

## Effects of Chronic Antidepressant Drug Administration and Electroconvulsive Shock on Locus Coeruleus Electrophysiologic Activity

To the Editor:

We read with great interest the paper by Grant and Weiss (2001) published in the January 15, 2001, issue of *Biological Psychiatry*. It is noteworthy that their table 1 summarizing the reports on the modification of the spontaneous firing activity of norepinephrine (NE) neurons by chronic antidepressant treatments is not complete. Results obtained with paroxetine and citalopram, the most selective serotonin (5-HT) reuptake inhibitors being able to attenuate locus coeruleus (LC) activity after a prolonged administration only, should have been included in the table (Szabo et al 1999). The antidepressant milnacipran, which also decreases spontaneous NE neuron firing rate, was omitted as well (Mongeau et al 1998). Furthermore, and in support of their hypothesis, a similar effect was reported with the dual 5-HT/NE reuptake blocker venlafaxine after acceptance of their manuscript and just recently with the selective NE reuptake inhibitor reboxetine (Béique et al 2000; Szabo and Blier 2001). More important, however, the  $\alpha$ 2-adrenoceptor antagonist mirtazapine augments LC firing activity after both acute and sustained administration (Haddjeri et al 1997). The latter report thus represents an important omission because Grant and Weiss's conclusion and inference that all antidepressants attenuate LC activity after chronic administration (p. 127) is incorrect.

Their finding that antidepressant agents and electroconvulsive shock treatment are able to attenuate the sensory-evoked burst firing is nevertheless intriguing. Indeed, the absolute firing activity of LC NE neurons elicited by pinching the contralateral paw is decreased; however, the increase of LC activity relative to baseline to such a paw pinch is unaltered. Thus, these results would appear to depend on an attenuated basal firing activity in the antidepressant-treated groups to yield a decreased absolute sensory evoked firing. It would seem that their hypothesis would be best tested by assessing whether rats treated with a sustained administration of mirtazapine, which produces an increase in LC activity, would present an attenuation of relative or absolute increase in firing compared with control animals using the paw pinch paradigm.

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### Reply

We are indebted to Szabo and Blier for indicating that we had omitted some relevant references from Table 1 of past results in our recent article regarding the influence of antidepressant (AD) treatment on locus coeruleus (LC) electrophysiological activity (Grant and Weiss, 2001). They correctly point out that three additional references should have been included, and took the opportunity of their communication to indicate two more that have appeared since our article was submitted. The omissions were an oversight. In view of the recent increase in findings, including those reported in Grant and Weiss (2001), we take this opportunity to show here a revised table (Table 1, in this letter) which hopefully includes all results, up to the present date, that describe the effects of effective AD treatments on LC electrophysiological activity.

As these investigators point out, it is noteworthy that their additional references add five more drugs to the list of antidepressants that decrease LC electrophysiological activity, at least in terms of spontaneous firing rate, under conditions of prolonged administration. These drugs are paroxetine, citalopram, milnacipran, venlafaxine, and reboxetine—two SSRIs, two atypical antidepressants, and a norepinephrine reuptake inhibitor. They also add one drug, mirtazapine, as being a possible exception to the effect of AD treatments as decreasing LC activity. Mirtazapine as well as another closely related AD treatment drug, mianserin, block somatodendritic alpha-2 receptors on LC neurons, and therefore can increase LC activity rather than decrease it. This well-known effect was discovered by Aghajanian and colleagues in the late 1970s (Cedarbaum and Aghajanian, 1976; Freedman and Aghajanian, 1984). We were quite familiar with this possibility, having ourselves published several papers in regard to the influence of somatodendritic alpha-2 receptor blockade on LC activity (Simson et al., 1988; Simson and Weiss, 1987; Simson and Weiss, 1989). Consequently, we view evaluation of the effect of prolonged adminis-

Table 1. Effects of Chronic Treatment (1 Week or Longer) with Antidepressant Drugs or a Series of Electroconvulsive Shocks on Spontaneous and Sensory-Evoked Firing Rate of Locus Coeruleus Neurons

		Spontaneous	Evoked
Tricyclics	Desipramine	↓	Huang et al. (1980)
		↓	McMillen et al. (1980)
		—	Valentino et al. (1990)
		↓	Grant and Weiss (2001)
Norepinephrine Reuptake Inhibitors	Imipramine	↓	Svensson and Udsin (1978)
		↓	Grant and Weiss (2001)
		↓	Szabo and Blier (2001)
Monamine Oxidase Inhibitors	Phenelzine	↓	Blier and de Montigny (1985)
		↓	Valentino and Curtis (1991)
		↓	Grant and Weiss (2001)
		↓	Grant and Weiss (2001)
Selective Serotonin Reuptake Inhibitors	Sertraline	—↓	Valentino et al. (1990) <sup>b</sup>
		↓	Grant and Weiss (2001)
	Paroxetine	↓	Szabo et al. (1999)
		↓	Szabo et al. (1999)
Atypicals	Fluoxetine	↓	Grant and Weiss (2001)
		↓	Grant and Weiss (2001)
	Mianserin	—?	Curtis and Valentino (1991) <sup>c</sup>
		↑	Haddjeri et al. (1997)
Electroconvulsive Shock	Venlafaxine	↓	Béique et al. (2000)
		↓	Mongeau et al. (1998)
		↓	Grant and Weiss (2001)
	Milnacipran	↓	Grant and Weiss (2001)

The firing rate shown by animals receiving drug or electroconvulsive shock in comparison with animals not receiving such treatment was ↓, decreased, ↑, increased, or —, unchanged.

