Anterior Cerebellar Vermal Stimulation: Effect on Behavior and Basal Forebrain Neurochemistry in Rat

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Stimulation of the anterior cerebellar vermis (ACV) has been shown to be of therapeutic value in several patients with chronic intractable psychiatric disorders, although the mechanism of action of ACV stimulation remains obscure. The present study sought to clarify how cerebellar stimulation might function by investigating the behavioral and biochemical effects of ACV stimulation in rats. Stimulation was found to increase the amplitude of the acoustic startle response and to produce a borderline enhancement of the potentiated startle effect, results that were interpreted as evidence that ACV stimulation enhances responsiveness to significant environmental cues. A concurrent increase in dopamine turnover and a decrease in serotonin release in the nucleus accumbens suggest possible mechanisms of action of the stimulation. It is proposed that cerebellar stimulation may exert a positive therapeutic effect only in Type II schizophrenia (negative symptomatology), a category of cases possibly associated with an underactive mesolimbic dopamine pathway and, hence, not responsive to neuroleptic treatment.

Introduction

Electrical stimulation of the anterior cerebellar vermis (ACV) has been reported (Heath 1977) to produce marked improvement in affective state and a sustantial reduction or elimination of a range of psychopathological symptoms, including violence and rage, in a diverse group of psychiatric patients (many of whom were schizophrenic). Heath (1966) has attributed the efficacy of cerebellar stimulation to the elimination of limbic system dysrhythmias, which he observed to be associated with the occurrence of psychotic symptoms. This view is based on the observations that ACV stimulation blocks limbic system seizure activity in animals (Heath et al. 1980a) and depresses single unit activity in temporal lobe structures (hippocampus and amygdala) in which electrical activity increases during negative affective states, such as fear and rage. In contrast, ACV stimulation enhances single cell activity in brain regions (rostral septal area and nucleus accumbens) in which electrical activity increases during positive affective states, for example, sexual activity (Heath et al. 1978). Thus, according to Heath, vermal stimulation has the general effect of depressing negative affect and augmenting positive emotional states.

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It has recently been observed that the cerebellum makes efferent connections with a number of brain stem nuclei, including the dopaminergic cell bodies located in the ventral tegmental area of the midbrain (Snider et al. 1976). Based on these anatomical connections, Snider (1982) has proposed that stimulation of the ACV might produce its therapeutic effects by depressing activity in the mesolimbic dopamine (DA) system, which projects to a number of limbic system structures, including the hippocampus, amygdala, nucleus accumbens, and septal area. This hypothesis views cerebellar stimulation as essentially equivalent to the administration of antipsychotic medication, thus making the effects of cerebellar stimulation compatible with the dopamine hypothesis of schizophrenia, which is the leading explanation of this psychotic state.

Although this view does have the advantage of parsimony, it presents some difficulties. Clinical reports of ACV stimulation suggest that it has effects more general than, and perhaps qualitatively different from, those of antipsychotic medication. For example, ACV stimulation has been reported to reverse not only positive symptoms of schizophrenia (e.g., hallucinations and delusions), but also negative symptoms (social withdrawal, blunting of affect) and to do so in chronic patients, who respond poorly to antipsychotic medication. ACV stimulation has also been reported to greatly reduce intense anxiety states (Heath 1977) in patients with neurotic symptoms. It has similarly been reported to reduce tension or anxiety in a large percentage of nonpsychiatric patients (Riklan et al. 1977).

