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Cognitive effects of L-deprenyl in Alzheimer's disease

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Abstract. Monoamine neurotransmitter systems, along with cholinergic systems, are known to play important roles in cognition, and are disrupted in at least some patients with dementia of the Alzheimer type (DAT). This suggests that monoamine-enhancing drugs might ameliorate cognitive symptoms in certain patients with DAT. L-Deprenyl is a monoamine oxidase (MAO) inhibitor which may selectively inhibit MAO-B at low doses, while at high doses it nonselectively inhibits MAO-A as well as MAO-B. We studied its effects on several types of cognitive function in 17 patients with DAT. Two doses of L-deprenyl (10 mg/day and 40 mg/day) and placebo were compared in a double-blind, serial treatment design. Episodic learning and memory, knowledge memory, attention, recognition, and performance on a continuous performance task were assessed at baseline and under these drug and placebo conditions. Statistically significant improvement was noted in performance on an episodic memory and learning task requiring complex information processing and sustained conscious effort during treatment with L-deprenyl 10 mg/day. Knowledge memory, intrusions, and other cognitive functions relevant to DAT were not altered by L-deprenyl at either dose.

Key words: Alzheimer's disease – Cognition – Dementia – Deprenyl – Monoamines – Monoamine oxidase inhibitors

Ascending monoamine brain pathways have been shown to play important roles in normal human and animal cognition as well as in other behaviors (Kety 1970; Anzelark et al. 1973; Gorelick et al. 1975; Wise 1978; Squire and Davis 1981; McGaugh 1983; Hopkins and Johnston 1984). Some of the evidence for this is derived from neuropharmacologic studies demonstrating that drugs that selectively affect monoaminergic functions can influence such complex behaviors. Central monoamine systems are disturbed in at least some patients with dementia of the Alzheimer type (DAT) (Adolfsson et al. 1979; Mann et al. 1980; Cross et al. 1981; Bondareff et al. 1982; Yates et al. 1983; Arai et al. 1984). It is therefore reasonable to investigate the effects of monoamine-enhancing drugs in this disorder. To the extent that functional monoaminergic deficits exist and contribute to the cognitive dysfunction evident in DAT, such drugs might enhance cognition, and improve our understanding of the relationship between neurochemical and behavioral changes.

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L-Deprenyl is a centrally active monoamine-enhancing drug (Knoll et al. 1965) that offers a number of potential advantages for a trial in DAT. It is an irreversible monoamine oxidase (MAO) inhibitor that is relatively safe and is relatively selective for monoamine systems, while lacking significant cholinergic effects (Knoll 1976; Mendis et al. 1981; Birkmayer et al. 1982). The neurochemical and clinical effects of L-deprenyl vary in a dose-dependent fashion. At doses of up to 10 mg/day in humans, L-deprenyl appears to selectively inhibit MAO-B and have minimal antidepressant efficacy, while at doses of approximately 40 mg, it also inhibits MAO-A, may result in amphetamine-like effects not evident at 10 mg/day, and may have more antidepressant efficacy (Knoll 1976; Elsworth et al. 1978; Reynolds et al. 1978; Mendis et al. 1981; Karoum et al. 1982; Mann et al. 1982; Mendlewicz and Youdim 1983; Quitkin et al. 1984). We report a double-blind, placebo-controlled, serial study of the cognitive effects of L-deprenyl 10 mg/day and 40 mg/day in 17 DAT patients, doses expected to produce different neurochemical and thus clinical effects.

Materials and methods

Subjects

Subjects consisted of 17 patients residing on a unit at the NIH Clinical Center who met DSM III criteria for primary degenerative dementia and NINCDS-ADRDA Work Group criteria for probable Alzheimer's disease (McKhann et al. 1984), but not for current or prior major depressive disorder. Our inclusion criteria are summarized elsewhere (Tariot et al. 1986). The mean age was 59.3 years (range 42–72) and the mean duration of symptoms was 4.6 years (range 1–15). The average years of education was 14.1 (range 8–20). All patients experienced mild-to-moderate severity of dementia symptoms, with an average Global Deterioration Scale (GDS) score of 4.3 (range 3–5, Reisberg et al. 1982). The average Hamilton Depression Rating Scale (HDRS) score was 9.9 (range 1–16, Hamilton 1967), with scores predominantly in items assessing difficulty working, impaired concentration, and agitation.

