

Effect of Anxiolytics on Cognitive Flexibility in Problem Solving

Jennifer A. Silver,* John D. Hughes, MD,† Robert A. Bornstein, PhD,* and David Q. Beversdorf, MD*

Objective: Our purpose is to examine the effect of different classes of anxiolytics on cognitive flexibility.

Background: Situational stressors and anxiety impede performance on “creativity” tests requiring cognitive flexibility. Noradrenergic agents have been shown to modulate cognitive flexibility as assessed by performance on anagrams. To determine whether these findings on noradrenergic modulation of cognitive flexibility are specific to the noradrenergic system or are a nonspecific anxiety effect, we compared the effects of propranolol, lorazepam, and placebo on the anagram task.

Methods: Subjects attended 3 test sessions. Prior to each session, subjects were given 1 of the 3 drugs. As in previous research, the natural log of the solution latency of each test item was summed for each test session and compared across drug conditions.

Results: For subjects able to solve the anagrams, solution times after propranolol, but not lorazepam, were significantly lower than after placebo.

Conclusions: Therefore, this suggests that the phenomenon of noradrenergic modulation of cognitive flexibility does not result from a nonspecific anxiolytic effect, but rather is specific to the noradrenergic system.

Key Words: cognitive flexibility, norepinephrine, executive function, problem solving, benzodiazepine, anxiolytic

(*Cog Behav Neurol* 2004;17:93–97)

It has been proposed that 2 types of intelligence, fluid intelligence and crystallized intelligence, are used to solve problems.¹ Crystallized intelligence includes declarative knowledge such as naming the president of the United States. However, many problems cannot be solved by knowledge alone. Fluid intelligence, such as trial and error approaches and cognitive flexibility, is used for complex problem solving when

knowledge alone will not suffice. As one moves from the initial problem to a solution, various actions can be taken. At times, the most dominant option may not be the most optimal step toward the solution. Cognitive flexibility, a form of fluid intelligence, allows one to inhibit strong response preferences to consider the alternative solutions.²

Converging evidence has suggested that the noradrenergic system may modulate cognitive flexibility. Cognitive flexibility is known to decline in the face of situational stressors,³ and such stressors are associated with an increase in activity of the noradrenergic system.^{4,5} Research involving adolescents with known stress-induced cognitive impairment has demonstrated that treatment with beta-adrenergic antagonists, such as propranolol, resulted in significantly improved scores on the Scholastic Aptitude Test (SAT).⁶ This finding suggests that in certain individuals, the noradrenergic system plays a role in stress-related modulation of performance in some types of problem solving.

More recent research has demonstrated a direct role of the catecholamine neurotransmitter systems in modulation of cognition. In a priming experiment, administration of L-dopa, which is converted into both dopamine and norepinephrine, resulted in restriction of the semantic network.⁷ Normal volunteers were asked to press a button as soon as they knew whether a string of letters formed a meaningful word or a nonword. After placebo, subjects could quickly recognize meaningful words if they were either directly or indirectly related to the prime word as compared with a slower response to an unrelated word. After taking L-dopa, the quick response only occurred with the directly related words and not with the indirectly related words. Therefore, the activation of the catecholamine neurotransmitter system results in restriction or narrowing of the semantic network. The semantic network is a large-scale neuronal network, which may resemble other large-scale networks such as the “network of possible solutions” that must be searched in problem-solving tasks involving cognitive flexibility.

Further research examined possible effects of the noradrenergic system on cognitive flexibility in problem-solving tasks.² Subjects performed various types of problem solving tasks 45 minutes after taking propranolol (a beta-adrenergic blocker), placebo, or ephedrine (a beta-adrenergic agonist).

Received June 29, 2003; revised January 12, 2004; accepted January 15, 2004. From *Ohio State University, Columbus, Ohio; and †Bethesda Naval Hospital, Bethesda, Maryland.

Reprints: David Q. Beversdorf, MD, Means Hall 469, 1654 Upham Drive, Ohio State University, Department of Neurology, Columbus, OH 43210 (e-mail: beversdorf-1@medctr.osu.edu).

