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Development of the baroreflex in the young rat

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Abstract

The baroreceptor-heart period reflex was assessed in conscious, freely behaving rat pups on postnatal days 6 and 14. The baroreceptor-heart period reflex was elicited using the α_1-adrenergic agonist phenylephrine to increase blood pressure and the vasodilator, sodium nitroprusside, to decrease blood pressure. The autonomic effects of the baroreceptor manipulations were determined using pharmacological autonomic blockade. The data demonstrate that vasoconstriction produces a potent baroreflex-mediated bradycardia as early as postnatal day 6, which had previously been demonstrated only in anesthetized pups. In the anesthetized pup, the bradycardia is mediated by vagal activation, while we demonstrate that both vagal activation and sympathetic withdrawal occur in unanesthetized animals. In addition, the results replicate previous findings in rats demonstrating minimal cardiac sympathetic activation or vagal withdrawal following vasodilation during the first week of life, but substantial baroreflex-mediated tachycardia by the second week.

Keywords: Development; Heart period; Ontogeny; Parasympathetic; Sympathetic

1. Introduction

One important function of the autonomic nervous system is to regulate the baroreflex (e.g., Bartolome et al., 1980; Hageman et al., 1986; Palmisano et al., 1990). The baroreceptor-heart period reflex is evoked when pressure-sensitive receptors, found both in the great vessels near the heart and in the carotid sinus region, relay signals along afferents in the glossopharyngeal and vagus nerves to reflex networks in the medulla. From the medulla, efferent signals are relayed to vasomotor areas of the brainstem and to central autonomic nuclei, such as the dorsal motor nucleus of the vagus and nucleus ambiguus (Spyer, 1990). In adult mammals, increases in pressure result in both increased vagal and decreased sympathetic activation of the heart with a resultant lengthening of heart period. These autonomically mediated effects maintain pressure within a relatively narrow range (Head and McCarty, 1987; Spyer, 1990; Stornetta et al., 1987). In the young animal without fully functional autonomic control of target organs, or without mature central or afferent reflex components, one might observe different baroreflex-mediated autonomic cardiac responses to changes in arterial pressure than would be seen in adults.

Previous studies of the baroreflex in the young rat have usually focused on the maturation of the sympathetic limb of the reflex (Bartolome et al., 1980; for review see Slotkin, 1986). Bartolome et al. (1980) used vasodilator-induced decreases in blood pressure to demonstrate that the sympathetic portion of the baroreflex was intact by around postnatal day (PND) 14 in the rat, but not at earlier ages. In addition, using a small sample of PND 9 rats, these investigators did not observe any effect on heart period of a blood pressure increase induced by the vasoconstrictor, phenylephrine. These results contrast with a more recent study that did find a heart period increase after intravenous phenylephrine in PND 5/6 pups (Kasparov and Paton,

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1997). This later study was performed in urethane anesthetized animals. In light of these inconsistencies, it was important to explore the phasic autonomic capabilities of the young rat in a sample where environmental and strain effects were held constant, and no anesthesia was used.

Consistent with other recent investigations of the baroreflex, we used a pharmacological approach for both direct manipulation of blood pressure, and for determining the underlying autonomic contributions to heart period changes evoked by pressor and depressor manipulations (Head and McCarty, 1987; Stornetta et al., 1987). We produced increases in arterial blood pressure with the vasoconstrictor, phenylephrine, and decreases in pressure with the vasodilator, sodium nitroprusside. These two agents are commonly employed to explore the full range of activation of the baroreflex (Head and McCarty, 1987). Autonomic contributions to the baroreflex-induced changes in heart period were assessed using pharmacological blockades of each of the autonomic branches alone, as well as dual autonomic blockade.