Experimental design

Compounds were administered in the following sequence: placebo (mean duration, 7 days), L-deprenyl 10 mg/day (mean, 28 days), L-deprenyl 40 mg/day (mean 35 days including step-up and step-down periods), and placebo

(mean, 14 days). All patients on the unit consumed a modified low monoamine diet and were monitored for side effects. Two patients in this study did not complete the 40 mg/day deprenyl treatment period because of mild orthostatic hypotension. There were no other drop-outs.

Patients underwent cognitive testing before receiving medications and at the end of the 3rd week of each period of L-deprenyl administration. The last 11 patients underwent further testing at the end of the second period of placebo administration. This was added to the study in order to help preserve the "blind" nature of the cognitive testing.

Cognitive methods

The following tests were chosen because they assess cognitive processes that may have distinct psychobiological determinants and that can be selectively altered by drugs and disease states. These methods are described in detail elsewhere and are briefly summarized below.

Selective reminding task (Buschke 1973). Twelve unrelated mouns were read to the subject, who was then asked to recall these. The subject was prompted with those words that had not been recalled, and asked to recall the entire list. This process was repeated for a total of eight trials. The mean number of words recalled on trials 1–4 and 5–8 were scored separately, providing measures of episodic learning and memory requiring complex information processing as well as conscious effort and attention sustained over time. Data from late and early trials may reflect different kinds as well as degrees of cognitive and non-cognitive demands (see Discussion). The mean number of words produced consistently without prompting from trial to trial was scored for early (1–4) and late (5–8) trials, providing a measure of the reliability of episodic memory in this type of task. "Intrusions" represent inappropriate responses and provide an indirect measure of episodic memory.

Vigilance task (Cohen et al. 1983). Six once- and six twice-presented categorically related words were read to the subject, who was instructed to interrupt the tester whenever a word was presented for the second time. The number of words correctly identified as having been presented twice ("vigilance attention") was used as an operational measure of the subject's attentional and working memory capacities. Subjects were then asked to recall as many words as possible. Recall on the vigilance task provided another measure of episodic memory that was less complex cognitively and required less sustained conscious effort and attention than the selective reminding task, and also did not assess learning. Intrusions were scored as a further indirect measure of episodic memory. Subjects were next read a list of the original stimuli and 12 categorically related but different items ("distractors"). Correctly identified stimuli and distractors were used to derive d′ as a measure of the accuracy of recognition (Elliott 1964). Of the words correctly identified as stimuli, subjects were asked to judge the original frequency of presentation. Accuracy of frequency monitoring was measured by subtracting the mean judged frequencies for once-presented words (maximum = 1) from that for twice-presented words (maximum = 2). This score was used as a measure of "automatic" episodic memory processes (Weingartner et al. 1981).

