Correlation of the Glycoside Response, the Force Staircase, and the Action Potential Configuration in the Neonatal Rat Heart

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ABSTRACT

The rat heart demonstrates marked alterations in its responses to ouabain and increased frequencies of stimulation and in the duration of its action potential during the initial 21 days of life. At an age of 6.2 days, 5 x 10^{-5} M ouabain produced a 158.2% increase in dP/dt compared with a 17.2% increase at 21.1 days (P < 0.001). At 6.2 days dP/dt increased by 53.4% when the heart rate was accelerated from 30 to 90 beats/min compared with an increase of 12.2% at 21.1 days (P < 0.005). The positive glycoside and staircase responses at the younger age were virtually eliminated when the hearts were perfused with a solution containing 50% [Na+]o and 25% [Ca2+]o ([Ca2+]o/ [Na+]o = maintained constant). The duration of the ventricular action potential progressively decreased from 350-400 msec at birth to 100-150 msec at 21 days of life. This decrease was due to a shortening and a decrease in the potential level of the plateau phase. The prominent plateau typical of the early neonatal period was significantly diminished by perfusion with 50% [Na+]o. The results suggest that Na+ flux through a slow membrane channel plays a significant role in the positive staircase and glycoside responses of the early neonatal rat heart. As the heart matures and becomes functionally anomalous relative to other mammalian species, the slow channel progressively closes.

KEY WORDS sodium flux calcium excitation-contraction coupling slow sodium channel ouabain dP/dt action potential plateau

The adult rat heart demonstrates a number of unique physiological and pharmacological characteristics. It has an action potential of short duration with little evidence of a plateau (1) and an interval-force relationship (staircase) which is atypical in that it is dominated by a tendency for contractile strength to decrease with increasing frequency (2); moreover, the adult rat heart is particularly resistant to the action of digitalis glycosides (3, 4). The neonatal rat heart however has strikingly different characteristics with respect to all of these phenomena. The purpose of the present study was to document these characteristics over the early neonatal period. If the sequential changes related to age are interrelated, an understanding of them might provide further clues to the ionic mechanisms important in the control of the myocardial contractile response.

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Methods

Sprague-Dawley rats were used for all of these studies. The standard perfusion medium had the following millimolar composition: NaCl 142, KCl 4, MgCl2 1.0, CaCl2 1.0, and glucose 5.56. When it was buffered with 3 mM HEPES (N-2-hydroxyethylpiperazine-N'-2-ethane sulfonic acid), the perfusate was equilibrated with 100% O2; when it was buffered with 12 mM NaHCO3, the NaCl content was lowered to 130 mM and the perfusate was equilibrated with 98% O2-2% CO2. The standard solution was modified to give a "low Na"-"low Ca" solution by replacing 71 mmoles NaCl/liter with 71 mmoles choline chloride/liter and decreasing the Ca2+ concentration to 0.25 mM; thus, [Ca2+]o/[Na+]o was maintained at an unchanged value. All choline-containing solutions also contained atropine (0.01 g/liter). All experiments were done at a pH of 7.3-7.4 and a temperature of 24-26°C. A number of techniques were employed.

Action Potential Recording.—Small ventricular trabeculae or left ventricular papillary muscles were dissected from the excised neonatal hearts, mounted in a small Lucite chamber, and point-stimulated with a pair of platinum electrodes at one end of the muscle. Stimuli were rectangular pulses 3-5 msec in duration and two to three times threshold. Intracellular recordings were made using flexibly mounted KCl-filled glass microelectrodes with tips less than 0.5μ in diameter and a Brush 220 recorder or a Tektronix storage oscilloscope.

Mechanical Recording.—Left ventricular papillary muscles were removed from the neonatal hearts, and each end was tied with a strand of 13/15 denier silk.
The papillary muscles were 0.3-0.5 mm in diameter.

A loop of 13/15 denier silk was made around the vessel near its origin. A specially tapered polyethylene cannula made from PE 50 tubing was then inserted through a cut in the aorta and passed into the proximal septal artery through the coronary ostium. Once it was lodged in the artery, the previously fixed loop was tied proximally to a flange near the tip of the cannula. Perfusion was started with the standard HEPES-buffered solution; the perfused area could be identified easily, since the vasculature was cleared of blood. The perfused area was then dissected from the remainder of the heart; a tie was placed at the extremity opposite the region of cannula. The septum was suspended at its widest portion and its time derivative (dP/dt) recorded on a Sanborn direct-writing recorder or a Brush 220 recorder. Flow through the chamber was maintained at 2-3 ml/min.

