Table 1. Estimates, averaged over assay replications, of the differences in geotactic score between the structurally heterozygous and the structurally homozygous forms of the chromosome pair of a column for the population of a row. Rows (roman type): estimates and standard errors for geotactic effects of chromosomes; (*italic type*): differences between homologues from selected and unselected populations, with standard errors.

Chromosome		
X	II	III
Geopositive population		
1.39* ± 0.13	1.81* ± 0.14	0.12 ± 0.12
0.36 ± 0.24	*0.07 ± 0.19*	*0.41† ± 0.20*
Unselected population		
1.03* ± 0.21	1.74* ± 0.12	−0.29 ± 0.17
−0.56‡ ± 0.26	*−1.41§ ± 0.23*	*−0.78‡ ± 0.23*
Geonegative population		
0.47‖ ± 0.17	0.33 ± 0.20	−1.08‖ ± 0.16

Degrees of freedom: *17; †34; ‡35; §31; ‖18.

a free-mating population during selection of the two derived populations. For each population, ten replications were made of the assay. From most replications behavioral measurements were made on two samples of approximately 200 females each.

Table 1 presents (i) estimates and standard errors for the effects on geotaxis of the three chromosomes in the three populations; (ii) differences between estimates in the selected and unselected populations, with standard errors; and (iii) degrees of freedom from Student's t distribution for both the estimates and the differences which are significant ($P < .05$). Interactions among chromosomes were all negligible and are therefore omitted. The estimates are averages over assay replications of the differences in geotactic score between the structurally heterozygous and the structurally homozygous forms of the chromosome pair of a column for the population of a row.

The results of these experiments reveal the polygenic nature of individual differences in geotaxis. Genes on two chromosomes respond to selection for positive and for negative geotaxis; genes on another respond to selection for negative geotaxis only.

Selection studies have shown how large a part of the range of individual differences in geotaxis can be accounted for by differences in genotype. For the genetic background provided by the cross to the tester stock, the assay now shows (i) the extent of the difference between the selected populations attributable to differences in each of the three chromosomes; (ii) the different roles that the three chromosomes play in geotaxis; and (iii) how each chromosome in the two selected populations has changed in comparison with its unselected homologue in the foundation population. In the foundation population, chromosomes X and II contain factors which produce positive geotaxis, while chromosome III is slightly negative. All three chromosomes respond to selection for negative geotaxis: the positive effect of chromosomes X and II is markedly diminished, while the negative effect of chromosome III is considerably enhanced. In response to selection for positive geotaxis, chromosome III changes from negative to positive, chromosome II remains unchanged, and chromosome X has probably become slightly more positive. Clearly there are genes distributed over most of the genome which influence the response to gravity.

Analysis of the role of the chromosomes in behavioral variation suggests that it is now possible to specify with greater precision than ever before the structural basis of behavior. In organisms whose chromosomes are well mapped against their morphology, the chromosome map will suggest what structures intervene between a given chromosome and the behaviors with which it correlates. Furthermore, the chromosome-behavior correlations should contribute to the chromosome map, since each behavior will, in turn, suggest the structures that are involved in its execution.

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5. The multiple inversion stock used in the assays contains the inversions and mutants listed for stock No. 107 in the Yale stock list, *Drosophila Inform. Serv.* **32** (1958): Sc^{S1} *B InS* w^a sc^8; *SMI Cy/Pm; Ubx/Sb.*
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Reversal of Phenylalkylamine Tachyphylaxis by Norepinephrine

Abstract. Since the responses to "neurosympathomimetic amines" are reduced in the reserpinized animal and restored by norepinephrine administration, it was postulated that norepinephrine might also affect the development of their tachyphylaxis. We found that norepinephrine infusion restored, at least partially, certain tachyphylactic responses to amphetamine or ephedrine and fully prevented the development of tachyphylaxis to tyramine.

The class of drugs known as neurosympathomimetic amines (*1*) exhibit tachyphylaxis. These amines, for example ephedrine, amphetamine, or tyramine, which produce greatly reduced effects or no effects in chronically reserpinized animals, have been shown to release norepinephrine; the administration of norepinephrine in such animals may restore the responses to these amines (*2*). We showed that the pressor response to ephedrine, abolished by large amounts of cocaine, could be restored by the infusion of norepinephrine itself or by agents which act as norepinephrine-sparing compounds (*3*). Therefore, it was postulated that the loss of norepinephrine from critical sites might be the etiological factor in the development of neurosympathomimetic amine tachyphylaxis. Experiments discussed below were devised to test this hypothesis.

Four parameters were measured in male cats, weighing from 2 to 4 kg, anesthetized with α-chloralose (80.0 mg/kg, intraperitoneally) and pretreated with atropine sulfate (2.0 mg/kg, intravenously) and with polygalacturonic acid glycoside (Mepesulfate, 10.0 mg, total dose): (i) mean arterial blood pressure, (ii) heart rate, (iii) tonus, and (iv) contractions of the nictitating membrane. Blood pressure from the carotid artery was recorded with a Sanborn transducer (No. 267B), and the nictitating membrane responses with Grass transducer (No. FT03) on a Sanborn four-channel polygraph. One femoral vein was canulated for the injections of the neurosympathomimetic amines, and the other for norepinephrine infusions. The nictitating membrane was set up for recording after removal of the lens.