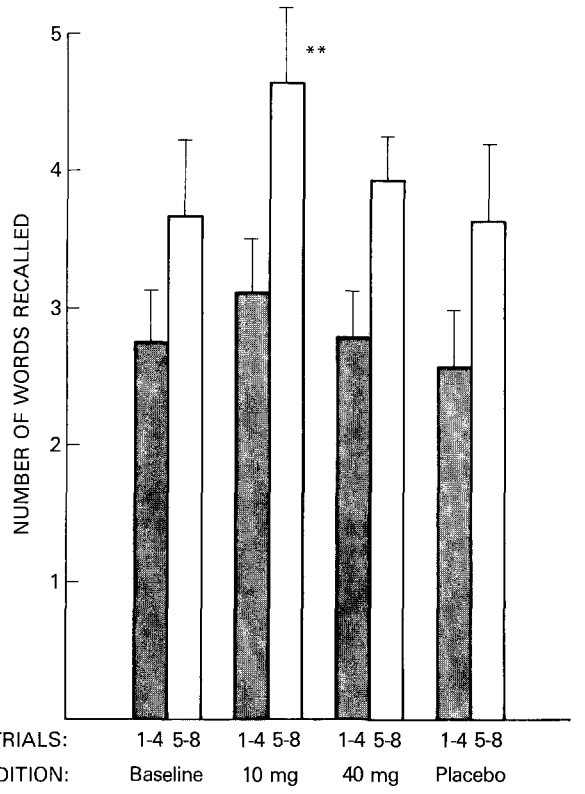

Fig. 1. Selective reminding task performance before and during treatment with two doses of L-deprenyl and placebo: Mean (SEM) free recall or words for early and late trials. $^{**}P<0.01$ for free recall compared to baseline (pre-drug) condition by ANOVAR with paired comparisons using Tukey's Honestly Significant Difference

Category retrieval. Subjects were asked to generate as many associated words or phrases as possible to two verbal stimuli standardized in normal subjects (Palermo and Jenkins 1964). Appropriate and inappropriate responses were scored. Mean values were used as measures of "knowledge memory", i.e., information in long-term memory used to evaluate and synthesize ongoing experience.

Continuous performance task (CPT) (Rosvold et al. 1956). Single letters were generated on a visual monitor for approximately 10 min, and patients instructed to press a button whenever a particular letter sequence appeared. Correct responses increased the rate of stimulus presentation. This task was used as a measure of visuomotor attentional capacities requiring sustained conscious effort but of minimal cognitive complexity. The mean per cent of correct and incorrect responses were used as measures of accuracy. The mean interval between stimulus and response ("mean reaction time") was used as a measure of efficiency, as was the mean interval between stimuli. Eleven subjects completed baseline and both drug testing sessions.

Analysis

The data were analyzed using an analysis of variance with repeated measures (ANOVAR). This was performed first with data from baseline, 10 mg/day L-deprenyl, and 40 mg L-deprenyl conditions, and then with data from subjects

Table 1. Mean (SEM) values for cognitive measures before and during treatment with L-deprenyl and placebo

	Baseline ($n=17$)	10 mg/d ($n=17$)	40 mg/d ($n=15$)	Placebo ($n=11$)
1) Episodic learning and memory				
a) Selective reminding task				
Free recall trials 1–4	2.70 (0.39)	3.12 (0.40)	2.79 (0.35)	2.16 (0.42)
5–8	3.55 (0.49)	4.56[a](0.52)	3.95 (0.39)	3.53 (0.55)
Consistency trials 1–4	0.22 (0.05)	0.19 (0.05)	0.32 (0.08)	0.12 (0.06)
5–8	0.21 (0.05)	0.39[b, c](0.06)	0.34 (0.07)	0.22 (0.08)
Intrusions trials 1–4	2.0 (0.47)	2.0 (0.48)	1.8 (0.69)	1.8 (1.01)
5–8	2.1 (0.54)	2.2 (0.47)	2.4 (0.67)	2.5 (1.23)
b) Vigilance task				
Free recall	3.1 (0.38)	3.3 (0.55)	2.9 (0.42)	2.6 (0.59)
Intrusions	1.9 (0.61)	1.6 (0.35)	1.6 (0.31)	0.7 (0.28)
Frequency monitoring	0.10 (0.11)	0.09 (0.08)	0.15 (0.11)	0.09 (0.09)
2) Knowledge memory				
Category retrieval				
Appropriate	9.7 (1.43)	9.5 (1.64)	7.9 (1.30)	7.3 (1.01)
Inappropriate	1.1 (0.51)	2.0 (1.40)	1.0 (0.54)	1.0 (1.00)
3) Attention				
Vigilance Attention	3.5 (0.48)	3.3 (0.50)	2.7 (0.55)	3.0 (0.63)
CPT ($n=11$, $n=5$ for placebo)				
Correct hits (%)	48 (8)	42 (9)	42 (9)	49 (10)
Incorrect hits (%)	114 (42)	78 (24)	148 (43)	94 (30)
Mean reaction time (ms)	505 (54)	581 (39)	581 (39)	531 (35)
Inter-stimulus interval (ms)	704 (64)	705 (69)	781 (61)	673 (109)
4) Recognition				
Vigilance task				
Recognition (d^1)	1.12 (0.21)	1.26 (0.25)	1.15 (0.18)	1.11 (0.23)