2. Materials and methods

2.1. Subjects

Subjects were postnatal day 6 ($n=96$) and 14 ($n=96$) Wistar rats (day of birth=day 0). Half of these animals were used to produce dose response curves for phenylephrine and nitroprusside (6 litters for each age), and half for the autonomic blockade analyses (6 litters for each age). Untimed pregnant dams (Hilltop, Scottdale, PA) gave birth to the subjects no earlier than one week after arrival at the New York State Psychiatric Institute colony where pups were raised. Animals were housed under a reversed 12 : 12 h light : dark cycle. Dams were provided food and water ad libitum. Litters were culled to 9 pups 24–48 h after birth. This protocol was approved by the IACUC of the New York State Psychiatric Institute. It complies with federal, state, and international guidelines on the conduct of animal experiments.

2.2. Pharmacological agents

2.2.1. Vasoactive drugs

For dose response determination, 3 doses of the vasoconstrictor, phenylephrine HCl were used (0.3, 3.0, and 15 mg/kg, s.c.) and 3 doses of the vasodilator, sodium nitroprusside (0.25, 2.5, and 5.0 mg/kg, s.c.). Each litter provided a single pup at each dose and two pups that received normal saline (vehicle) injections. Based on the dose response values, we chose a phenylephrine dose of 3.0 mg/kg, s.c., and a nitroprusside dose of either 0.25 or 2.5 mg/kg, s.c. to be used in the autonomic blockade study. These selected doses appeared to cause no distress to the pups. All pups interacted normally with littermates during the test. Higher doses that did appear to cause some distress were eliminated from the study.

The fact that these selected doses were effective in altering blood pressure at these young ages was verified from pilot animals implanted with carotid catheters and tested under urethane anesthesia (2 g/kg, i.p.). The pups did not feel any pain during the procedure as they remained unconscious and unresponsive to tactile stimulation throughout. The surgery itself was as follows. A pup was cut on the ventral side so as to expose either the right or left common carotid artery. The artery was ligated just caudal to its bifurcation to prevent back flow of blood when the artery was later cut. The artery was then clamped using a microvascular clamp as close as possible to the clavicle. A loose ligature was placed around the artery just rostral to the clamp. Cannulae were made using Silastic tubing, fine and flexible, connected to polyethylene tubing PE50. The Silastic end of the cannula was cut on an angle to aid in the insertion of the cannula into the artery. A small cut was made in the carotid and the heparin-filled cannula was inserted. Microforceps were used to ease the artery up around the outside of the cannula. The loose ligature was then tightened to hold the cannula in place and the clamp was opened. Once a pulse was observed, the caudal ligature was secured. The cannula was then anchored with the threads of the rostral carotid ligature as well. A drop of superglue was placed on the knots to prevent untying. The wound was closed with glue (Hofer et al., 1988; Shair and Jasper, 2003). Blood pressure responses to vasoactive agents (s.c.) were recorded at day 6 (mean basal systolic blood pressure = 40.0 ± 6.7 mmHg, $n=7$; phenylephrine blood pressure response = +14.4 ± 1.2 mmHg, $n=3$; nitroprusside blood pressure response = −18.2 ± 8.3 mmHg, $n=4$), and day 14 (mean basal systolic blood pressure = 56.8 ± 4.4 mmHg, $n=6$; phenylephrine blood pressure response = +21.0 ± 7.5 mmHg, $n=3$; nitroprusside blood pressure response = −21.3 ± 3.8 mmHg, $n=3$). Despite the small number of animals the effect of vasoactive drugs on blood pressure was robust in all cases (change score t test against zero, ps = 0.1 or better). Moreover, we believe we are justified in generalizing from the effects of nitroprusside and phenylephrine in these anesthetized animals to awake animals because similar results have previously been shown in unanesthetized PND 14 animals (Hofer et al., 1988; Shair and Jasper, 2003).

