also failed to detect an antidepressant-induced reduction in nigral neuronal sensitivity to apomorphine. Another possibility is that the population of neurones sampled by Chiodo and Antelman differed from those in our experiments despite the similarity of the respective selection criteria. For example, in experiments by ourselves and others[3], a 4 μg per kg dose of apomorphine caused approximately one-half the degree of inhibition reported by Chiodo and Antelman.

Evidently, some of the methodological variables essential to the neurophysiological demonstration of antidepressant-induced nigral neuronal subsensitivity have not yet been characterized fully. Until these variables are better understood, we suggest that this phenomenon be regarded as a provocative finding awaiting confirmation.

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CHRONIC treatment with an antidepressant has been reported[1] to induce a subsensitivity of presynaptic dopamine receptors. Chiodo and Antelman observed that the low-dose, apomorphine-induced reduction in the firing rate of dopaminergic cells located in the substantia nigra zona compacta was attenuated by chronic treatment with imipramine, amitriptyline or iprindole.

We have attempted to reproduce the subsensitivity effect. Groups of rats were treated chronically with imipramine or saline using the same 2-day or 10-day treatment conditions as Chiodo and Antelman. Sprague–Dawley rats (Charles River) were housed at two per cage and handled daily during the chronic treatment period. In preparation for recording from dopaminergic cells, the rats were anaesthetized with chloral hydrate (400 mg per kg, intraperitoneally) and the femoral vein was cannulated for drug administration.

Although the animals treated with imipramine lost weight and became more irritable, there was no significant difference in the response of nigral dopaminergic cells to the low-dose apomorphine challenge between the treated and the control groups. In addition, we did not obtain the magnitude of response to apomorphine in control rats that Chiodo and Antelman reported; they obtained a reduction of ~70% in firing rate with 4 μg per kg apomorphine, whereas we found a reduction of ~35%. Our control response agrees more with the results of Skirboll, Grace and Bunney[2].

The subsensitivity phenomenon reported by Chiodo and Antelman seems to be elusive and may not be a general effect, but rather may be related to some unidentified aspect of their technique. This is supported by the failure of at least one other laboratory to replicate their finding (Welch *et al.*, see above).

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CHIODO AND ANTELMAN REPLY—Welch *et al.* and MacNeil and Gower report that they were unable to replicate our findings of dopamine autoreceptor subsensitivity after repeated tricyclic antidepressant treatment[1] and state that our results are 'elusive' and 'provocative' at best. Quite the contrary! Our results are part of a growing body of diverse evidence supporting the notion that repeated antidepressants do indeed induce dopamine autoreceptor subsensitivity. This evidence can be divided into behavioural, neurochemical and neurophysiological categories.

(1) Behavioural evidence: As stimulation of dopamine autoreceptors with low doses of apomorphine decreases locomotion, reduction of this hypokinesia by treatments which do not compete for the same receptor is thought to reflect autoreceptor subsensitivity. Tricyclic antidepressants[2,3], mianserin[2], monoamine oxidase (MAO) inhibitors[4], rapid-eye-movement sleep deprivation[4], electroconvulsive shock (ECS)[5] and lithium[6], all significantly reduce apomorphine-induced hypokinesia after repeated treatment. These data indicate that almost all antidepressant treatments can induce subsensitivity of dopamine autoreceptors. Neither Welch *et al.* nor MacNeil and Gower cite any of these findings.

(2) Neurochemical evidence: Two types of biochemical data support the notion of antidepressant-induced dopamine autoreceptor subsensitivity. First, repeated administration of tricyclic antidepressants[2,11] and atypical antidepressants[2] decrease the ability of autoreceptor-specific doses of apomorphine to reduce dopamine metabolism. Second, Lee and Tang[7] have recently demonstrated that chronic treatment with desmethylimipramine or nomifensine decreased H^3-dopamine binding in the striatum. As H^3-dopamine is thought to bind preferentially to presynaptic dopamine receptors, these data indicate that antidepressants induce a subsensitivity of the autoreceptors located on both dopaminergic terminals and cell bodies. In addition, Koide and Matsushita[8] have reported a reduction in striatal H^3-spiperone binding after repeated tricyclic administration, suggesting that antidepressants can also induce a subsensitivity of at least some postsynaptic dopamine receptors.

(3) Neurophysiological evidence: Neurophysiological support for dopamine autoreceptor subsensitivity following repeated antidepressant treatments is also of two types. In addition to our finding that tricyclic antidepressants and iprindole can induce such subsensitivity[1], we have obtained similar results after ECS[9] and with the MAO inhibitor, phenelzine[3]. The phenelzine study used a decrease in the inhibitory effects of microiontophoretically applied dopamine rather than a decrease in the effects of intravenously administered apomorphine to index dopamine autoreceptor sensitivity. Interestingly, subsensitivity after phenelzine was evident even in response to dopamine ejection (4–10 nA) which inhibited dopaminergic neuronal discharge by only 20–40%—the same degree of inhibition reported by Welch *et al.* and MacNeil and Gower after apomorphine. These data obviate the argument of these investigators that they may have been recording from a different population of neurones which were only mildly inhibited by apomorphine adminstration relative to those sampled in our studies. Moreover, Groves *et al.*[12] (using a treatment paradigm identical to ours) have reported that repeated ECS induces a subsensitivity of dopamine autoreceptors as shown by significant reduction in the inhibitory effects of low doses of apomorphine on dopamine cell firing. A second line of neurophysiological evidence supporting dopamine autoreceptor subsensitivity following antidepressant treatments is provided by the work of Mereu *et al.*[10] showing that the electroencephalograph synchronization which results from autoreceptor doses of apomorphine is eliminated by repeated ECS.

We have now cited at least 11 studies from 5 independent laboratories which we believe strongly support the idea that repeated treatment with antidepressants reduces the sensitivity of dopamine autoreceptors. In view of this extensive support we find no basis for the statement of MacNeil and Gower that "the subsensitivity phenomenon reported by Chiodo and Antelman appears to be elusive and may not be a general effect...". The paucity of procedural detail and the absence of their actual data make it virtually impossible to guess why Welch *et al.* and MacNeil and Gower were unable