[a] $P<0.01$ vs baseline
[b] $P<0.05$ vs baseline
[c] $P<0.01$ for change (early vs late) vs baseline
Levels of significance determined by ANOVAR with paired comparisons using Tukey's Honestly Significant Difference

who were tested both at baseline and during the second placebo period. The selective reminding task was the only task with repeated trials on a given day. Mean recall and consistency values for early (1–4) and late (5–8) trials were analyzed with a two-way ANOVAR. Degrees of freedom were corrected for nonhomogeneity of variance by the Greenhouse-Geisser approximation. Where significant variation occurred, means were compared using Tukey's Honestly Significant Difference with degrees of freedom again corrected. Two subjects did not complete the L-deprenyl 40 mg/day treatment period. Consequently, the data missing from these cells were interpolated for all cognitive measures except CPT performance for purposes of statistical analysis using a multiple correlation procedure. This was judged to introduce less error into the analysis than would have resulted from dropping these subjects entirely. Means and standard errors were minimally affected by this interpolation, and the power was increased slightly. Pearson product-moment correlation coefficients were determined (without interpolation) in order to assess possible relationships between baseline clinical and demographic characteristics and change in cognitive performance from baseline to each drug condition. Where appropriate, stepwise regression coefficients were determined.

Results

The results from this experiment are organized in terms of their relevance to cognitive functions that may be psychobiologically different.

Episodic memory and learning

Free recall scores on the selective reminding task are summarized in Fig. 1 and Table 1. There was a drug × trial (i.e., early versus late trials) interaction ($P<0.05$). Free recall in early trials of the selective reminding task did not vary across treatment conditions, whereas late trial recall increased significantly during L-deprenyl 10 mg/day treatment ($P<0.01$ versus baseline, $P<0.05$ versus 40 mg/day condition). Late trial free recall increased during L-deprenyl 40 mg/day treatment, but only at a trend level ($P<0.10$). Free recall in late compared to early trials (within drug conditions) was significantly higher on all test days ($P<0.001$). Consistency of recall on the selective treatment reminding task is summarized in Fig. 2 and Table 1. There was a significant drug × trial interaction ($P<0.01$). Consistency of recall in early trials did not vary across conditions, while consistency of recall in late trials increased significantly during 10 mg/day L-deprenyl treatment ($P<0.05$

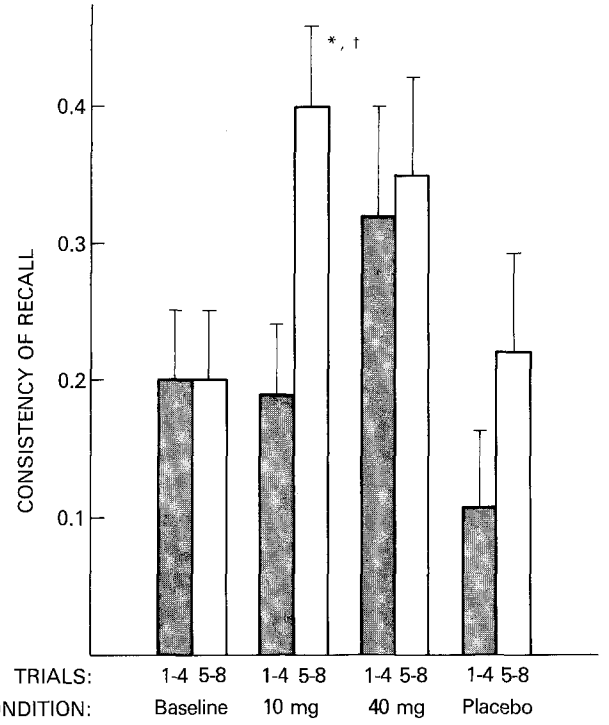

Fig. 2. Selective reminding task performance before and during treatment with two doses of L-deprenyl and placebo: mean (SEM) consistency of recall for early and late trials. $*P<0.05$ for consistency compared to baseline (pre-drug) condition; $+P<0.01$ for change in consistency (early to late trials) compared to baseline by ANOVAR with paired comparisons using Tukey's Honestly Significant Difference

versus baseline only, NS versus 40 mg/day condition). Change in consistency in late compared to early trials (within drug conditions) did vary across treatment conditions ($P<0.01$), and showed a significant increase during L-deprenyl 10 mg/day treatment ($P<0.01$ versus baseline) without significant increases during baseline, 40 mg/day, or placebo conditions.