The tension and dP/dt responses at 5 and 10 minutes after the addition of ouabain were summarized and compared statistically (Student’s t-test) in Table 1. The responses at 6.2 and 13.9 days and at 6.2 and 21.1 days were different at a high level of significance, but those at 13.9 and 21.1 days were not statistically different even though the trend remained downward with age.

The effect of altering the composition of the perfusate on the staircase response is illustrated in Figure 2. The typical response of a papillary muscle from the young neonatal heart to 50% [Na+]o, and 25% [Ca2+]o (with maintenance of the [Ca2+]o/[Na+]2 ratio) indicated that tension and dP/dt remained close to the control levels with a frequency of stimulation of 30/min. The staircase response to an abrupt increase in frequency to 95/min was, however, markedly affected by the perfusate change. The dP/dt response declined from +125% to +33% and the tension response from +82% to +6%. This response was essentially the same in five muscles from rats less than 7 days old. A reduction in [Ca2+]o alone tended to amplify the percent increase in the staircase response rather than diminish it.

Ouabain Response.—The variation of response to a high concentration of ouabain (5 x 10^-5M) with age is typified in Figure 1B. The inotropic responses at 5 and 10 minutes after the addition of ouabain to the perfusate are shown. Ten minutes was sufficient time for the full response to develop. As with the staircase response, the inotropic effect of ouabain declined with increasing age. A dP/dt response of +160% at 5 days declined to +12% at 22 days with the 14-day response being an intermediate one. The responses to ouabain are summarized and compared statistically in Table 1. The differences between 6.2 and 13.9 days as well as those between 6.2 and 21.1 days were highly significant, whereas those between 13.9 and 21.1 days did not reach the significant level.

Results

Staircase Response.—The tension and dP/dt responses after an abrupt increment in stimulation frequency from 30 to 90 beats/min at three different ages are shown in Figure 1A. The responses declined as age increased. A markedly positive staircase was present at 5 days, but at 22 days there was a slightly negative response; the response at 14 days was an intermediate one. The responses were summarized and compared statistically (Student’s t-test) in Table 1. The responses at 6.2 and 13.9 days and at 6.2 and 21.1 days were different at a high level of significance, but those at 13.9 and 21.1 days were not statistically different even though the trend remained downward with age.

To check the remote possibility that the development of adrenergic nerve endings accounted for the sequence of the staircase response with age, papillary muscles from young and old neonates were treated with propranolol in a dose (1.6 x 10^-4M) that eliminates the inotropic response to epinephrine (5 x 10^-4M). The staircase pattern was not significantly altered.

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To determine the dependence of the response to ouabain on the ionic milieu, specifically with respect to Na⁺ and Ca²⁺, a group of seven papillary muscles from the youngest age group (5.4 ± 0.4 days) was tested. The muscles were exposed to a perfusate that contained 50% [Na⁺]₀ and 25% [Ca²⁺]₀, so as to maintain the [Ca²⁺]₀-[Na⁺]₀² ratio at an unchanged value. Osmolality was maintained by adding choline chloride, and atropine (0.01 g/liter) was added to eliminate any cholinergic effects. The muscles were allowed to equilibrate with the perfusate for 20 minutes at which time

**TABLE 1**

<table>
<thead>
<tr>
<th>Mean age (days)</th>
<th>Tension (% change)</th>
<th>dP/dt (% change)</th>
<th>OUABAIN responses (5 × 10⁻⁶ M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.2 ± 0.6</td>
<td>+35.9 ± 8.6* (16)</td>
<td>+53.4 ± 11.7† (16)</td>
<td>+136.4 ± 34.5‡ (18)</td>
</tr>
<tr>
<td>13.9 ± 0.3</td>
<td>+50.0 ± 4.6 (17)</td>
<td>+18.7 ± 3.8 (17)</td>
<td>+18.3 ± 6.9 (18)</td>
</tr>
<tr>
<td>21.1 ± 0.2</td>
<td>-1.37 ± 4.0 (17)</td>
<td>+12.2 ± 4.4 (17)</td>
<td>+12.14 ± 5.3 (18)</td>
</tr>
</tbody>
</table>

All values are means ± se. Number of muscles tested is given in parentheses.