Furthermore, some biochemical evidence appears to conflict with the view that ACV stimulation effectively depresses DA activity in the brain. Tabbador et al. (1978) reported that chronic cerebellar stimulation in two patients increased cerebral spinal fluid (CSF) levels of the DA metabolite homovanillic acid (HVA), suggesting an increase rather than a decrease in DA turnover. However, this interpretation is weakened by the recognition that HVA in the CSF is known to arise primarily from striatal DA neurons, rather than from mesolimbic DA neurons, which are thought to be most critically involved in psychosis. Another recent study (Dempesy et al. 1983) concludes that ACV stimulation increases catecholamine release within the basal forebrain (nucleus accumbens and rostral septal area). However, this conclusion may also be challenged by hypothesizing that a large increase in norepinephrine (NE) release masked a decline in DA release. A final observation, which is less susceptible to criticism, is the finding that lesions of the ACV augment the locomotor stimulating effect of apomorphine (Jackson et al. 1980). As a similar effect of apomorpine administration is seen after destruction of the mesolimbic pathway with the catecholamine neurotoxin 6-hydroxydopamine (Ungerstedt et al. 1973), this result would seem to be best interpreted as being due to a lesion-induced reduction in mesolimbic DA activity and a subsequent development of receptor supersensitivity. If lesions of the vermis produce effects opposite to stimulation, this finding would suggest that stimulation should enhance DA release.

In summary, there is sufficient confusion about the mechanism of ACV influence on limbic states that further investigation is warranted. The present study was designed to reevaluate the effects of ACV stimulation, both behaviorally and biochemically, in rats.

Methods

The behavioral investigation employed the "potentiated startle" paradigm (Davis 1980). If ACV stimulation directly inhibits negative emotional states, it would be expected to attenuate the emotion of fear. To test this supposition, animals are first classically conditioned to associate a light cue and foot shock. Later, loud auditory tones are presented to elicit startle

responses, which have been shown on the average to be significantly greater in the presence of the light cue (light–tone, LT) than in its absence (tone alone, TA). The difference between the average responses to tone during the light cue and in its absence is referred to as the "potentiated startle effect" (PSE = LT − TA). The PSE has been reported to be blocked or depressed by all drugs with known anxiolytic effects in humans and to be enhanced by all drugs known to have anxiogenic effects in humans that have thus far been tested (Davis 1980). The PSE appears to be a valid and sensitive animal model of fear or anxiety, and ACV stimulation would thus be expected to diminish it.

The biochemical investigation employed chemical assay of basal forebrain area homogenates for evidence of altered DA turnover in response to ACV stimulation. As the cerebellum has recently been reported to make efferent connections with raphe nuclei (Chan-Palay 1977), which are primarily serotonergic, evidence for altered levels of 5-hydroxytrytophan (5-HT) and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) under ACV stimulation was also assessed in these homogenates.

Startle Experiment

Eight male Sprague-Dawley rats (250–300 g) were used in this study. Animals were housed in pairs and maintained on a 12-hr light–dark cycle with food and water continuously available. All eight animals were operated on and implanted with Silastic-insulated stimulators such that the electrically active portion (two bilateral silver disks) rested subdurally on the fifth vermal lobe of the cerebellum (2 mm posterior to the lambdoid suture). These operations were performed stereotaxically under chloral hydrate (400 mg/kg), and the animals were allowed 1 week postoperative rehabilitation before startle training and testing.

The PSE format requires that subjects be trained for 2 days prior to testing. Training (days 7 and 8 postoperatively) consisted of placing animals in 8 × 15 × 15 cm Plexiglass cages (the same cages later used for startle testing) with floors composed of stainless steel bars. The conditioning stimulus (CS) was provided by two 15-w incandescent bulbs located 15 cm from the cages. Shock (the unconditioned stimulus, UCS) was delivered from a shocker–scrambler driven by a 15-amp power supply. The output of this scrambler, in series with a 100-K resistor, was applied across adjacent bars of the cage. Shock intensity was monitored with an oscilloscope placed across a 1-K resistor connecting a pair of bars, and was expressed as current (ma) = 0.707 × 0.5 × peak-to-peak voltage. Timing control was obtained by using a two-circuit tape reader. Each animal received 10 light–shock pairings on each of the training days. The 0.6-ma shock was presented for the last 0.5 sec of the 1-sec CS, and the intershock interval was 5 min. White noise (65 dB) was delivered throughout the training sessions.