Copyright © 2004 by Lippincott Williams & Wilkins

Among subjects best able to perform this task, the time taken to solve anagrams (word unscrambling tasks) was significantly longer when the noradrenergic system was activated (ephedrine) than when it was suppressed (propranolol).² The increased time taken to solve such a problem during increased activity of the noradrenergic system suggested that activation of the noradrenergic system resulted in decreased cognitive flexibility in problem solving. This effect on cognitive flexibility may relate to what has been observed with the effect of situational stress on cognitive flexibility.³

Recent research has demonstrated both phasic and tonic changes in the activity of the noradrenergic locus coeruleus corresponding to changes in attentional performance in monkeys.⁸ Pharmacologic modulation of cognitive flexibility may act through a related mechanism by altering the tonic activity of the noradrenergic neurons.

To determine whether noradrenergic modulation of cognitive flexibility is a centrally or peripherally mediated phenomenon, a comparison was made among the effects of propranolol (a peripheral and central beta-blocker), nadolol (a peripheral beta-blocker), and placebo on performance of the anagram task. Anagram solution times after propranolol were significantly lower than after nadolol. This suggests that the modulatory influence of the noradrenergic system on cognitive flexibility is mediated exclusively by a central nervous system mechanism rather than by the central nervous system response to feedback from the peripheral nervous system.⁹ Norepinephrine may influence this central-only mechanism by modulating the signal-to-noise ratio within the cortex.¹⁰

This study compares the effects of a peripheral and central beta-blocker (propranolol) on cognitive flexibility to other anxiety modulating drugs not directed at the noradrenergic system. Benzodiazepines, which interact with the GABA receptor complex and are commonly used as anxiolytics, were used to test whether the effect is due to any form of modulation on anxiety/arousal or whether it is specific to the noradrenergic system. Our hypothesis is that modulation of cognitive flexibility is specific to the noradrenergic system. With this hypothesis, we would predict that propranolol would demonstrate a benefit, whereas the benzodiazepine would not demonstrate an effect. Otherwise, if cognitive flexibility can be augmented by a general reduction of anxiety, then both propranolol and lorazepam would have a beneficial effect on cognitive flexibility.

EXPERIMENTAL DESIGN AND METHODS

The study protocol was approved by the Ohio State University Institutional Review Board. All subjects were recruited for the anxiolytic study from the campus area via flyers and mass e-mails within the medical center. Twenty-one normal subjects were included in this study. Subjects were screened for medical contradictions to beta-blockers and benzodiazepines and were excluded if they were taking beta-blockers,

were not native English speakers, or had a known history of any verbal learning disability, such as dyslexia. All subjects signed a written informed consent prior to participating in the study. Subjects participated in 3 test sessions, each 1 week apart. Prior to each test session, the subject's blood pressure was recorded. They then received oral lorazepam (120 minutes prior) (GABAergic anxiolytic), 40 mg oral propranolol (60 minutes prior) (central and peripheral beta-adrenergic blocker), or placebo (60 minutes prior) in a double-blinded manner (the examiner knew the time delay after drug administration before testing, but not the name of the drug).

A pilot study using a 2-mg dose of lorazepam was performed based on previous research examining the cognitive effects of anxiolytics.¹¹ The 3 subjects to take this dose (Table 1) complained of excessive fatigue and inability to concentrate on completing the task. The data from these 3 subjects were analyzed separately. For the remaining 18 subjects (Table 1), the dose of lorazepam was 1 mg.

Each subject received all 3 drugs (1 mg lorazepam, placebo, and 40 mg propranolol) by the end of the 3 test sessions. The order of drug administration and test administration was counterbalanced across equal numbers of male and female subjects to account for differences in test difficulty and improvements with practice over time.

Immediately prior to the testing session, the blood pressure was measured again. Subjects were also asked to rank their level of anxiety on a scale of 1 to 9, 1 reflecting no anxiety and 9 representing a high anxiety level. This anxiety ranking served to determine if the subjects consciously experienced significantly different levels of anxiety depending on which drug they received.