* Significantly different from the values at 13.9 days (P < 0.01) and 21.1 days (P < 0.001).
† Significantly different from the values at 13.9 days (P < 0.02) and 21.1 days (P < 0.005).
‡ Significantly different from the values at 13.9 days (P < 0.005) and 21.1 days (P < 0.005).
§ Significantly different from the values at 13.9 days (P < 0.001) and 21.1 days (P < 0.001).
dP/dt and tension responses to an increase in the frequency of stimulation (30/min to 95/min) of a papillary muscle from a 3-day-old rat heart. The responses in standard, control perfusate are on the left, and the much reduced responses in 50% [Na+]o-25% [Ca2+]o perfusate are on the right.

Ouabain (5 x 10^-5M) was then added and the response followed. A typical sequence is illustrated in Figure 3. A transient slight positive inotropism was noted at 5 minutes and at 10 minutes amounted to +4%. In the group of seven muscles, systolic tension was increased by 5.1 ± 0.06% and dP/dt was increased by 1.0 ± 0.04% at 10 minutes. Note that in this age group (6.2 days, Table 1) systolic tension was increased by 136% and dP/dt by 158% when the muscles were exposed to 5 x 10^-5M ouabain in perfusate with normal concentrations of Na+ and Ca2+. The differences in inotropic response were highly significant (P < 0.005). Reduction of [Na+]o alone also produced a diminution in the response to ouabain. In three muscles from 4-day-old rats, 5 x 10^-5M ouabain induced a mean increase of 33% in dP/dt, whereas the response in the same muscles perfused with control solution was 108%. The difference, however, was difficult to interpret, since alteration of the [Ca2+]o-[Na+]o ratio not only reduces the availability of extracellu-
lar Na⁺ but also greatly increases the availability of contractile-dependent Ca²⁺. Reduction of [Na⁺]₀ with maintenance of a constant [Ca²⁺]₀/[Na⁺]₀ ratio is a more valid test.

In addition, to ascertain whether decreased [Ca²⁺]₀ alone was responsible for the greatly diminished inotropic response to ouabain, a group of ten muscles (mean age 7.2 ± 0.4 days) was allowed to equilibrate with 25% [Ca²⁺]₀. This procedure reduced systolic tension to 16.6 ± 4.1% and dP/dt to 19.8 ± 4.1% of control. The muscles were then exposed to 5 × 10⁻⁴M ouabain. At 10 minutes, systolic tension was increased by 530 ± 129% and dP/dt by 457 ± 93% (relative to the low Ca²⁺ level). Thus, the response was greatly augmented when [Ca²⁺]₀ was reduced in the presence of normal [Na⁺]₀.

**Response of Potassium Exchange to Ouabain.**

Figure 4A shows the mechanical response to and the effect on ⁴²K exchange of 5 × 10⁻⁵M ouabain in an arterially perfused septum from a 7-day-old rat. Associated with a marked increase in systolic tension (120%) and dP/dt (110%) was a clearly demonstrable net loss of K⁺ indicated by the increase in ⁴²K effluent activity in the absence of any alteration in the slope of the tissue plot. The effluent ⁴²K activity during perfusion with ouabain increased 15–20%. If this increase were due to an increase in the steady-state exchange rate, it would have produced an easily recognizable change in the slope of the tissue plot, as has been clearly demonstrated in a previous study on K⁺ exchange in the rat ventricle (2). The increase in ⁴²K activity can be more accurately quantified if the effluent curve is plotted rectilinearly. Such a plot of the effluent curve in Figure 4A is reproduced in Figure 4B. The solid line represents the monoexponential line and its extrapolation through the period of ouabain administration illustrated in Figure 4A. During and for a period after ouabain administration all venous effluent drops were collected. ⁴²K activity obviously increased above control; in fact, it averaged greater than 12 SD above control through the 24–42-minute period.