Twenty-four hours after the final training day, the animals began 2 days of startle testing (days 9 and 11 postoperatively). On the first test day, four of the animals underwent startle testing coupled with ACV stimulation ("stimulation condition"), and the other four underwent startle testing without ACV stimulation ("no stimulation condition"). On the second test day, the procedure was repeated with the two groups of animals interchanged: the "stimulation condition" animals became the "no stimulation condition" group and vice-versa. Thus, all eight animals were tested under both conditions, and the results could be grouped and analyzed by condition. This protocol is referred to as a "within-subjects" design and permits each animal to serve as its own control. Its validity in the present circumstances depends on the PSE training responses persisting undiminished

over the 2 days of testing. Observations on other PSE-trained animals indicated that the effect remains significant for at least 4 days posttraining.

For startle testing, the cages were suspended between eight compression springs. A sudden movement of a cage triggered a sensor in a PA Electro-Mike mounted on the back of the cage, causing a voltage change. After being sent to a sample-and-hold circuit, which measured the peak voltage during a 500-msec interval folowing onset of the auditory tone, the output of each cage was displayed as a digital readout. A 4000-Hz, 100-msec tone was employed at a 115 dB level. The same background white noise provided during training was continued throughout the entire testing procedure. The room housing the training and testing chamber, and the chamber itself, were kept dark (except for the CS) during the entire procedure.

During testing, all subjects were placed in their original training cages, provided a 5-min adaptation period, and then presented with 80 tones over the following 40 min (30-sec interstimulus interval, ISI). On half of the tone presentations (light–tone trials), the two 15-w bulbs were switched on 0.5 sec before the tone presentation and remained on for 1.0 sec. The other half of the tone presentations (tone alone trials) occurred in darkness. The LT and TA trials were presented irregularly through the test sessions with the restriction that each trial type occurred five times within each block of 10 trials. The group of four animals designated for the "stimulus condition" on either test day was given 1 hr of ACV stimulation (100 Hz, 2 ma peak-to-peak, 1 msec biphasic square waves, with 5-min stimulation periods alternating with 5-min rest periods) immediately before startle testing. For these animals, the ACV stimulation was also delivered during the 45-min testing session. Care was taken to train and test subjects during the dark part of their circadian cycle, as startle amplitudes have been shown to be higher and less variable during this period (Davis and Sollberger 1971).

Forebrain Homogenate Studies

To study the effect of ACV stimulation on forebrain neurochemistry, a "between-subjects" design was employed. Rather than each animal serving as its own control, as in the startle experiment, two groups with eight rats in each were created. One group was designated as the stimulation group, and the other group was designated as the control (sham) group. All animals received cerebellar stimulator implants to control for an effect of the operation alone on neurochemistry. Two subjects from the stimulation group were unusable in the end because of failure of their stimulators to function properly. Thus, the final groups used in the analysis consisted of six subjects in the stimulation group and eight subjects in the control group.

All subjects in both groups were pretreated with alpha-methyl-para-tyrosine (AMPT) methyl ester HCl (50 mg/kg ip injections calculated as the base and dissolved in 1 ml of saline). This blocks the synthesis of new catecholamines and permits the evaluation of the effect of ACV stimulation on the existing dopaminergic pool. These injections were given 6 and 4 hr before decapitation. Stimulation group subjects were given 1 hr of ACV stimulation (using the same parameters as in the startle experiment) 1 hr before decapitation.

Following decapitation, the whole brain of each subject was removed and rinsed with tap water. The brain stem, including the cerebellum, was separated by a transverse cut 1 mm anterior to the colliculi and was preserved in formalin for histological verification of vermal electrode placement. Then a ventral block of neural tissue containing the nucleus accumbens and a portion of the septal nuclei (especially the medial septum) was dissected

out. This block was bounded caudally by the optic chiasm, laterally by the lateral olfactory tracts, and dorsally by the anterior commissure. Tissue samples were weighed and then frozen on dry ice until homogenization.

Individual tissue samples were homogenized in 2 ml of 0.1 M perchloric acid and centrifuged at 15,000 rpm at 0°C for 20 min. The clear supernatant was then injected into a high-pressure liquid chromatograph with electrochemical detection (Bioanalytical Systems, West Lafayette, IN). The system employed a reverse-phase column (C-18) and a monochloroacetic acid mobile phase (pH 3.05, with 0.25 mM sodium octyl sulfate for ion-pairing and 8% methanol as an organic modifier). Peaks were obtained for DA, dihydroxyphenyl acetic acid (DOPAC), HVA, 5-HT, and 5-HIAA. Concentrations of transmitters and their metabolites were determined by comparing observed peak heights with peak heights of known quantities of authentic chemicals obtained fronm Sigma Chemical Co., St. Louis, MO.

