sponses (*14*). The areas dorsal or ventral to area AI are the nonprimary auditory areas, where the response latency was usually longer than in AI (6 to 10 msec), and the response was not necessarily as strong as in AI. In the part of AI indicated as zone c in Fig. 2B, there is a clear tendency for high-frequency-sensitive neurons to be located anteriorly and low-frequency-sensitive ones to be located posteriorly, exactly as in the AI of other mammals. However, in three respects this tonotopic representation is quite unique in the mid-frequency range. (i) Neurons tuned between 50 and 60 khz or between 64 and 79 khz were not found along this anteroposterior axis, that is, neurons concerned with main components in the FM signals are not on the main tonotopic axis. (ii) The areas concerned with the CF components in the orientation sounds and Doppler-shifted echoes occupy most of the auditory cortex. In particular, the 61- to 63-khz sensitive area is represented with considerable magnification. (iii) The 60.5- to 63-khz sensitive area is concentrically organized. These three significant points are shown by the distribution of best frequencies in a narrow strip along the anteroposterior axis of area AI (Fig. 2, A and C). There is a tendency for a progressive change in best frequency between 80 and 100 khz in the area lying anterior to the 60.5- to 63.0-khz area (dashed lines in Fig. 2B). But areas concerned with 50 to 60 khz and 64 to 79 khz were not on the anteroposterior axis. The area concerned with 64 to 79 khz was obscure in area AI, but the area processing 50- to 60-khz sounds is large and is located in the anterodorsal part of the AI. Thus, the area processing the FM component in the predominant harmonic is isolated from the others and appears to be specialized. The tonotopic representation in this area appears to be orderly. Independent processing of the FM component is essential. Otherwise, the information carried by the FM component would be disturbed by the overwhelmingly intense CF component.

In the nonprimary auditory cortex, the tonotopic representation is not easily defined. Neurons sensitive to 20 to 70 khz are found on both sides of the AI. However, most of the ventral nonprimary auditory cortex is devoted to 50- to 63-khz sounds, and neurons tuned above 70 khz were not found in this area. The dorsal nonprimary auditory cortex contains mostly neurons tuned between 75 to 100 khz. These neurons appear to show a coiled tonotopic representation. Although not shown in Fig. 2, the nonprimary auditory cortex has another intriguing feature—that is, multiunit activity often showed multiple peaks in sensitivity, and these peaks were roughly harmonically related in most cases (*15*).

As is described above, the auditory cortex of the mustache bat shows a highly disproportionate frequency representation. Since squeaks, which may be termed "distress calls," are broadband noise (Fig. 1C) and since other communication sounds also differ from the orientation sound, the disproportionate frequency representation is due to the specialization of the auditory system for processing the stereotyped species-specific echolocation signals (*16*). As one would expect, afferent fibers innervating cochlear hair cells show some regional variations in innervation density (*17*). Within an area on the basilar membrane between 5.5 and 7.0 mm from the round window, the densities of sensory hair cells and dendrites of primary auditory neurons are higher than those at other areas, while these densities are lower between 3.8 and 5.0 mm from the round window (*13*). We suspect that the high-density area is tuned at 60.5- to 63.0-khz sounds and the low-density one is for the reception of 64- to 79-khz sounds. The general rule, that the disproportionate cortical representation reflects a corresponding distribution of sensory cells or peripheral nerve fibers (or both), is therefore also applicable to the auditory system of the mustache bat.

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14. The 4.4- to 5.2-msec latency of responses is too short to be those of cortical neurons. Tonal responses with such short latencies were probably recorded from nerve fibers from the medial geniculate body. In a study of the single unit in AI (unpublished), the majority of neurons sampled showed a response latency of 7 to 10 msec, and a few of them showed a latency of 5 to 6 msec. In our experiments the best frequencies of neurons were measured in terms of their responses, mainly appearing after 7 msec. In other words, the best-frequency contour map in Fig. 2 was for cortical neurons.
15. Some of the single neurons studied in such an area showed two peaks, which were approximately harmonically related. Since no neurons with a double peaked tuning curve were found at the periphery (*12, 13*), it is evident that harmonically related components in acoustic signals are converging on some single neurons in higher levels of the auditory system.
16. N. Suga [*J. Physiol. (London)* **203**, 729 (1969)] studied the effect of the ablation of the auditory cortex on a wire-avoidance performance in *Myotis lucifugus* and suggested that the auditory cortex was less important for sound localization in bats than in cats, because the bat can avoid wires without the auditory cortex on both sides. This does not mean at all that the auditory cortex plays no role in echolocation. In *Myotis*, the auditory cortex contains specialized neurons at a higher percentage than the inferior colliculus does [see (*8*)]. Our results show that the AI receives ascending impulses with a very short latency. The auditory cortex is probably important in the performance of echolocation tasks which are more complex than the simple wire avoidance.
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3 March 1976; revised 28 April 1976

Stratospheric Ion Chemistry and the 11-Year Variation in Polar Ozone

Ruderman *et al.* (*1*) have proposed a specific stratospheric negative-ion reaction scheme to account for an observed 11-year variation in the total O_3 concentration at high latitudes and especially at high altitudes. Their mechanism hinges on the reaction (*2*)

$$NO_3^- + O_3 \rightarrow NO_2^- + 2O_2 + 0.35 \text{ ev} \quad (1)$$

We would like to point out two fatal defects to this hypothesis: (i) on the basis of known laboratory ion chemistry, unhydrated NO_3^- will not be a significant ion in the stratosphere, and (ii) we find the rate constant for reaction 1 to be less than 10^{-13} cm^3 molecule^{-1} sec^{-1}, which is too low a value for the reaction to have a significant role.