Figure 6, minimum inotropism (+ 5% in tension and +7% in dP/dt and no discernible net K⁺ loss were produced in a septum from a 29-day-old rat despite the administration of ouabain at the high dose level (5 × 10⁻⁴M).

It should be noted that the K⁺ loss quantified on the basis of effluent analysis alone underestimates the total loss of K⁺ from the cell. In addition to the net increase in passive K⁺ efflux induced by ouabain (associated with the osmotic response to retained cellular Na⁺), there is an inhibition of active influx of K⁺ (5). This loss is, of course, attributable to the specific inhibition of the Na-K pump by the glycoside. Therefore, we used the...
effluent analysis only to detect a significant inhibition of the Na-K pump, and we do not suggest that we have accurately quantified the net ionic changes.

In a series of seven septums from rats of a mean age of 8.9 days, $5 \times 10^{-7}$M ouabain produced an increase in systolic tension of $71.7 \pm 0.1\%$ and in dP/dt of $75.0 \pm 0.1\%$ with a mean net loss of K$^+$ equal to $4.35 \pm 1.8$ mmoles/liter tissue water. In another group of eight septums from rats of a mean age of 31.9 days, $5 \times 10^{-6}$M ouabain produced a systolic tension increase of $31.3 \pm 0.1\%$ and a dP/dt, increase of $33.8 \pm 0.1\%$ with a mean net loss of K$^+$ equal to $2.07 \pm 0.6$ mmoles/liter. The inotropic responses at the two ages were significantly different ($P < 0.05$). The K$^+$ losses in the two groups fell short of significance at the high dose of ouabain ($5 \times 10^{-5}$M) used, but a trend was clearly evident, i.e., less net K$^+$ loss at the older age. In every case in which significant inotropism (> 10%) occurred, the septum demonstrated a significant net K$^+$ loss.

**Action Potential Changes with Age.**—Striking changes occurred in the ventricular action potential as the rats matured. As shown in Figure 7A, repolarization time shortened progressively from a duration of 336 msec (time to 80% repolarization) in the 1-day-old rat to 192 msec in the 6-day-old rat and to 100 msec in the 26-day-old animal. Action potential amplitude, resting potential, and overshoot were little changed during tissue development.1

Figure 7B shows the manner in which the action potential responds to reduced [Na$^+$]o. In the 1-day-old rat the principal effect of low [Na$^+$]o was a typical reduction of the plateau level and duration, but membrane potential overshoot was not appreciably affected. Similar responses were obtained in the papillary muscles of ten 1-or-2-day-old rats. The simultaneous reduction of [Ca$^{2+}$]o to 25% of control had virtually the same effect on the action potential as did low [Na$^+$]o alone. In the older rat the plateau phase was already short in duration, and the main effect of [Na$^+$]o reduction was a reduction in the overshoot and the rate of depolarization dV/dt (Fig. 7B).

1The detailed quantification of action potential parameters during neonatal development is not the purpose of the present study. However, such a study is in progress by Dr. Nigel Roberts (Department of Pediatrics, UCLA), and he has given us permission to indicate the following. At a mean age of 3.2 days, resting potential is $-74.9 \pm 5.4$ (50) mv, overshoot is $4.08 \pm 4.0$ mv, and time to 90% repolarization is 243 $\pm$ 22 msec. At a mean age of 20.3 days, resting potential is $-75.8 \pm 2.2$ mv, overshoot is $8.71 \pm 4.7$ mv, and time to 90% repolarization is $147 \pm 18$ msec. The difference in time to 90% repolarization is significant ($P < 0.05$), but there is no significant difference in resting potential or overshoot.
A: Sequence of action potential configuration with age from 1 day to adult. Note the progressive shortening attributable to abbreviation of the plateau. B: Effect of a 50% reduction in \([\text{Na}^+]\) at 1 day and 26 days. Note that at 1 day the effect was primarily to reduce the level and the duration of the plateau but at 26 days the amplitude of the spike and \(dV/dt\) were principally affected.

**Discussion**

It is clear that a series of remarkable changes occurs in the rat heart during the first 2–3 weeks of postnatal life. There is (1) a marked diminution of the positive inotropic response (the Bowditch Treppe phenomenon) to an increase in the frequency of stimulation, (2) a progressive decline in the level and duration of the ventricular action potential plateau, and (3) a decrease in the response to the administration of ouabain. It is possible that these developments have a common basis, but before discussing that possibility it is pertinent to review what is presently known about postnatal changes in structure and function of the rat heart.