Test sessions consisted of 15 anagram tests, 6 each of 5- and 6-letter words and 3 7-letter words (Table 2).⁹ The time taken to complete each anagram was recorded. As with our previous work,^{2,9} subjects were allowed a maximum of 2 minutes to complete each anagram. Failure to complete an anagram within the 2 minutes was recorded as 2 minutes. This maximum allowable time was chosen to ensure that all subjects would be able to attempt all of the anagrams within each test session during the peak phase of drug action, and not get stuck on 1 test item.

Comparisons were made between propranolol and placebo, propranolol and lorazepam, and lorazepam and placebo on the natural logarithms of time to complete the anagrams using a 2-tailed t test, as in previous research.²

TABLE 1. Demographics of Subject Population

Lorazepam Dose	Sample Size	Male/Female	Age (Mean ± SD)
1 mg	18	9/9	24.4 ± 2.1 y
2 mg	3	2/1	23.0 ± 0.0

TABLE 2. Anagram Test Sets

Anagram Test 1	Anagram Test 2	Anagram Test 3
5-letter Words	5-letter Words	5-letter Words
IRBCK	SLAGS	ZAZPI
NYOME	NEHOY	TMOEL
OSEOG	ITAPO	OPNHE
AADLS	THETE	MOBOR
EKRCE	NECFE	NHBTU
HTRSI	EIYDL	GLAEE
6-letter Words	6-letter Words	6-letter Words
ROYEMM	WOERLF	PPLEUR
NHDLEA	CERCOS	IARTGU
GERUBR	KSTBEA	KPNNIA
SRREEA	OPCILE	NNIEAC
NECICS	CNLPIE	SNIIOV
ATESTE	AOGRNE	RBELRA
7-letter Words	7-letter Words	7-letter Words
ORYCTAF	DUNTERH	KNECIHC
LETKLIS	WEEJYLR	ILOADHY
CLEHIVE	LEGLOCE	NENTAAN

more than 80% of the anagrams were included. As with our previous research, the times to complete the anagram tasks were adjusted for test order and drug order, and the natural logarithms of these scores were compared among drug conditions^{2,9}: Due to the learning effect and the possibility of variation in difficulty among each test, scores were divided by co-factors derived from the relative difficulty of each test and the order of testing. Subjects receiving propranolol solved the anagrams in a significantly shorter period of time than after taking the placebo (Table 3). A trend toward propranolol completion times being shorter than those of lorazepam was also observed. No significant difference between placebo and lorazepam completion times was found. No difference existed in numbers of failed anagrams among drug conditions (Table 3). Perseverations were rare for all conditions.

There was no significant difference in anxiety ratings between the 2 anxiolytic drugs (Table 3). However, a significant anxiolytic effect was not achieved by either drug, perhaps due to the lack of significant anxiety at baseline. As expected, subjects' mean arterial pressures (diastolic pressure + 1/3[systolic pressure – diastolic pressure]) tended to be lower after receiving propranolol compared with placebo (Table 3).

RESULTS

The logarithmic scores of the 3 subjects receiving the 2-mg dose of lorazepam revealed subjects receiving the lorazepam took a significantly longer amount of time to complete the anagrams compared with placebo (48.2 ± 3.8 SD for lorazepam, 38.2 ± 4.5 SD for placebo, t(2)=8.495, P = 0.0135). These results are consistent with the subjects' reports of an inability to concentrate on the task at the 2-mg dosage.