To ascertain the rate and extent of tachyphylaxis development, control experiments were performed in six cats for each neurosympathomimetic amine studied (*4*). Hourly intravenous injections of *dl*-ephedrine sulfate (1.5 mg/kg) or *dl*-amphetamine sulfate (0.35

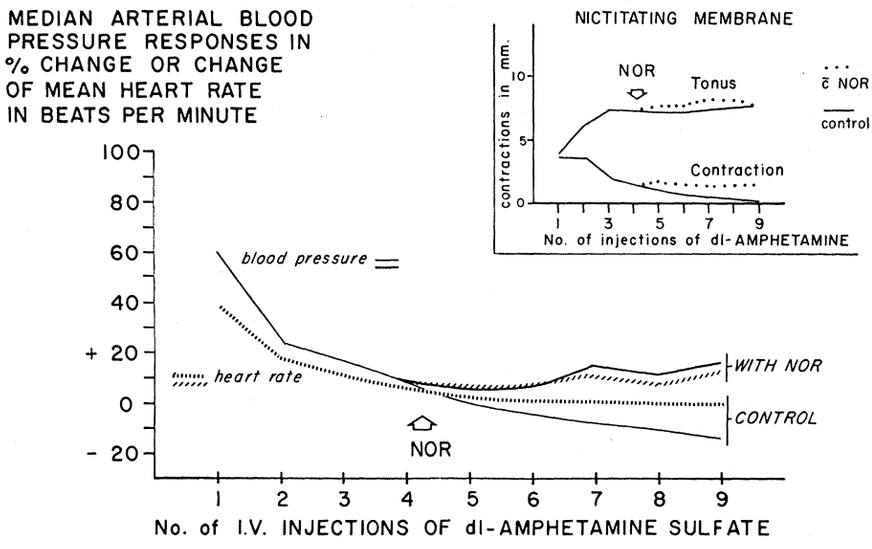

Fig. 1. *dl*-Amphetamine sulfate (0.35 mg/kg) was injected intravenously once every hour. In six cats (*CONTROL*) blood pressure, heart rate, and nicititating membrane contractions showed progressively reduced responses with repeated injections. Norepinephrine (*NOR*) infusion (0.83 μg/kg min) was started, indicated by the upward arrow, by the intermittent method in another six animals and hourly amphetamine injections continued (with *NOR*). Note the amphetamine effects on blood pressure, heart rate, and nictitating membrane contractions of the norepinephrine-infused animals as compared with the controls. Also note the unaltered increase of tonus of the nictitating membrane.

mg/kg) or one-half-hourly intravenous injections of tyramine hydrochloride (8.0 mg/kg) produced reliable tachyphylaxis in three of the four parameters measured—pressor effects, heart rate, and nictitating membrane contractions. Tyramine did not show tachyphylaxis of its effect on the heart rate. Both ephedrine and amphetamine increased the tonus of the nictitating membrane, whereas tyramine did not cause any change.

To test whether or not norepinephrine might influence the development of tachyphylaxis either in rate or extent, two methods for the administration of norepinephrine were employed: (i) either norepinephrine was infused for 30 min between the hourly injections of the tachyphylactogenic agent, starting after the fourth control response had been obtained (intermittent method), or (ii) norepinephrine was infused continuously, starting at zero hour. Amphetamine responses were obtained in six cats, using only the intermittent method of norepinephrine infusion (0.83 μg/kg per minute). The results are shown in Fig. 1.

It is obvious that the tachyphylaxis which had developed with the fourth injection of the drug was gradually reversed after several intermittent infusions. The tonus of the nictitating membrane, increased upon successive amphetamine injections, remained unaltered by norepinephrine. The augmentation of the pressor response and heart rate became statistically significant as early as the seventh injection of amphetamine, whereas the return of the nictitating membrane responses lagged behind, and the reinstitution of a statistically significant increased response was seen only with the ninth injection ($p < 0.01$ for all three parameters).

Using hourly intravenous injections of 2.5 mg/kg of ephedrine sulfate, norepinephrine infusion proved ineffective in reversing tachyphylaxis in five out of six cats. Significant results were obtained only when the dose of ephedrine was reduced to 1.5 mg/kg. With the latter dose schedule, tachyphylaxis could be as readily established as with the higher dose; and norepinephrine infusion, starting either at zero hour (2.5 μg/min) or after the full development of tachyphylaxis (2.5 μg/min), proved effective in either delaying the development of tachyphylaxis or in reversing the complete tachyphylactic responses to ephedrine.

The infusion of norepinephrine (2.5 μg/min) was started in six cats, before the administration of tyramine. The blood pressure responses under the influence of norepinephrine infusion were hardly changed, in contrast to the slow decrease in responses of the control animals, starting with the fourth half-hourly injection. The heart rate, as already mentioned, does not show tachyphylaxis to tyramine, and the nictitating membrane responses in the animals infused with norepinephrine were not measured.

It was found that the substitution of a pharmacologically similarly acting amine, phenylephrine, for norepinephrine increased rather than decreased the rate of development of tachyphylaxis. Thus, the mere infusion of a nontachyphylactogenic sympathetic stimulant or vasoconstrictor agent did not interfere with the development of tachyphylaxis. These observations further confirm the specificity of norepinephrine for the mechanism of tachyphylaxis.

The role of norepinephrine in tachyphylaxis must be different from its role in chronically reserpinized animals (*2*) since in the latter not only the responses to some sympathomimetic amines, but also to nerve stimulation are completely or partially lost. In our experiments, even at a time when amphetamine showed complete tachyphylaxis, the stimulation of the pre- or post-ganglionic fibers of the cervical sympathetic nerve elicited only slightly decreased contractions of the nictitating membrane. In other words, according to the terminology of Burn and Rand, the granular storage sites in the sympathetic nerve still contained adequate amounts of norepinephrine to induce responses obtained by nerve stimulation, despite the complete loss of reactivity to the tachyphylactogenic substances.

In summary, it appears that norepinephrine either prevents or partially restores the reduced responses seen with repeated administration of the three tachyphylactogenic neurosympathomimetic amines, amphetamine, ephedrine, and tyramine (*5*).

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