Rossum, 1973; Mogenson and Nielsen, 1984; Museo and Wise, 1990; Ungerstedt, 1971; Stricker and Zigmond, 1984; Yokel and Wise, 1975; Stellar and Stellar, 1985; Robbins et al., 1989). Thus, basic research investigating the relationship between monoamines in the brain and behavioral responses relevant to depression points to DA as being potentially important in depression, and much more so than NE.

In view of the foregoing, the challenge in addressing the neurobiological basis for depression relative to LC could be viewed as the need to integrate elevated activity of LC neurons with dopaminergic mediation of the behavior affected in depression. A potential resolution can be derived from a report by Grenhoff et al. (1993). These investigators presented data indicating that "burst" firing of LC neurons (i.e., rapid firing of LC) will release galanin (GAL) from terminals on axons of LC neurons projecting to the ventral tegmental area (VTA), and that the hyperpolarizing influence of GAL on DA cell bodies in the VTA will decrease the activity of these DA neurons. This finding gave rise to the formulation that the hyperactivity of LC neurons observed in depression might bring about such depression-related responses 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 of rats brought about a reduction in their motor activity in both the home cage and in a Porsolt-type swim test (Weiss et al., 1998; see also Kuteeva et al., 2008 and Mitsukawa et al., 2009). 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 behavioral 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. As indicated earlier, effective AD treatments decrease activity of LC neurons. If this reduction in LC activity indeed decreases GAL release from LC axon terminals in VTA and thereby releases VTA-DA neurons from GAL-mediated inhibition, then effective AD treatments should increase VTA-DA neuronal activity. We have recently reported (West and Weiss, 2011) that chronic administration of six AD drugs (two tricyclics, three SSRIs, one SNRI, and one NDRI) as well as electroconvulsive shock produces an increase in VTA-DA neuronal activity, with the most consistent effects on spontaneous firing rate but also increasing burst firing in some instances; only the monoamine oxidase inhibitor tested, which will, by its biochemical action, increase extracellular DA and thereby directly inhibit VTA-DA neuronal activity (e.g., Adell and Artigas, 2004), did not have this effect. An increase in VTA-DA neuronal activity resulting from chronic administration of DMI (Chiodo and Bunney, 1983) and SSRIs (Sekine et al., 2007) also has been reported previously.

In the investigation reported here, we sought to further examine the formulation described above. Insofar as therapeutic administration of AD drugs (i.e., chronic treatment) decreases LC activity, the anticipated effect of this would be to decrease activity-dependent peptides in LC neurons, predominantly tyrosine hydroxylase (TH) and also GAL. A decrease in GAL in LC neurons would appear to subserve the function of decreasing GAL release in VTA to reduce an inhibitory influence on VTA-DA neurons. As a first step in assessing this, we report here measurement of mRNA for GAL and TH in LC neurons resulting from chronic administration (for 14 days) of three different AD drugs – a tricyclic (desipramine, DMI), an SSRI (paroxetine, PAR), and a monoamine oxidase inhibitor (phenelzine, PHE). Additionally, to possibly assess effects on stimulation of GAL receptors in VTA, mRNA for galanin type 1, 2, and 3 receptors was also measured. Measurement of these mRNAs was made in LC and VTA; however, these measures were also made in cells of the dorsal raphe (DRN) and ventrolateral medulla (A-1, C-1 cell body region) as these brain regions contain serotonergic and catecholaminergic cell bodies of interest. In all of these brain regions GAL is colocalized in neurons containing monoamine transmitters (Melander et al., 1986; Hökfelt et al., 1987; Xu and Hökfelt, 1997), and the three types of GAL receptor have also been identified in these brain regions (Smith et al., 1998; O'Donnell et al., 1999; Waters and Krause, 2000; Branchek et al., 2000).

2. Materials and methods

2.1. Subjects

Sprague–Dawley male rats were used for this study. A total number of 36 animals were used for this experiment. Subjects were mature adult rats aged 5–7 months at the time of the experiment. Prior to inclusion in the experiment and throughout the experimental period (i.e., drug administration), animals were group housed 2–3 per cage. They were maintained on a 12:12 light:dark cycle at a temperature of approximately 21 °C with laboratory chow and water available *ad libitum*.

2.2. Groups and drugs

Rats were allocated to four groups of eight rats each. Three groups each received a different AD drug. The three AD drugs represented three major types of AD medication: a monoamine oxidase inhibitor, phenelzine (PHE), a tricyclic AD, desipramine (DMI), and an SSRI, paroxetine (PAR). A fourth group (VEH), also with eight rats, was the non-drug group, and received the vehicle in which the drugs were dissolved. The rats in the four groups were matched for age and body weight. The mean body weight (and standard error) of the groups at the time drug administration began was: PHE, 710.6 ± 23.4 grams (g); DMI, 707.2 ± 27.7 g; PAR, 690.8 ± 33.0 g; and VEH, 710.1 ± 23.6 g. PHE and DMI were dissolved in distilled water. PAR was dissolved in 50% dimethyl sulfoxide (DMSO), 25% polyethylene glycol (PEG), and 25% distilled water due to its low solubility in water alone. For the VEH group, half of the rats received distilled water as the vehicle and half received the vehicle used for PAR (DMSO, PEG, and distilled water). Following sacrifice of all animals described above, four additional rats were added to the study when it became evident that some rats in the DMI group had experienced problems with drug delivery via the implanted minipump; three of these additional rats