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INFLUENCE OF THE ALPHA$_2$ NORADRENERGIC ANTAGONIST PIPEROXANE ON LONGEVITY IN THE FISCHER-344 RAT: A PRELIMINARY REPORT [1]

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Summary.—Piperoxane is an α_2-noradrenergic antagonist with demonstrated excitatory effects on neurons in the locus coeruleus, causing a corresponding increase in norepinephrine in many forebrain areas. 16 male Fischer-344 rats approximately 16 months of age were injected with 3 mg/kg of piperoxane or .09% saline. The piperoxane-treated rats lived an average of 127.1 days longer than the saline-treated rats. The results are discussed in terms of the effects of strategies designed to enhance brain levels of catecholamine and their effect on the aging process. A discussion of further research is also presented.

Investigations in which animal models are used to explore the mechanisms that underlie the process of aging, including the extension of average and maximum life span, have produced some exciting early results (e.g., Knoll, Yen, & Miklya, 1994; Piantanelli, Zaia, Rossolini, Viticchi, Testa, Basso, & Antogognini, 1994; Weindruch & Walford, 1988). Of the different therapeutic strategies employed, caloric restriction has been the most promising (Weindruch & Walford, 1988; Yu, Masaro, & McMahon, 1985; Yu, Masaro, Murata, Bertrand, & Lynd, 1982).

Recently, implementation of an effective pharmacologic strategy using the type B monoamine oxidase inhibitor (MAO-I), L-deprenyl, has been reported to increase longevity (Ivy, 1990; Ivy, Rick, Murphy, Head, Reid, & Milgram, 1994; Milgram, Racine, Nellis, Mendonca, & Ivy, 1990; Piantanelli, *et al.*, 1994). MAO inhibitors increase central and peripheral catecholamine release (Pletscher, 1968), leading to an increase in brain catecholamines, including norepinephrine (Feldman & Quenzer, 1984).

Piperoxane is an α_2-noradrenergic antagonist with demonstrated excitatory effects on neurons in the locus coeruleus (Cedarbaum & Aghajanian, 1976). While the exact mechanism of action is unclear, research suggests that the activation effect of piperoxane in the locus coeruleus is the result of autoreceptor and collateral inhibition blockade, leading to an enhanced firing rate in locus coeruleus neurons (Feldman & Quenzer, 1984). In turn, elevations in locus coeruleus cell firing should cause a corresponding increase in norepinephrine in many forebrain areas (Zornetzer, 1985), includ-

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ing the cerebral cortex, hippocampus, amygdala, and hypothalamus (Feldman & Quenzer, 1984).

Past research suggested that the use of piperoxane enhanced the cognitive ability of aged rodents (Zornetzer, 1985). While the primary goal of research in our laboratory was to extend these findings using a more complex series of tasks (Dietrich & Compton, submitted), one unexpected result was the effect of piperoxane on longevity.

Method

Subjects

Sixteen male Fischer-344 rats, weighing between 339 and 413 gm, served as the subjects. The rats, 16 months of age at the start of the experiment, were randomly assigned to either the saline-treatment group or the piperoxane-treatment group. All rats were permitted *ad lib.* access to food (standard Purina Rodent Chow) and water, individually housed, and maintained on a reverse 12-hr. light/12-hr. dark cycle (lights on at 7:00 A.M. local time).

Procedure

All rats received either intraperitoneal injections of 3 mg/kg of piperoxane or a comparable volume of .09% saline. Injections were given once every 48 hours for four months and, to avoid peritoneal irritation, injection site was systematically varied. At the end of the 4-mo. drug injection period, all rats were permitted a 1-wk. drug-free period before behavioral testing. The experimental protocol and results are described elsewhere (Dietrich & Compton, submitted).

Results and Discussion

Table 1 is a summary of the mean life expectancies for the saline- and piperoxane-treated animals. Groups were compared through the use of two-tailed t tests. Animals who died before 24 months of age are included by subtracting from 730 days (i.e., two years) and calculated as negative days (Kitani, Kanai, Carrillo, & Ivy, 1994). The percentage increases in mean survival in piperoxane-treated rats relative to saline-treated rats were 16.7% (from birth), 61.8% (from 18 months), and 137.7% (from 24 months). In fact, six of the eight piperoxane-treated animals were alive at 27 months of age but were sacrificed shortly thereafter. Body weights were similar in both groups. However, no necropsies or histological analyses were performed.

Although preliminary in nature, the present results are intriguing. Further research in our laboratory will assess the specific effect of piperoxane on target tissues, including an examination of blood serum chemistry, body weight, and cortical as well as subcortical analysis of the brain. However, a few tentative statements about the putative cause of the observed group differences are possible.

TABLE 1
MEANS AND STANDARD DEVIATIONS FOR LONGEVITY IN DAYS FOR THE SALINE- AND PIPEROXANE-TREATED RATS

Time Period	Saline-treated Rats ($n=8$)		Piperoxane-treated Rats ($n=8$)		$M_{Diff.}$*	% Increase
	M	*SD*	*M*	*SD*		
From Birth	634.4	56.83	761.5	43.04	127.1	16.7
From 18 months	78.4	56.83	205.5	43.04	127.1	61.8
From 24 months	−34.8	56.83	92.3	43.04	127.1	137.7

*Significant ($t_{14}=5.04$, $p<.01$).