Schiebler and Wolff (5) have done a careful electron microscopic study of the heart through the first 4 weeks of life. At the first day the myofibrils are sparse. The sarcolemma is coated with an identifiable basement membrane (perimembrane), the sarcotubular system is poorly developed, and the transverse tubular system (T system) is not yet developed. During the first week there is continuing sarcotubular development, and during the second week progressive maturation of the mitochondria occurs. By 12 days the longitudinal sarcotubular system is well developed. At the 2-week stage all structural elements are at a relatively advanced state with the exception of the T system which is not clearly in evidence until the third week. At 30 days the ultrastructure is hardly distinguishable from that of the full-grown rat.

With respect to mechanical function, Hopkins et al. (6) have found that the rat heart appears to reach functional maturity at about 16 days after birth. This conclusion was reached by analyzing the length-tension relationship of 10-, 16-, and 20-day-old and adult rat hearts perfused by the Langendorff method. Mass-dependent changes were clearly separated from time-dependent changes, and Hopkins et al. (6) found that by 16 days incremental tension, peak active tension, and peak passive tension had progressed to adult levels when corrections for mass were made.

The progression of electrical function has not been systematically studied in the neonatal rat heart, but two studies during the prenatal period are of interest. Bernard and Gargouil (7) and Couch et al. (8) have demonstrated an increasing resting potential and a decreasing action potential duration from 10 days gestation to birth (21 days). In addition, Bernard and Gargouil (7) have shown that at 10 days gestation the action potential amplitude and configuration are insensitive to tetrodotoxin at concentrations as high as \(10^{-5}\)M. Tetrodotoxin sensitivity increases later in the gestational period. The response to tetraethylammonium is such that at 10 days gestation it has no effect on the ventricular action potential whereas at 21 days the plateau is markedly prolonged by the drug. These findings indicate that during the course of gestation a fast \(\text{Na}^+\) channel develops and a tetraethylammonium-sensitive \(\text{K}^+\) channel, operative during the plateau phase, appears.

The courses of structural development and mechanical maturation do not provide an explanation for the age-dependent sequence of action potential configuration, staircase tension, and ouabain response changes observed in the present study. The younger the postnatal rat heart, the more its responses resemble those of hearts from other adult species, i.e., prominent action potential plateau, positive or ascending staircase response, and significant increases in contractility following glycoside administration. As the rat heart matures, over the course of the first 2–3 weeks of postnatal life, all of the responses become anomalous. The changes in each of the parameters remain closely related in time (Figs. 1 and 7, Table 1), suggesting a possible common mechanism.

From studies in adult mammalian hearts other than the rat, there is increasing evidence for a coupling between \(\text{Na}^+\) and \(\text{Ca}^{2+}\) movements at the myocardial cell membrane (9–13). We have recently demonstrated, quite directly, in the adult rabbit heart that an increment in cellular \(\text{Na}^+\) is positively inotropic (10). The results strongly sup-
ported the presence of a Na-Ca exchange system such that an increase in [Na\(^+\)], results in an enhancement of Ca\(^{2+}\) influx with the latter directly responsible for the inotropic effect. We have proposed that, in those tissues that demonstrate an ascending tension staircase and a positive inotropism following digitalis administration, a net increment in [Na\(^+\)], occurs which stimulates the Na-Ca exchange system and thus leads to a positive inotropic response (13).

The study of Blesa et al. (2) in the adult rat heart showed that at heart rates between 15 and 140 beats/min a positive staircase was not demonstrable; moreover, there was no evidence for an increase in [Na\(^+\)], when the frequency of stimulation was increased. The present study indicates the same for digitalis in the adult rat heart, i.e., absent or minimum inotropic responses to relatively high doses of ouabain with evidence for little increase in [Na\(^+\)], (derived from the fact that only small net losses in cellular K\(^+\) were observed in the adult rat heart (Figure 6)).