Several subjects had difficulty performing the anagrams. To avoid a floor effect, only those subjects who could solve

DISCUSSION

The goal of this study was to determine whether the modulation of cognitive flexibility is specific to the noradrenergic system or whether such effects can be observed with other anxiolytics, such as the GABA receptor complex modulators, the benzodiazepines. Cognitive flexibility, as measured by the time required to solve anagrams, was enhanced after subjects received a beta-adrenergic blocker compared with placebo. This finding supports previous research suggesting the modulatory role of the noradrenergic system in cognitive flexibility.² In contrast, no significant difference in scores was

TABLE 3. Summary of Results for 1-mg Lorazepam Dose

Drug	Sum of Latency (natural log) Avg. Across Subjects (Mean ± SD)	Sum Unsolved Avg. Across Subjects (Mean ± SD)	Anxiety Score Avg. Across Subjects (Mean ± SD)	Average MAP (Mean ± SD)
Lorazepam 1 mg	36.6 ± 7.9	1.9 ± 1.6	3.0 ± 1.7	87.9 ± 7.2
Placebo	38.3 ± 6.5	1.7 ± 1.1	2.8 ± 1.8	90.5 ± 5.8
Propranolol 40 mg	33.5 ± 5.6	1.3 ± 1.2	3.6 ± 2.2	87.8 ± 4.4
Lorazepam vs. placebo	t(13) = 1.097 P = 0.292	t(13) = 0.385 P = 0.706	t(13) = 0.479 P = 0.640	t(13) = 1.726 P = 0.108
Propranolol vs. placebo	t(13) = 2.815 P = 0.015	t(13) = 0.877 P = 0.396	t(13) = 1.674 P = 0.118	t(13) = 2.051 P = 0.061
Lorazepam vs. propranolol	t(13) = 1.819 P = 0.092	t(13) = 1.385 P = 0.189	t(13) = 1.014 P = 0.329	t(13) = 0.070 P = 0.945

MAP, mean arterial pressure.

found between the placebo and the benzodiazepines. Propranolol also tended to improve anagram-solving times compared with the benzodiazepines. Such a finding supports the hypothesis that the modulation of cognitive flexibility is specific to the noradrenergic system. Furthermore, there was no difference between propranolol and lorazepam in anxiety ratings, although comparisons to placebo suggest that there was a lack of significant anxiety at baseline such that neither drug could yield an anxiolytic effect. However, the higher dose of lorazepam resulted in poor performance. This suggests against our findings being secondary to an inadequate anxiolytic dose of lorazepam. Therefore, the previous research supporting a central noradrenergic mechanism of modulating cognitive flexibility^{2,9} appears not to be generalized to other anxiolytics. However, due to the small sample size, these findings would need to be confirmed by a larger study before a firm conclusion can be made. Furthermore, the possibility must also be considered that the soporific effects of lorazepam may interfere with any potential problem-solving benefit, allowing propranolol to appear to be relatively beneficial.

This mechanism may occur through modulation of the signal-to-noise ratio within the cortex by the noradrenergic system.¹⁰ Primate research does reveal alterations in cognitive performance associated with changes in activity of the noradrenergic locus coeruleus.⁸ In the case of anagrams, the increased “noise” in the state of low noradrenergic tone may be beneficial to problem solving by allowing broader access to the lexical-semantic network.

Understanding the mechanism by which stressors and the noradrenergic system affect cognitive flexibility may lead to a further understanding of the mechanism of treatment of test anxiety as well as understanding the mechanisms that influence “creativity.” The anagram task has long been considered a method of assessing “creativity”^{12–14} and has been used to assess learned helplessness.¹⁵ The anagram task has also been widely used in studies of anxiety, demonstrating a decrement in performance in anxious subjects,^{16–18} and has furthermore been proposed as a marker for anxiety.¹⁹ As described above, propranolol has shown a beneficial effect on scores on the SAT in adolescents with stress-induced cognitive impairment.⁶ Perhaps this benefit arises not only from an anxiolytic effect, but also from augmented access to networks in problem solving due to modulation of the noradrenergic system. Furthermore, propranolol has demonstrated efficacy in stress-induced impairment in performance on other tasks, including public speaking.^{20,21}

