lapse x-radiography of animals permitted to burrow in narrow sediment-filled aquaria. Downward movement in all three species is nearly vertical (before assumption of normal feeding positions). Burial is achieved through a succession of distinct downward movements, each of which is accomplished by a well-patterned muscle contraction sequence. The sequence is nearly identical for the great majority of bivalve species and usually culminates in a forward-and-back rocking motion (*2*). In the three circular species under discussion, shell rotation is remarkably smooth, and the angle of rotation is relatively large (30° to 45°).

Mechanical operation of the asymmetrical chevron-shaped ridges is illustrated by *Divaricella* (Fig. 1). During forward rotation from position B, the steep dorsal ridge slopes posterior to the demarcation line (*D-D'*) grip the sediment in a rasplike manner, carrying sediment upward and forcing the shell downward. The gentle ventral ridge slopes anterior to the demarcation line slip through the sediment with less friction. During backward rotation from position A, the frictional disparity is reversed, and the anterior parts of ridges aid in penetration. The anterior position of the demarcation line reflects the anterior direction of rocking movement from position B.

In *Tellina similis*, a more elongate species, the discordant ridges pass obliquely across the shell surface (Fig. 2A). The species lives in muddy sand and, being a deposit feeder, requires an efficient burrowing mechanism for lateral migration when it depletes local food supplies. Rocking movements are rapid and pass through a very small angle (less than 15°). Anterior and posterior portions of ridges alternately grip and slide through the sediment (Fig. 2C) to aid in substratum penetration. The ridges are oriented at approximately right angles to the direction of substratum penetration, which maximizes their effectiveness.

Asymmetrical discordant ridges are apparently restricted to sand-dwelling species. Most subtidal muds are too fluid to be gripped effectively. The ridges are also apparently restricted to species with some cause for periodic burrowing, such as need to offset sediment scour or to migrate during deposit feeding.

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Ontogeny of Adrenergic Arousal and Cholinergic Inhibitory Mechanisms in the Rat

Abstract. *With spontaneous activity as a measure of arousal, dose response curves were established for scopolamine and amphetamine administered to 10-, 15-, 20-, 25-, and 100-day-old rats. Amphetamine always increased activity, but scopolamine had no effect on younger rats, which suggests that adrenergic excitatory areas in the brainstem mature more rapidly than cholinergic inhibitory areas in the forebrain.*

Generalized excitatory and inhibitory systems in the brain regulate overall levels of arousal. The major excitatory center is thought to be the brainstem reticular formation. When activity in this area is destroyed by lesions, stupor results (*1*); when the area is activated by electrical stimulation, electrocortical and behavioral arousal occurs (*2*). Acting in opposition to this excitatory region are certain forebrain structures which serve to modulate reticular excitability. When these centers or their connections with the brainstem are impaired, the effects of reticular stimulants are greatly augmented (*3*). When this area is activated by electrical stimulation, arousal is depressed (*4*).

The biochemical substrates of the arousal areas in the hindbrain and inhibitory centers in the forebrain are distinct, with the former primarily adrenergic in nature and the latter predominantly cholinergic (*5*). Amphetamine, which mimics adrenergic transmission by release of norepinephrine (*6*), particularly in the brainstem (*7*), induces large increments in locomotor activity, while adrenolytic agents depress arousal and generally lead to sedation (*8*). The anticholinergic drug scopolamine, which blocks acetylcholine transmission by occupation of postsynaptic sites (*9*), produces marked increments in activity (*10*), while anticholinesterases (*11*) and cholinomimetic agents (*12*) depress arousal.

It is now generally accepted that the development of the brain proceeds rostrally with phylogenetically primitive hindbrain structures maturing earlier than the younger forebrain systems (*13*). Thus neonatal animals should pass through a phase during which they are responsive to reticular stimulants and unaffected by cholinergic blocking agents because of the functional absence of forebrain inhibitory mechanisms. We now show that the neonatal rat is responsive to the reticular stimulant amphetamine, before it is responsive to scopolamine, an inhibitor of forebrain cholinergic activity.