Results

All animals used in this study showed weight gain after the operation and prior to testing and were therefore judged to be healthy. Histological examination verified electrode placement on the fifth vermal lobe in all subjects. Mean startle values were computed for tone alone and for light–tone trials for the vermal stimulation and control conditions. Contrary to expectations, ACV stimulation was found to augment, rather than diminish, startle response for both trial types (Figure 1). The data were analyzed using a two-way ANOVA, with both stimulation (stimulation versus no-stimulation) and lighting condition (light–tone versus tone alone trials) as within-subject variables. Results of the analysis revealed a significant effect of lighting condition ($F = 14.97$, df $= 1,7$, $p < 0.01$), but a nonsignificant effect of stimulation condition ($F = 1.73$, df $= 1,7$) and a nonsignificant interaction effect ($F = 1.84$, df $= 1,7$), despite the greater mean startle amplitudes under stimulation. Inspection of the data suggested that the failure of stimulation to produce statistically reliable increases by this analysis was due to substantial between-animal

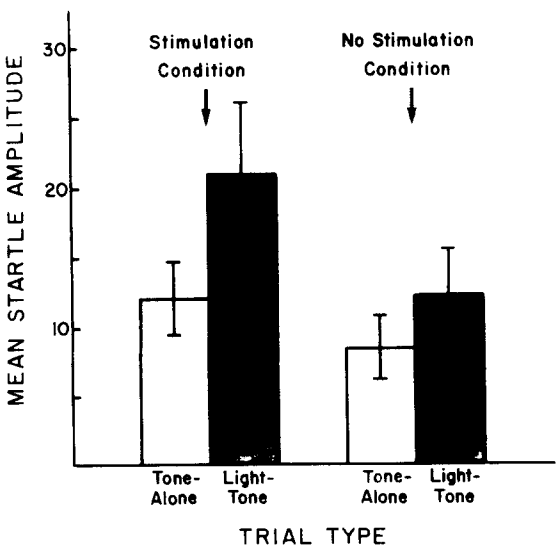

Figure 1. Comparison of light–tone startle amplitude and tone alone startle amplitude, with and without anterior cerebellar vermal stimulation. The averages (mean ± SEM) are over eight animals used in this behavioral study over 2 days, without regard to order of stimulation. Each rat served as its own control. (See text for details.)

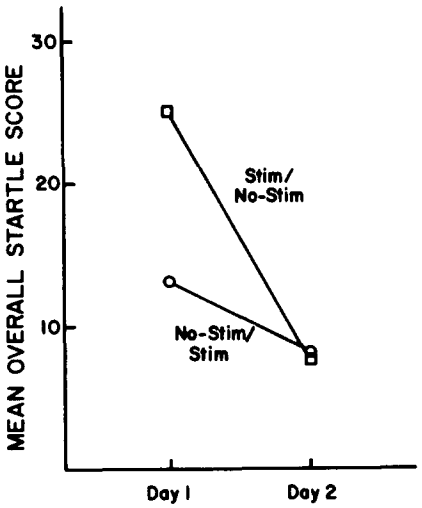

Figure 2. The effect of order of stimulation (day 1/day 2) on mean overall (tone alone + light–tone) startle score, as emphasized by the three-way ANOVA analysis. Each average is over four animals, constituting the stimulation or no-stimulation group for each day (see text for details.)

variability produced by the averaging of scores over two days, with scores on the second day of testing being much lower than scores on the first day due to habituation.