The remaining data are summarized in Table 1. Intrusions in the selective reminding task did not vary significantly across conditions, nor as a function of number of trials. Free recall in the vigilance task, another measure of episodic memory (but one that does not assess performance as a function of trial number) did not vary significantly across conditions, nor did intrusions. The ability to monitor and judge the frequency of stimuli presented, presumably reflecting automatic episodic memory processes, did not vary across conditions.

Knowledge memory. Category retrieval performance did not vary significantly across treatment conditions for either appropriate or inappropriate responses.

Attention. Attention assessed by the vigilance task and accuracy and efficiency of visuomotor attention assessed by the continuous performance task did not change with drug treatment. It should be noted that the patients performed poorly on the version of continuous performance task selected for this study. Six patients were unable to complete testing during all conditions, and those who did performed poorly at baseline. Most patients required more time to respond to the stimuli than the maximum allowed in the procedure (1 s).

Recognition. Recognition as assessed by the vigilance task was not affected by drug treatment.

Comparison with placebo. Performance on all cognitive tasks during the second placebo period was unchanged in comparison to baseline performance ($n=11$).

Correlations. Correlations were performed using only free recall and consistency data from late trials of the selective reminding task. Since Pearson product-moment correlation coefficients were similar for both low and high dose conditions, results were pooled for simplicity of presentation. Change in late trial free recall and consistency correlated moderately with severity as baseline assessed by Global Dementia Severity (GDS) ratings ($r=0.56$, $P<0.01$ and $r=0.55$, $P<0.01$, respectively); and with duration of dementia ($r=0.38$, $P<0.05$ for both). Change in free recall or consistency did not correlate with age, years of education, or baseline depression ratings (HDRS). Stepwise regressions were performed using severity and duration versus change in late trial free recall, with multiple r values being 0.56 ($P<0.01$) and 0.68 ($P<0.01$), respectively. When this process was repeated for change in late trial consistency, the values were 0.55 and 0.65 respectively.

Discussion

Study limitations

Since the data were obtained through a sequential trial, with drug conditions and testing in a fixed order, it is possible that the selective reminding task performance might have changed over time due to a practice effect. The fact that performance peaked during L-deprenyl 10 mg/day treatment with decreased improvement on 40 mg/day, however, makes this unlikely. In addition, a subgroup of 11 patients was also tested on placebo after receiving drug, and all aspects of selective reminding task performance fell to baseline levels. Parenthetically, when this subgroup was analyzed separately, improvements on L-deprenyl were observed as described for the entire patient group. The mean values for baseline, 10 mg, 40 mg, and placebo conditions for late trial free recall were 3.36, 4.19, 3.56 and 3.53, respectively; and for late trial consistency were 0.20, 0,38, 0.32, and 0.22, respectively, for this subgroup. These findings suggest that a practice effect is not the explanation for the observed changes in selective reminding task performance.

Random change in task performance seems unlikely because it was assessed at four timepoints during the study and changes were observed under drug conditions only (albeit at a trend level during 40 mg/day conditions). Furthermore, similarly dose-dependent behavioral changes were observed (see below). Finally, these and other DAT patients participated in other neuropharmacologic studies (Sunderland et al. 1987; Tariot et al. 1986) prior to participation in the L-deprenyl study, in which selective reminding task performance did not vary during placebo administration and did not differ from baseline in the L-deprenyl study. These findings collectively argue against random occurrence (as well as practice effect) as the explanation for the in-

creased selective reminding task performance observed during low dose L-deprenyl treatment.