As previously noted, recent research has focused on the life extending properties of the MAO inhibitor, L-deprenyl. Normally, mitochondrial membrane bound MAO degrades dopamine into inert metabolites such as 3,4-dihydroxyphenylacetaldehyde (Feldman & Quenzer, 1984). Through its inhibitory action on type B MAO, L-deprenyl produces an increase in dopamine. In turn, the dopamine is taken up by vesicles and converted to norepinephrine via the enzymatic action of dopamine-β-hydroxylase (see Feldman & Quenzer, 1984).

Similarly, via inhibition of the modulatory$_2$ norepinephrine receptor, piperoxane produces an increase in norepinephrine. While the mode of action for the two drugs is quite different, they both share the common feature of increasing catecholamine levels; however, any attempts to explain the underlying physiological mechanism responsible for the observed group differences would be premature. The average life span of Fischer-344 rats is 23.1 mo. (Woodruff-Pak, 1990). In the saline-treated group, the mean life expectancy was approximately 21 months; the average life expectancy of the piperoxane-treated rats was approximately 26 months. However, because of the small sample, the results could simply be due to sampling error, producing a Type I error (Howell, 1987).

As is the case for L-deprenyl (Kitani, *et al.*, 1994), even if it is determined that piperoxane increases longevity, the optimal dose, mode and length of administration, and variables such as gender must be considered. If the effect of piperoxane can indeed promote a life-prolonging effect, then the drug could provide an additional experimental model for the assessment of the physiological mechanisms that influence the aging process.

REFERENCES

CEDARBAUM, J. M., & AGHAJANIAN, G. K. (1976) Noradrenergic neurons of the locus coeruleus: inhibition by epinephrine and activation by the α_2-antagonist piperoxane. *Brain Research*, 112, 413-419.

DIETRICH, K. L., & COMPTON, D. M. (submitted) Noradrenergic modulation of learning and memory in rats: effects of piperoxane.

FELDMAN, R. S., & QUENZER, L. F. (1984) *Fundamentals of neuropsychopharmacology*. Sunderland, MA: Sinauer.

HOWELL, D. C. (1987) *Statistical methods for psychology.* (2nd ed.) Boston, MA: PWS-Kent.

IVY, G. O. (1990) Maintenance of L-deprenyl prolongs life in aged male rats. *Life Sciences*, 47, 415-420.

IVY, G. O., RICK, J. T., MURPHY, M. P., HEAD, E., REID, C., & MILGRAM, N. W. (1994) Effects of L-deprenyl on manifestations of aging in the rat and dog. *Annals of the New York Academy of Science*, 717, 45-59.

KITANI, K., KANAI, S., CARRILLO, M. C., & IVY, G. O. (1994) (–) deprenyl increases life span as well as activities of superoxide dismutase and catalase but not of lutathione peroxidase in selective brain regions in Fischer rats. *Annals of the New York Academy of Science*, 717, 60-71.

KNOLL, J., YEN, T. T., & MIKLYA, I. (1994) Sexually low performing male rats die earlier than their high performing peers and (–) deprenyl treatment eliminates this difference. *Life Sciences*, 54, 1047-1057.

MILGRAM, N. W., RACINE, R. J., NELLIS, P., MENDONCA, A., & IVY, G. O. (1990) Maintenance of L-Deprenyl prolongs life in aged male rats. *Life Sciences*, 47, 415-420.

PIANTANELLI, L., ZAIA, A., ROSSOLINI, G., VITICCHI, C., TESTA, R., BASSO, A., & ANTOGOGNINI, A. (1994) Influence of L-Deprenyl treatment on mouse survival kinetics. *Annals of the New York Academy of Science*, 717, 72-78.

PLETSCHER, A. (1968) Monoamine oxidase inhibitors: effects related to psychostimulation. In D. H. Efron (Ed.), *Psychopharmacology: a review of progress 1957-1964.* Washington, DC: U.S. Government Printing Office. (Pub 1836) Pp. 649-654.

WEINDRUCH, R., & WALFORD, R. L. (1988) *The retardation of aging and disease by dietary restriction.* Springfield, IL: Thomas.

WOODRUFF-PAK, D. S. (1990) Mammalian models of learning, memory, and aging. In J. E. Birren & K. W. Schaie (Eds.), *Handbook of the psychology of aging.* (3rd ed.) San Diego, CA: Academic Press. Pp. 234-257.

YU, B. Y., MASARO, E. J., & MCMAHON, E. (1985) Nutritional influences on aging of Fischer 344 rats: I. Physical, metabolic and longevity characteristics. *Journal of Gerontology*, 40, 657-670.

YU, B. Y., MASARO, E. J., MURATA, I., BERTRAND, H. A., & LYND, F. T. (1982) Life span study of SPF Fischer 344 male rats fed *ad libitum* or restricted diets: longevity, growth, lean body mass and disease. *Journal of Gerontology*, 37, 130-141.

ZORNETZER, S. F. (1985) Catecholamine system involvement in age-related memory dysfunction. *Annals of the New York Academy of Science*, 444, 242-254.

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