Degree of behavioral arousal was measured in stabilimeter activity cages scaled to the size of the animal. The largest cages, those used for the adults (*14*) consisted of wire mesh cages, 17.5 by 20.0 by 37.5 cm, mounted on a central axle which permitted the cage to tip slightly and activate a sensitive switch as the rat moved from one end to the other. For 10-day-old rats the cage dimensions were scaled down to 6.3 by 7.5 by 13.7 cm, and for 15-, 20-, and 25-day-old rats the cage was 8.7 by 10.0 by 18.7 cm. The activity cages were housed in temperature-controlled cubicles maintained at 29°C for the 10-, 15-, 20-, and 25-day-old rats and at 22°C for the 100-day-old rats.

Dose response curves for both amphetamine and scopolamine were determined at five different ages: 10, 15, 20, 25, and 100 days. At each dose 10 to 16 rats were tested, and each rat was tested only once. A total of 772 Sprague-Dawley rats were used, half of which were male and half female.

Rats were removed from living cages in a central colony room, placed in the activity cages for a 30-minute habituation period, and then injected with one dose of either *d*-amphetamine sulfate (0.250, 0.50, 1.0, 2.0, 4.0, or 8.0 mg/kg, salt weight), scopolamine hydrochloride (0.125, 0.250, 0.50, 1.0, 2.0, or 4.0 mg/kg, salt weight) or an equivalent volume of the 0.9 percent saline vehicle. They were then returned to the cages for 2 hours; during this time the number of crossings was recorded on printing counters every half hour. In addition, methylscopolamine hydrobromide (0.125, 0.250, 0.50, 1.0, 2.0 or 4.0 mg/kg, adjusted for equivalent amounts of scopolamine), a drug which does not cross the blood-brain barrier in significant quantities (*15*), was administered to a group of 25-day-old rats for control of the possible peripheral effects produced by the sco-

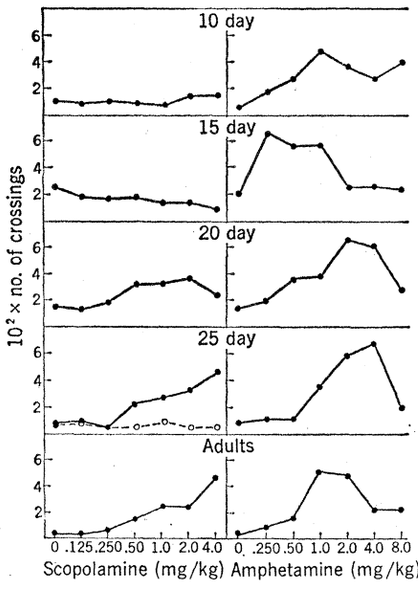

Fig. 1. The effects of scopolamine hydrochloride and *d*-amphetamine sulfate on spontaneous activity of rats of five different ages. The effect of methyl scopolamine is shown by the dotted line in the 25-day panel.

polamine hydrochloride. All drugs and the saline control were administered intraperitoneally in a volume of 1 ml per kilogram of body weight.

Figure 1 shows the mean amount of activity occurring during the entire 2-hour test period for all groups. Amphetamine produced an increment in activity, proportional to dosage, in animals at all of the ages studied, while scopolamine increased activity only in animals 20 days of age and older. Methylscopolamine had no systematic effect on activity, which indicates that the scopolamine-induced increase in activity was the result of central rather than peripheral effects. No consistent sex differences in response to the drugs were found except in the 100-day-old group, where the females were more active regardless of whether drugs were given or not.

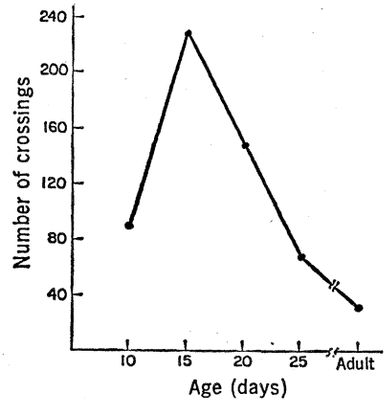

Fig. 2. Spontaneous activity as a function of age in nondrugged animals.