With regard to the first point, it is quite clear that the ambient ions in the stratosphere will be extensively hydrated (*3*). This follows readily from the use of known laboratory three-body association rate constants (*4*), which lead to hydration times of the order of 10^{-3} second for NO_3^- ions at an altitude of 20 km, for example. The hydration reactions will be so rapid in the stratosphere that one can almost assume a thermodynamic distribution of cluster ions. We estimate that less than 1 percent of NO_3^- ions would be unhydrated at 20 km, based on available thermodynamic data on the clustering of H_2O to NO_3^- (*5*). This is consistent with the observation (*6*) that the terminal NO_3^- ions are hydrated extensively at much higher altitudes (73 to 90 km), where both the total pressure and the water concentrations are much less, so that hydration would be much slower than in the stratosphere. Ruderman *et al.* noted the probability that the longer-lived ions would be hydrated, but assumed that rate coefficients would not be affected by the hydration. However, since the addition of the first water molecule to NO_3^- renders reaction 1 endothermic, it necessarily kills any reactivity (*2*). It is quite possible that hydration at early stages of the negative-ion reaction sequence will prevent formation of NO_3^-, but we do not need to evoke that prospect for the present purpose. It is also possible that as yet unrecognized chemical processes circumvent the production of NO_3^- as a terminal ion in the stratosphere; however this could only further diminish the role of reaction 1.

In regard to the second point, we have examined reaction 1 in our laboratory by using the NOAA (National Oceanic and Atmospheric Administration) flowing afterglow system, which has been extensively applied to atmospheric negative-ion reactions (*7*). We find $k_1 < 10^{-13}$ cm^3 $molecule^{-1}$ sec^{-1} to be a conservative upper limit for this rate constant at 300°K. This makes reaction 1 insufficient for the proposed O_3 removal, even if NO_3^- were a major stratospheric ion reactions (*7*). We find $k_1 < 10^{-13}$ man *et al.*, which required a value of k_1 at least as large as 10^{-12} cm^3 $molecule^{-1}$ sec^{-1} (*1*).

These considerations clearly eliminate the specific reaction mechanism proposed by Ruderman *et al.* (*1*).

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14 June 1976; revised 10 August 1976

Dopamine Receptors and Average Clinical Doses

Creese *et al.* (*1*) have convincingly demonstrated that the relative affinities of an extensive series of butyrophenones, phenothiazines, thioxanthenes, and other dopamine antagonists in competing with [^{3}H]haloperidol binding to the dopamine receptor of calf striatal membranes predict their clinical potencies in psychiatric patients as well as pharmacological properties in animal behavioral tests. Their conclusions are based on a correlation coefficient of .87 relating the inhibition constant K_i, the concentration that produces 50 percent receptor occupation, for each drug, to "average clinical dose."

We would like to point out several problems with the two measures Creese *et al.* have correlated. The calculation of K_i by the formula given in their table 1 does not take into account the fact that most of the neuroleptics are highly absorbed, each having a different tissue solubility (*2*). The formula only holds if the unbound drug concentration is used; thus it is better to report only the experimental 50 percent inhibitory concentration (IC_{50}). The authors' sources for average clinical doses are general review articles [see (*1*)] and they used the averages of midpoint values of listed ranges of daily dose from these sources. Only 8 of the 22 drugs for which the average clinical daily dose is provided are in approved clinical use in the United States. Most of the rest have had limited general use abroad and limited, if any, clinical testing in the United States. Because of the frequently demonstrated enormous interindividual differences in the pharmacokinetics of antipsychotic drugs, it is difficult to make meaningful comparisons between drugs across groups unless the groups are very large. A small group of studies may produce conflicting and misleading results. Thus, there may be significant problems with the dosages for two of the drugs included in the study by Creese *et al.*

The sources consulted by Creese *et al.* indicated that clozapine is clinically half as potent as chlorpromazine (*1*) and that the average clinical dose of chlorpromazine is 12 μmole kg^{-1} day^{-1} (260 mg/day for a 70-kg human), a figure I believe most clinicians would agree is too low. For example, Klein and Davis (*3*) indicate that the average daily dose of chlorpromazine is 692 mg. I checked three clinical studies of clozapine which permit an assessment of the average daily dose; comparing this with an average dose of chlorpromazine of 260 mg/day, the estimated potency of clozapine is 0.6 to 1.25 times the potency of chlorpromazine (*4*). If 692 mg/day is taken as the average dose of chlorpromazine, clozapine is 2.3 to 4.2 times as potent as chlorpromazine. The available data for (+)-butaclamol are also suspect since in most of the limited clinical trials of this drug mixtures of the inactive stereoisomer with the active compound have been used (*5*). The average clinical dose utilized by Creese *et al.* for (+)-butaclamol is markedly greater than that consistent with the regression equation derived from their data. Despite the problems with clozapine and (+)-butaclamol, the Spearman rank-order correlation coefficients for the 8 drugs in general use and the 14 other drugs are virtually identical: .863 and .837, respectively. Thus it is reasonable to conclude that the average clinical dose for at least 12 of the 14 less used drugs are in correct relationship to each other.

The work of Creese *et al.* as well as of others (*6*) strongly supports the role of dopamine blockade in the antipsychotic action of the majority of neuroleptic drugs. However, their work leaves unsettled the mechanism of action of clozapine, which is a weak receptor blocker in their in vitro system (in the 100 n*M* range) and a weak dopamine receptor blocker in vivo (*7*). On the other hand, Seeman *et al.* (*8*) found that clozapine can block haloperidol binding in the range 10 to 20 n*M*. Other evidence points to an effect of clozapine as an inhibitor of dopamine release (*9*).

Finally, I would like to question the desirability of using the method of