To determine whether or not variabilty produced by within-subject habituation obscured an effect of stimulation, the data were reanalyzed using a three-way ANOVA, with order of testing (stimulation/no-stimulation condition versus no-stimulation/stimulation condition) as a between-subject variable, and lighting condition and day (day 1 versus day 2) as within-subject variables. As expected, this analysis revealed a significant effect of day of testing ($F = 25.95$, df = 1,6, $p < 0.01$) and a significant order × day interaction ($F = 7.82$, df = 1,6, $p < 0.05$). This interaction shows that the four animals receiving stimulation on the first day habituated significantly faster than did the four animals receiving stimulation on day 2 (Figure 2). As the only difference between these two groups of subjects was the order of stimulation, these results suggest that stimulation augmented mean overall (TA + LT) startle scores in day 1 animals and competed with habituation in the subjects receiving stimulation on day 2. The three-way interaction (order × lighting conditions × day) just failed to reach statistical reliability ($F = 3.91$, df = 1,6, $0.05 < p < 0.1$, two-tailed test). A significant three-way interaction would have shown that stimulation increased potentiated (LT − TA) as well as overall startle amplitudes. It seems likely that with more subjects stimulation would be found to have such an effect.

Table 1. Levels of Dopamine, Serotonin, and Their Metabolites in the Nucleus Accumbens of AMPT-Pretreated Animals after 1 hr of Anterior Vermal Electrical Stimulation and in Control Animals with No Stimulation

Neurotransmitter or metabolite	Control (ng/g) ($n = 8$)	Stimulation (ng/g) ($n = 6$)	p Value
DA	3911 ± 589	2354 ± 588	<0.05
DOPAC	677 ± 61	848 ± 70	<0.05
HVA	175 ± 71	134 ± 60	NS
5-HT	518 ± 41	459 ± 27	NS
5-HIAA	208 ± 15	136 ± 16	<0.01

Results for the biochemical experiment are shown in Table 1. Cerebellar stimulation caused a significant decrease in DA levels ($t = 1.87$, df = 12, $p < 0.05$, two-tailed test), but a significant increase in the DOPAC/DA ratio ($t = 2.08$, df = 12, $p < 0.05$, two-tailed test). These results thus suggest an increase in DA turnover. No change was seen in HVA or 5-HT levels between conditions. However, 5-HIAA was greatly reduced in stimulated animals ($t = 3.24$, df = 12, $p < 0.01$, two-tailed test), suggesting a decrease in 5-HT release in stimulated subjects.

Discussion

Stimulation of the ACV using parameters previously reported to elicit therapeutic effects in pacemaker patients (Heath 1977; Heath et al. 1980b) was found to augment mean overall startle amplitudes and to produce a borderline enhancement of the PSE. The most straightforward interpretation of these findings is that ACV stimulation augments fear. However, this interpretation seems to be inconsistent with clinical reports (Heath 1977, Riklan et al. 1977). An alternative explanation is that stimulation elicits an increased responsiveness to environmental cues. This interpretation is consistent with clinical reports showing that cerebellar stimulation has "alerting" effects (Heath 1977; Riklan et al. 1977) and increases responsiveness of patients to social cues (Heath 1977). It is also consistent with the observed increase in DA turnover in the basal forebrain reported in this study. It has been reported that the administration of a low dose of amphetamine, which increases DA activity in the brain and has alerting effects in humans, enhances the PSE in rats (Bridger and Mandel 1967). Higher doses of amphetamine increase startle baseline (Davis et al. 1975). A special involvement of mesolimbic DA systems in these effects is suggested by the observation that direct application of DA to the nucleus accumbens (NAcc) in monkeys (Dill et al. 1978), or stimulation of the mesolimbic pathway by application of the GABA antagonist bicuculline to the ventral tegmental area in cats (Stevens et al. 1974), has been reported to increase the responsiveness of these animals to the environment and to stimulate searching behaviors. Finally, the NAcc has been hypothesized to participate in a neural circuit also involving the substantia innominata and the inferior parietal lobule, which may regulate attentional processes and may be disturbed in schizophrenia (Mesulam and Geschwind 1978).