<sup>a</sup>Evoked response assessed, but results not reported for this measure. Report presents only the ratio of evoked to spontaneous rate, because spontaneous rate was decreased by phenelzine, effect on evoked rate could not be determined from data presented.

<sup>b</sup>Spontaneous firing rate of sertraline-treated rats was not different from untreated rats but was significantly lower than that of rats that received a similar schedule of injections of vehicle.

<sup>c</sup>Spontaneous and evoked firing rate of mianserin-treated rats was not different from untreated rats but was less than that of rats that received a similar schedule of injections of vehicle; however, the statistical significance of the comparison of mianserin-treated rats with vehicle-treated rats was not presented (see Curtis and Valentino 1991 [Figure 4, 334]).

tration of AD drugs that block alpha-2 receptors (i.e., mirtazapine and mianserin) as representing a very important test for the possibility that effective AD treatments have the common effect of reducing LC activity. But we would not yet agree that it is clear that AD drugs that block alpha-2 receptors increase LC activity when the drugs are used clinically. First, the increase in LC spontaneous activity reported by Haddjeri et al. (1997) was small (an increase from 2.0 to 2.5 Hz in their animal subjects). Second, as indicated in our Table 1, Curtis and Valentino (1991) reported no change in LC activity as a result of chronic administration of mianserin when firing rate was compared with untreated animals, but comparison with animals that received a similar schedule of vehicle injections showed a reduction of firing produced by mianserin. In addition, and perhaps most significant, Mendlewicz et al. (1982) reported a reduced level of the noradrenergic metabolite 3-methoxy-4-hydroxy-phenylglycol (MHPG) in the cerebrospinal fluid of human subjects following two weeks treatment with mianserin. Thus, it is not yet established what effect AD drugs that block alpha-2 receptors have on LC activity when these drugs are administered chronically and in clinically relevant doses.

With respect to Szabo and Blier's observations regarding sensory-evoked "burst" firing of LC neurons, we believe that this is a potentially important aspect of LC activity to examine as

well as spontaneous firing rate. Commenting on their statement that the decrease in sensory-evoked activity can be accounted for simply by the decrease in spontaneous depolarization rate, we do not believe that this is the case. First, the reduction in number of spikes that was noted by us after chronic treatment with AD drugs was larger than what can be accounted for by the decrease in spontaneous firing rate. For example, our data (Grant and Weiss, 2001) showed groups in which sensory-evoked activity was decreased to 3.0 Hz from the norm of approximately 6.0 Hz, while the spontaneous depolarization rate in the same groups had decreased to .5 Hz from 1.5 Hz; such a decrease in sensory-evoked activity is numerically larger than can be accounted for on the basis of its simply "piggybacking" on the decreased spontaneous firing rate. This is not to say, however, that similar underlying processes do not account for both phenomena. But, second, it is also important to note that sensory-evoked activity of LC neurons has been found to vary independently of spontaneous firing rate. Spontaneous firing rate of LC neurons has been observed to change markedly without a change occurring in sensory-evoked activity (e.g., the effect of intraventricular Corticotropin-releasing hormone [i.c.v. CRH] [Valentino and Foote, 1988; Borsody and Weiss, 1996]). Conversely, we have reported instances in which sensory-evoked activity was altered without a change occurring in spontaneous firing rate (Simson and Weiss,

1987; Simson and Weiss, 1989). It is possible to completely block sensory-evoked "burst" firing of LC neurons by pharmacological manipulation (i.e., local kynurenic acid) without diminishing their spontaneous firing rate (e.g., Svensson et al., 1989; Saunier et al., 1993). One reason why sensory-evoked activity is interesting to examine in addition to spontaneous firing rate is that these parameters can vary independently.

Finally, Szabo and Blier refer to our conclusion, based on the data discussed and presented in Grant and Weiss (2001), that LC activity is reduced by AD treatments as being "their hypothesis." While their statement represents standard language usage, we would like to emphasize that we have no vested interest in the possibility that all AD treatments decrease LC activity. We view the existing results as intriguing, and for this reason have articulated this possibility for the psychiatric community. We wish to emphasize that the eventual data bearing on this issue will be paramount, and that, should the effect of AD treatments not be found to have a common effect of decreasing LC activity, we will readily move on.

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