Selection of measures

Cognitive deficits reported to be useful in distinguishing patients with DAT from normal subjects, or showing sensitivity to drug treatment, should be considered in a study of this nature. Consequently, verbal recognition (Moss et al. 1986), knowledge memory (Weingartner et al. 1983), episodic learning and memory, particularly in late trials of a serial task (Weingartner et al. 1981), and intrusions in a learning task (Fuld et al. 1982) were assessed in our study. In addition, patients with depression experience clinical, cognitive, and neurochemical disturbances somewhat similar to those reported in DAT and experience improved mood, cognitive function, and neurotransmitter modulation during treatment with monoamine-enhancing drugs (Murphy et al. 1972; Henry et al. 1973; Sternberg and Jarvik 1976; Reus et al. 1979; Glass et al. 1981; Cohen et al. 1984). It follows that a study of monoamine-enhancing drugs in DAT should also include measures of cognitive processes which are impaired in depression, specifically episodic learning and memory tasks requiring complex information processing (Weingartner et al. 1981; Cohen et al. 1982; Roy-Byrne et al. 1986). The array of measures selected for this study reflected the above considerations, although omitted some other potentially important cognitive functions (e.g., visuo-spatial processing, Brinkman and Gershon 1983; Moss et al. 1986).

Findings

The DAT patients' recall of words on late trials of the selective reminding task improved significantly during treatment with L-deprenyl 10 mg/day and improved at a trend level with 40 mg/day. This was coupled with an increase in consistency on the same task also most evident at the 10 mg/day dose. These findings can be interpreted as drug-related improvement of episodic learning and memory. The improvement appears to be selective for the processes requiring the most complex information processing. This is based on the fact that the words used in this task were not categorically related, thereby increasing the cognitive "load". In addition, information processing demands may have increased with trial number on the basis of ongoing rehearsal, repeated efforts to relate new information to information in working memory, and continuous formation of new organizational strategies (Hasher and Zacks 1979), processes that may be particularly difficult for DAT patients, whose stored information decays very rapidly (Moss et al. 1986). Finally, this task required a high degree of sustained conscious effort and attention, cognitively related behaviors necessary for information processing and ameliorated by L-deprenyl. This requirement set the selective reminding task apart from most other cognitive tasks.

The finding that free recall in the vigilance task did not change significantly appears in consistent with the selective reminding task data. However, this task 1) did not assess learning, 2) required relatively less cognitive capacity by virtue of the use of categorically related words and the absence of ongoing complex information processing, and 3) did not require as much sustained conscious attention. The vigilance task would therefore not be expected to yield the same results as the selective reminding task despite also assessing episodic memory.

There were not effects on other cognitive realms assessed in this study. These included automatic episodic memory processes, knowledge memory, attention, and recognition. The continuous performance task was also intended to assess sustained conscious effort and attention (in addition to the selective reminding task), but our patients were essentially unable to complete this due to the requirement of high speed of processing and the length of the task.

Is this isolated cognitive to L-deprenyl selective for DAT? It has been suggested that increased intrusions on a learning task and knowledge memory impairments are cardinal features of DAT (Fuld et al. 1983; Weingartner et al. 1983). However, no changes were observed in these aspects of cognition. Furthermore, there was not even partial improvement in a number of other measures of cognitive function, which might have been expected if a drug were to improve cognition in DAT. In the absence of changes in any of these cognitive realms it may be preferable to conceptualize the cognitive improvement that did occur not as an "antidementia" effect, but rather enhanced performance on those tasks requiring both increased complexity of cognitive processes and sustained conscious effort.

Behavioral change

The value of using behavioral data to enhance understanding of cognitive changes in a study such as this has previously been proposed, although the difficulties of meaningful scaling are unresolved (Tariot and Weingartner 1986). Behavioral changes were observed in these patients while receiving L-deprenyl but not during baseline or the two placebo conditions. This will be detailed elsewhere (Tariot et al. 1987). In brief, "blind" ratings and non-blind global ratings indicated increased energy and social interactions, with reduced anxiety, tension, and depressed mood, which were generally more marked during 10 mg/day treatment. The mood effect was relatively minor. There was increased irritability at the 40 mg/day dose. It is possible that the enhanced sociability played an important role in the apparently selective effects of L-deprenyl 10 mg/day for the one cognitive task that involved sustained interaction with a tester (i.e., the selective reminding task).