The results also suggest that the maximum effective dose of amphetamine was somewhat dependent on age. The 15-day group appeared to be more sensitive to amphetamine than the older animals insofar as they showed maximum activity increases in response to low dosages, whereas higher dosages were required to elicit maximum response in the older animals.

These results demonstrate that reactivity to amphetamine and scopolamine matures at different rates in the neonatal rat. To interpret these results, it is most plausible to assume that amphetamine acts by releasing endogenous norepinephrine in primitive hindbrain arousal centers and that these centers mature earlier than the forebrain inhibitory centers do. In turn, scopolamine cannot act to block the cholinergic forebrain inhibitory centers until these centers are functionally mature and exerting a chronic inhibitory influence on hindbrain activity.

Additional evidence for the delayed maturation of forebrain inhibitory centers is found in the activity pattern of the saline control groups. When these data (combined means for all saline control groups of the same age) are plotted separately so that the age-related trends are not masked by the larger drug effects (Fig. 2), it is apparent that spontaneous activity in a novel environment reaches a peak in rats at about 15 days of age and declines rapidly in the subsequent 10 days. The increase in activity between days 10 and 15 undoubtedly reflects increasing skeletal muscular development plus increasing sensory responsiveness (*16*). The decline in normal activity corresponds strikingly to the increasing effectiveness of scopolamine as a behaviorally arousing drug, which suggests that forebrain cholinergic inhibitory centers also act to modulate exploratory activity in novel environments.

Moreover, this period of declining arousal and increasing sensitivity to anticholinergics also parallels functional development of the forebrain. Primitive electroencephalographic activity is first noted at 6 days after birth, but the spectral composition does not approximate that of the adult until the rat is between 25 and 30 days of age (*17*). Myelin, which is present in the brainstem at birth, is not seen in the forebrain until 10 days after birth, with the greatest deposition occurring between 15 and 30 days of age (*18*). Similarly, the number of synaptic junctions in the cortex undergoes massive proliferation between 15 and 25 days of age (*19*).

Considerable evidence from studies of humans supports the view that the forebrain areas exert inhibitory control over hindbrain mechanisms (*20*). Both the human infant and the rat display little more than simple involuntary responses at birth. With maturation, many of these reflexes disappear and then reappear with corticol atrophy in senescence or after cortical injury (*21*). Forebrain development thus appears to modulate both primitive reflexes and behavioral arousal. Our data suggest that at least some portion of this inhibitory mechanism is cholinergic.

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Dendritic Spikes Revisited

In the dendritic spikes controversy, a number of separate issues have been raised by Llinás *et al.* (*1*) in their original paper, by the subsequent comments of Hellerstein and me (*2*), and now by Zucker (*3*). Because extracellular waveshape reconstruction has been markedly clarified by the recent work of Rall and Shepherd (*4*), it has been of particular interest to see their model applied to the original data (*1*) by Zucker (*3*).

1) Do dendritic spikes exist? Undoubtedly somewhere. It is essential, however, that commonplace passive spread not be mistaken for dendritic spikes. The issue is more likely to be settled by improved experimental design than by free-parameter theoretical models, perhaps similar to the way in which the A spike was identified as coming from the initial segment region (*5*).

2) Does the Llinás *et al.* (*1*) data represent dendritic spikes or an interaction of passive sources and sinks? Because Llinás *et al.* in their original paper (*1*) did not appear to consider passive explanations despite similar prior controversies and because they interpreted "conduction velocities" quite literally, we pointed out (*2*) that a simple alternative theory (the cable model) could also easily yield conduction velocities in the same numerical range as the Llinás *et al.* data. Rall and Shepherd (*4*) have now contributed additional information which indicates that extracellularly measured conduction velocities can be quite ambiguous even when the intracellular conduction velocity is known.