Developmental conditions such as autism are also associated with impairments in cognitive flexibility²² and are known to benefit from drugs that decrease the activity of the noradrenergic system.^{23–26} Perhaps better understanding of this process can help optimize treatment of autism. Our findings also relate to the treatment of the spectrum of attention deficit disorders. Some studies had suggested that stimulant

therapy might impair cognitive flexibility in attention deficit disorder.²⁷ However, more recent studies have not revealed this finding and have even shown improvements in cognitive flexibility with stimulants.^{28,29} Reexamination of this issue may be fruitful with our testing paradigm. Furthermore, the upregulation of the noradrenergic system occurring during cocaine and opiate withdrawal^{30–34} may be responsible for an impairment of cognitive flexibility, leading to maladaptive behavior and relapse during the withdrawal process. Therefore, a clearer understanding of the cognitive processes affected by the activation of the noradrenergic system may eventually lead to a pharmacotherapeutic treatment to help patients improve their cognitive flexibility during the drug withdrawal process, leading to a higher percentage of successful withdrawals. Noradrenergic modulation of cognitive flexibility is also important in our understanding of how problem-solving tasks are carried out by normal individuals.

Whereas the neural mechanisms underlying noradrenergic modulation of cognitive flexibility are not fully understood, the influence of the frontal lobes may be implied due to their roles in strategy shifting in problem solving.³⁵ Future research is also needed to determine the range of cognitive tasks affected by the noradrenergic system and to further examine the pharmacology as well as the neuroanatomical substrate of this process.

ACKNOWLEDGMENTS

This project was funded by an award from the Roessler Scholarship Fund at the Ohio State University. Portions of this research were presented at the Cognitive Neuroscience Society, 2001.

REFERENCES

1. Cattell RB. Theory of fluid and crystallized intelligence: A critical experiment. *J Educ Psychol.* 1963;54:1–22.
2. Beversdorf DQ, Hughes JH, Stenberg BA, et al. Noradrenergic modulation of cognitive flexibility in problem solving. *Neuroreport.* 1999;10:2763–2767.
3. Martindale C, Greenough J. The differential effect of increased arousal on creative and intellectual performance. *J Genet Psychol.* 1975;123:329–335.
4. Ward MM, Metford IN, Parker SD, et al. Epinephrine and norepinephrine responses in continuously collected human plasma to a series of stressors. *Psychosom Med.* 1983;45:471–486.
5. Kvetnansky R, Pacak K, Sabban EL, et al. Stressor specificity of peripheral catecholaminergic activation. *Adv Pharmacol.* 1998;42:556–560.
6. Faigel HC. The effect of beta blockade on stress-induced cognitive dysfunction in adolescents. *Clin Pediatr.* 1991;30:441–445.
7. Kischka U, Kammer T, Maier S, et al. Dopaminergic modulation of semantic network activation. *Neuropsychologia.* 1996;34:1107–1113.
8. Usher M, Cohen JD, Servan-Schreiber D, et al. The role of locus coeruleus in the regulation of cognitive performance. *Science.* 1999;283:549–554.
9. Beversdorf DQ, White DM, Chever DC, et al. Central β -adrenergic modulation of cognitive flexibility. *Neuroreport.* 2002;13:2505–2507.
10. Hasselmo ME, Linstet C, Patil M, et al. Noradrenergic suppression of synaptic transmission may influence cortical signal-to-noise ratio. *J Neurophysiol.* 1997;77:3326–3339.
11. Greenblatt DJ, Scavone JM, Harmatz JS, et al. Cognitive effects of beta-adrenergic antagonists after single doses: pharmacokinetics and pharma-