It is difficult to make inferences about the interaction between changes in mood and cognition in this as well as in other populations. It may be noteworthy that our patients did not have significant mood disturbance historically or at baseline, mood change with L-deprenyl was modest, and baseline HDRS scores did not correlated with cognitive change. In addition, the antidepressant efficacy of L-deprenyl in other populations is not firmly established, and it is possible that a clinical "antidepressant" effect is more likely to occur at high doses (Mendis et al. 1981; Mann et al. 1983; Quitkin et al. 1984). However, further study will be necessary to clarify the relationship between mood and cognitive effects of L-deprenyl in DAT patients.

Correlations

It appears that patients with longer duration of dementia symptoms as well as more severe symptoms experienced the greatest improvement in task performance. Stepwise multiple regression indicates that these variables contribute separately to the prediction of cognitive performance. This

finding must be considered in light of the selection bias of the study, since our patients represented a narrow range of symptom severity: the strength of these correlations might differ in a study of a broader range of severity and duration. Nonetheless, the correlations between cognitive improvement and severity and duration suggest an apparent contradiction, since other reports have suggested that DAT patients with the least impairments (and earliest onset) would be most likely to benefit from treatment with agents impinging on other neurotransmitter systems such as the cholinergic system (Francis et al. 1985). It has been reported that patients with an early onset of disease may have a more rapidly progressive course with relatively greater dysfunction of monoaminergic systems (Bondareff et al. 1982; Rossor et al. 1984). Perhaps patients with indolent courses of dementia, hence longer-lasting, with at least moderate severity of impairments, represent a subgroup with partial sparing of monoamine systems and increased responsivity to this drug.

Possible mechanisms

It is believed that administration of L-deprenyl 10 mg/day results in relatively selective inhibition of MAO-B, whereas administration of L-deprenyl 40 mg/day results in inhibition of both MAO-B and MAO-A, as well as other neurochemical effects (see Introduction). Since selective reminding task performance was greater at the 10 mg/day dose, one hypothesis is that the improvement observed may have been due to MAO-B inhibition with enhanced neurotransmission of certain monoamine systems. This in turn could have been related theoretically to the reported elevation of MAO-B levels in post-mortem studies of the brains of DAT patients (Robinson et al. 1972; Adolfsson et al. 1980; Gottfries 1985).

The less-evident improvement at the 40 mg/day dose may have also resulted from MAO-B inhibition partially masked by other neurochemical effects that occur primarily at the 40 mg dose. One such effect might be the formation of amphetamine, which is somewhat more likely to reach behaviorally significant levels at this dose but not at the 10 mg dose (Reynolds et al. 1978). Psychostimulants can cause confusion and irritability in some older and/or impaired subjects (Crook et al. 1977; Clark and Mankikar 1979; Wood et al. 1986). Since some of our patients were more irritable at the 40 mg/day dose, it is possible that this effect and clinically unobservable confusion could have been related to amphetamine-like effects of high dose L-deprenyl. Alternatively, it is possible that because patients with DAT are different biologically in a variety of ways from other populations studied, they demonstrate different dose-dependent effects of L-deprenyl treatment. The possible interaction between monoamine disturbances, neurochemical consequences of L-deprenyl administration, and drug-induced cognitive and behavioral changes in DAT are complex and merit further investigation.

Conclusion

Taken together, the findings of this study show that our DAT patients performed better on a task assessing learning and recall of new information while receiving L-deprenyl 10 mg/day, the dose at which selective MAO-B inhibition occurs. Since the improvement appears to have been mediated primarily by alterations in processes requiring the most complex information processing, it is possible that enhanced attention, effort, arousal, or sensitivity to reinforcement could be responsible for this effect. These cognitive changes were associated with changes in observed behavior, characterized by increased energy and social interaction and decreased anxiety and depressed mood, again maximal at the low dose. Such changes, in both cognitive and noncognitive realms, might have been expected to occur with administration of monoamine-enhancing drugs to DAT patients, since generally similar effects are observed when these drugs are administered to other populations with related cognitive and behavioral symptoms (i.e., depressed patients).

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