3) Is cable theory or volume-conductor theory appropriate for such recordings? Cable theory is more applicable to these recordings than volume-conductor theory, and Zucker (*3*) has provided a very useful basis for deciding which theory to use for a given set of data. The fate of the extracellular currents is the underpinning of the various waveshape interpretation models. Because the physical simplicity of the cable theory assumptions utilized by ourselves, Rall and Shepherd, and Zucker are not generally appreciated, Hellerstein has prepared an additional clarification (*6*) with which I am in complete agreement.

4) Was the cable model which we utilized (*2*) adequate for our purposes? Because we were not trying to "prove" postsynaptic potential (PSP) and "disprove" dendritic spikes but merely to show that the commonplace explanation for conduction velocities was as good as the more esoteric, we chose the simplest possible model consistent with our objectives. Whereas we assumed a truly indifferent second electrode, Rall and Shepherd (*7*) more realistically assume that it records some waveform which is then subtracted from the various voltages seen by the penetrating electrode. The location of this second electrode gives rise to additional "free" parameters in the model. Because this waveform may be polyphasic, it may indeed play havoc with latency, polarity, zero-crossings, and waveshape of the differential recordings called "extracellular recordings." It is this complex effect which Zucker (*3*) utilizes to reanalyze the Llinás *et al.* data (*1*). His analysis is divided into two relatively independent sections: analysis of the "early fast transient" which has previously been the object of concern, and analysis of an underlying "slow transient." The assumptions underlying each analysis differ considerably, and his final conclusion is not directly based upon much of his preceding analyses.

5) Is Zucker's use of Rall and Shepherd's cable-plus-voltage-divider model valid for the presumably passive slow transient? Probably. By modifying their parameters, Zucker does establish the model as clearly better than classical volume-conductor models for those particular data. This Rall and Shepherd model for passive dendrites also appears to fit the data better than our similar model which lacks the subtracted waveform. In the Rall and Shepherd model for the spherical olfactory bulb, however, surface-parallel currents were unlikely to contribute to the voltage-divider current; the voltage difference between the top and bottom of the current-generating layers of the tissue (radial currents) determined the current flow through the voltage divider. In cerebellar cortex, surface-parallel currents cancel only within the volume of active cells, but currents from middle lamina may also leak out into the voltage divider. Thus the waveshape at the distant electrode may not be identical to the potential difference between the top and bottom of the active cell mass, as was the case in the Rall and Shepherd model. Nevertheless, Zucker's analysis of the slow transient is a reasonable one and clearly more inclusive than our simple model. It should be noted that at least three "free parameters" were manipulated to achieve the fit: space constant, time constant, and voltage divider setting. Furthermore, such analyses assume that the underlying process is not composite, for example, not a sequence of excitatory and inhibitory PSP's (*8*), which can be difficult to distinguish from a spike-after-hyperpolarization sequence.

6) Is Zuckers' analysis valid for the "early fast transient"? His reasoning about this key phenomena is, unfortunately, not directly based upon either his volume conductor comparisons or upon his preceding slow transient analysis. Rather, Zucker merely replots a figure from Rall and Shepherd's original calculations for mitral cells with active dendrites (using their voltage divider setting, not his) and then remarks upon the similarity to the Llinás *et al.* data, saying that this similarity rather unequivocably identifies the fast transient as a spike. The similarity does indeed suggest the possibility of dendritic spikes. To effect a serious comparison between the Rall and Shepherd model and the early fast transient data, one should at least use the new voltage divider setting and should preferably superimpose the slow transient upon the active dendrite model, since it is assumed that these dendritic spikes are set up by preceding PSP's. While the casual similarity between the figures is intriguing, it hardly justifies Zucker's firm conclusion (*3*) that this "identifies the fast transient rather unequivocably as an active spike. . . ."

7) If dendritic spikes do exist, do they propagate actively or passively down the dendrite? We raised this issue earlier because, even if all-or-nothing properties should be independently established, spikes could spread passively down the dendrites, giving rise to an apparent conduction velocity in the same manner as does a PSP. The functional implications which have been attributed to dendritic spikes assume that the dendritic spike propagates ac-