- codynamics of propranolol, atenolol, lorazepam, and placebo. *Clin Pharmacol Ther.* 1993;53:577–584.
12. Kumar D, Kumari S. Problem solving as a function of creativity and personality. *Psychol Stud.* 1988;33:157–161.
 13. Shaw GA, Conway M. Individual differences in nonconscious processing: The role of creativity. *Pers Individ Diff.* 1990;11:407–418.
 14. Gavurin EI. Relationship of anagram solving to measures of divergent-production and letter-rearrangement ability. *J Gen Psychol.* 1975;92:231–235.
 15. Schmeck RR, Dunckley C. Anagram performance following initial exposure to insoluble anagrams. *Percept Mot Skills.* 1973;36:122.
 16. Dey MK. Anagram solution speed as a joint function of manifest anxiety and number of category sets. *Am J Psychol.* 1978;91:81–88.
 17. Tomasini J. Effect of peer-induced anxiety on a problem-solving task. *Psychol Rep.* 1973;33:355–358.
 18. Harleston BW, Smith MG, Arey D. Test-anxiety level, heart rate, and anagram problem solving. *J Pers Soc Psychol.* 1965;1:551–557.
 19. Thyer BA, Papsdorf JD. Discriminant and concurrent validity of two commonly used measures of test anxiety. *Educ Psychol Meas.* 1982;42:1197–1204.
 20. Lader M. Beta-adrenergic antagonists in neuropsychiatry: an update. *J Clin Psychiatry.* 1988;49:213–223.
 21. Laverdue B, Boulenger JP. Medications beta-bloquantes et anxiete. Un interet therapeutique certain [Beta-blocking drugs and anxiety. A proven therapeutic value]. *L'Encephale.* 1991;17:481–492.
 22. Ozonoff S, Strayer DL, McMahon WM, et al. Executive function abilities in autism and Tourette syndrome: an information processing approach. *J Child Psychol Psychiat.* 1994;35:1015–1032.
 23. Ratey JJ, Bemporad J, Sorgi P, et al. Brief report: open trial effects of beta-blockers on speech and social behaviors in 8 autistic adults. *J Autism Devel Disord.* 1987;17:439–446.
 24. Jaselskis CA, Cook EH Jr, Fletcher KE, et al. Clonidine treatment of hyperactive and impulsive children with autistic disorder. *J Clin Psychopharmacol.* 1992;12:322–327.
 25. Fankhauser MP, Karumanchi VC, German ML, et al. A double-blind, placebo-controlled study of the efficacy of transdermal clonidine in autism. *J Clin Psychiatry.* 1992;53:77–82.
 26. Koshes RJ, Rock NL. Use of clonidine for behavioral control in an adult patient with autism. *Am J Psychiatry.* 1994;151:1714.
 27. Tannock R, Schachar R. Methylphenidate and cognitive perseveration in hyperactive children. *J Child Psychol Psychiatry.* 1992;33:1217–1228.
 28. Tannock R, Schachar R, Logan G. Methylphenidate and cognitive flexibility: dissociated dose effects in hyperactive children. *J Abnorm Child Psychol.* 1995;23:235–266.
 29. Douglas VI, Barr EG, Desilets J, et al. Do high doses of stimulants impair flexible thinking in attention-deficit hyperactivity disorder? *J Am Acad Child Adolesc Psychiatry.* 1995;34:877–885.
 30. Harris GC, Williams JT. Sensitization of locus ceruleus neurons during withdrawal from chronic stimulants and antidepressants. *J Pharm Exp Ther.* 1992;261:476–483.
 31. Macey DJ, Smith HR, Nader MA, et al. Chronic cocaine self-administration upregulates the norepinephrine transporter and alters functional activity in the bed of the stria terminalis of the rhesus monkey. *J Neurosci.* 2003;23:12–16.
 32. Charney DS, Riordan CE, Kleber HD, et al. Clonidine and naltrexone: a safe, effective, and rapid treatment of abrupt withdrawal from methadone therapy. *Arch Gen Psychiatry.* 1982;39:1327–1332.
 33. Gold MS, Redmond DE Jr, Kleber HD. Clonidine blocks acute opiate-withdrawal symptoms. *Lancet.* 1978;2:599–602.
 34. Jasinski DR, Johnson RE, Kocker TR. Clonidine in morphine withdrawal. Differential effects on signs and symptoms. *Arch Gen Psychiatry.* 1985;42:1063–1066.
 35. Miller LA, Tippett LJ. Effects of focal brain lesions on visual problem-solving. *Neuropsychologia.* 1996;34:387–398.