The observation that ACV stimulation increases DA turnover in the area of the NAcc is consistent with the previous observation that ACV stimulation enhances tritiated CA synthesis and release in this area (Dempesy et al. 1983). Furthermore, this observation renders unlikely the possiblity that ACV stimulation produces its clinical effects by mimicking the pharmacological effects of antipsychotic medication, which is thought to act by blocking DA receptors, thus reducing DA transmission. It could be argued, however, that the therapeutic effect of ACV stimulation is mediated by a reduction of DA activity in a pathway whose activity was not measured in this study, for example, the mesocortical pathway projecting to the prefrontal cortex. It has been shown that DA turnover in the areas of the prefrontal cortex and NAcc are independent of each other, so this remains a possibility.

The findings of this study raise the provocative possibility that ACV stimulation produces its therapeutic effects, at least in part, by enhancing turnover in the mesolimbic DA system. Although this suggestion appears to contradict the dopamine hypothesis of schizophrenia, it is possible that it does not. Crow (1982) has pointed out that schizophrenic symptomatology falls into two relatively distinct clusters: "Type I" schizophrenia,

characterized by positive symptoms such as thought disorder, hallucinations, and delusions, and "Type II" schizophrenia, characterized by negative symptoms such as flat affect, poverty of speech, social deterioration and withdrawal, and intellectual impairment. Patients with positive symptoms typically have episodic rather than chronic disorders and respond better to antipsychotic medication. The schizophrenic patients who have received cerebellar stimulation appear to possess primarily "Type II" symptomatology. Their selection in part was based on their failure to respond to antipsychotic medication. In many cases, their disorders were chronic and up to 20 years in duration. Most of these patients were socially withdrawn and showed flat affect and a deterioration of social skills. These observations suggest that Type II schizophrenics might suffer from an underactivity of DA systems in the brain, in contrast to Type I schizophrenics, who are believed to have an overactivity in these systems.

There is some evidence supporting this speculation. Bowers (1974) has shown that "poor prognosis" schizophrenics, i.e., those with Type II symptomatology, show a reduced accumulation of CSF HVA after treatment with probenecid, which inhibits transport of acid metabolites from the CSF; this suggests a decrease in central DA turnover. Moreover, Gerlach and Luhdorf (1975) reported that the administration of L-DOPA, combined with a pheripheral decarboxylase inhibitor, partially reversed pathological behaviors in young patients with Type II symptomatology. These patients were reported to become more active, more alert, and much more interested in social contacts. Recently, a similar, though not as powerful, effect has been reported by Angrist et al. (1982) following amphetamine administration. These provocative findings were reported using acute administration of low doses of L-DOPA and amphetamine. Perhaps chronic administration of these compounds, particularly of L-DOPA, would produce even greater benefits.

The hypothesis that Type II schizophrenia involves an underactivity of DA systems and that ACV stimulation might be especially effective in reversing Type II symptomatology because of a stimulation of DA activity in the basal forebrain is not necessarily contradictory to the view that ACV stimulation acts by blocking limbic system dysrhythmia (Heath 1977). If, in fact, ACV stimulation blocks abnormal limbic system activity in patients who respond favorably to ACV stimulation, but fails to block dysrhythmic activity in nonresponders (which has not yet been shown), it is possible that the effect of ACV stimulation is mediated by DA release. This hypothesis could easily be tested in animals pretreated with the catecholamine neurotoxin 6-hydroxydopamine.

Stimulation of the ACV was also found to decrease 5-HT release in this study, a change that might also be linked to the therapeutic effect of ACV stimulation. It has been suggested that the symptoms of paranoid schizophrenia (Type I) might involve an underactivity in 5-HT systems as well as an overactivity in DA systems (Jacobs and Trulson 1979). There is some evidence that in patients with Type II symptomatology, a similar reciprocal relationship between DA and 5-HT activity exists, but in the opposite direction. Bowers (1974) reported a 60% higher turnover of 5-HT in poor prognosis patients, although this difference was not statistically reliable, because of the variability in 5-HIAA scores. If this observation holds in a larger sample, it raises the possibility that schizophrenia might reflect an imbalance in DA and 5-HT activity *in either direction* and that ACV stimulation is effective because it normalizes the DA/5-HT imbalance in patients with Type II symptomatology.

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