The absent or small staircase and digitalis responses parallel the decline in duration and level of the action potential plateau (Fig. 7). Before any suggestions can be made which indicate a cause and effect relationship, there are two major explanations for the progressive changes in the action potential plateau with age that need to be considered. (1) Diminution of anomalous rectification could occur with age such that the outward K\(^+\) current increases. This change is a very real possibility and has not been directly examined in the present study. If we grant that such a change is occurring, we must then examine the possibility that it is related to the decline in the staircase and glycoside responses. An increase in plateau potassium conductance (g\(_{\text{K}}\)) would augment steady-state K\(^+\) flux at any given frequency. Morad (14) has proposed that an augmentation of K\(^+\) exchange is coupled to enhanced Ca\(^{2+}\) uptake by the cell with the production of increased contractility. According to this proposal the rat heart should demonstrate greater potentiation with increased frequency as it ages. The results presented indicate the opposite effect. Therefore, although it is likely that g\(_{\text{K}}\) and K\(^+\) flux changes contribute to the changes in the plateau, they cannot be logically related, on the basis of present knowledge, to the functional changes demonstrated. (2) The fact that reduction of [Na\(^+\)], greatly reduces the duration and level of the plateau in the heart of the young neonate (Figure 7B) suggests the presence of a significant inward Na\(^+\) current during this period. Such a reduction attendant to a decrease in [Na\(^+\)], is probably not due to secondary effects on g\(_{\text{K}}\) since Deck and Trautwein (15) could not demonstrate any changes in slope conductance in Purkinje fibers exposed to low Na\(^+\) solutions. As the rat ages the plateau declines so that a reduction in [Na\(^+\)], affects only the overshoot and the rate of rise of the spike (Fig. 7B). This finding is consistent with further development of a fast Na\(^+\) channel and closure of a slow Na\(^+\) channel (16), which would have the effect of greatly diminishing the Na\(^+\) influx associated with excitation.

These studies raise the possibility that there is a reduced tendency for the adult rat to accumulate Na\(^+\) when the excitation frequency is increased or the Na\(^+\) pump is inhibited by ouabain. A similar reduction in Na\(^+\) influx would be produced by decreasing [Na\(^+\)], by 50% (Figs. 2 and 3) in the young neonatal heart. According to our hypothesis, such a reduction would diminish the staircase and ouabain responses such that they would become more typical of those found in the older neonatal group. If the rise in [Na\(^+\)], is minimum, it follows from the proposal just outlined that both the rise in Ca\(^{2+}\) influx and the inotropic response associated with an increase in stimulation frequency or ouabain administration would be minimum. Although other explanations are possible, such as primary alterations in Ca\(^{2+}\) flux per se, the present data support the suggestion that a progressive decline in Na\(^+\) influx per excitation as the rat heart ages accounts for the decline in the staircase and glycoside responses.

The increased resistance to ouabain with age has at least two possible explanations. First, as indicated earlier, the closure of a slow Na\(^+\) channel would diminish Na\(^+\) influx during excitation, unless there was a concomitant and marked increase in fast channel flux. A reduction of influx would diminish the load on the Na\(^+\) pump. A reduction in Na\(^+\) load could account for the trend toward less net K\(^+\) loss (evidence for net Na\(^+\) gain). Since a series of muscles in which the effect of ouabain on both 42K uptake and washout was not studied, the total net K\(^+\) loss was not quantified and, when present, was underestimated. However, the comparison of young and old neonates demonstrates the trend of less effect as the rat heart ages. Second, the resistance to ouabain with age might be attributed to the development of more rapid dissociation of the drug from membrane sites. The adult rat heart is known to demonstrate a particularly rapid dissociation for glycoside (3, 4, 17), and it is possible that the young neonate membrane demonstrates less rapid dissociation. This hypothesis does not contradict the tenet, however, that evidence for an increased level
of intracellular Na\(^+\) must be shown to demonstrate a glycoside-induced inotropism.

The electrophysiological and flux data reported in the present study are consistent with, but do not prove, the hypothesis that the Bowditch staircase and glycoside inotropic responses are based on an increment in cellular Na\(^+\) which, in turn, results in increased Ca\(^{2+}\) influx and enhanced contractility. It is possible that the changes in action potential configuration, functional responses and ionic fluxes are unrelated during maturation of the rat heart. Other studies, such as well-controlled voltage clamp analyses of the slow channel over the course of neonatal development, will aid in the further definition of the possible relationships.

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