2.2.2. Autonomic blockade drugs

Pharmacological autonomic blockade was used to determine the tonic adrenergic and parasympathetic contributions to heart period, as well as to phasic responses in heart period following changes in blood pressure. We used the quaternary muscarinic cholinergic antagonist, atropine methyl nitrate (1 mg/kg, free base weight, s.c.) for parasympathetic blockade. Adrenergic blockade was achieved using the β_1-adrenergic blocker, atenolol (10 mg/kg, s.c.). Dual autonomic blockade was achieved using a combination of atenolol and atropine methyl nitrate admin-

istered subcutaneously at the same doses used for single blockades (and in the same injection volume as single blockades). We have used these doses of autonomic antagonists in prior studies with young rats (Quigley et al., 1995, 1996), and they have been shown to be sufficient to block the effects of appropriate agonists in rats of this age (Tucker, 1981; Tucker and Johnson, 1984). Vehicle injections were made with physiological saline, and all vasoactive and autonomic drugs including vehicle were given in a volume of 2 ml/kg body mass. Eight pups from each of 12 litters were tested either on postnatal day 6 or 14 with each subject receiving an autonomic blockade (or control) pretreatment followed by a vasoactive drug. One pup in each litter received each of the following treatments: (a) saline+nitroprusside, (b) atropine+nitroprusside, (c) atenolol+nitroprusside, (d) dual blockade (atenolol and atropine)+nitroprusside, (e) saline+phenylephrine, (f) atropine+phenylephrine, (g) atenolol+phenylephrine, and (h) dual blockade (atenolol and atropine)+phenylephrine. The order of administration of vasoactive drugs and autonomic blockade drugs was counterbalanced across litters.

2.3. Physiological recordings

Electrocardiogram (ECG) signals were passed to a Grass Model 79D polygraph. R–R intervals from the ECG were measured by a preprocessor (K and M Interface; ±1 ms) and passed via a parallel port to a microcomputer for offline processing.

2.4. Experimental procedures

For both the dose response and autonomic blockade studies, pups were instrumented on the day prior to testing with subcutaneous silver wire electrodes (0.3 mm diameter; Sigmund Cohn, Mt. Vernon, NY) placed across the left and right flank for recording of the ECG (Shair, 1991). For implantation, younger subjects (day 5) were anesthetized using hypothermia (Phifer and Terry, 1986), and older subjects (day 13) with Metofane (Pitman Moore, Mundelein, IL). This minor surgery lasted under 5 min for each animal. After recovery from anesthesia (30–60 min), the dam and pups were returned to the home cage in the housing room. Pups were observed nursing, vigorously-nipple switching, and burrowing under the dam within an hour after reunion. Furthermore, no animals lost weight from the day of implantation to testing. The average weight gain was 15% for PND 5 to 6, and 6% for PND 13 to 14.

On the day of testing, the dam was removed from the home cage. The home cage with pups was placed on a thermoregulated heating pad (35–36 °C) in a remote testing room for 10 min while pups settled into a nest pile. Following acclimation, baseline recordings of ECG were made for 2 min from each pup using clip leads that were attached without picking up the pup. After baseline recordings, all subjects were removed from the home cage and weighed. After the weight of the last pup was taken, there was a minimum 2 min pause before testing began. In the autonomic blockade study, the first subject was then given its autonomic blockade drug, and returned to the home cage for 8 min at which time a 2 min post-blockade baseline was recorded. Immediately thereafter, the vasoactive drug was administered without picking up the pup. For subjects receiving nitroprusside, recordings continued for a minimum of 3 min, and for subjects receiving phenylephrine, recordings continued for either 5 min or until maximal cardiodeceleration had been achieved and the heart period was returning toward basal levels. This regimen was repeated for all 8 subjects in the litter. The procedures were the same for the dose response study except there was no preliminary injection with an autonomic blocker.

2.5. Data analysis

For analyses of the effects of vasoactive drugs, a 30 s pre-drug baseline was derived from the heart period record just prior to administration of phenylephrine or nitroprusside (during the 2 min post-blockade recording described above). The maximal effects of phenylephrine and nitroprusside were assessed by taking the longest (for phenylephrine) or shortest (for nitroprusside) 1 min mean heart period following vasoactive drug administration. This minute was chosen by dividing the post-injection period into 15 s epochs, and choosing 4 consecutive epochs with the longest or shortest heart period values. Fifteen second epochs affected by movement were removed from analysis. Maximum effects were then derived from the mean of the remaining 15 s epochs. These estimates were always based on at least a 45 s epoch from a 1 min period and 73% of data was derived from a 60 s epoch. Latency to maximal drug effect was the time from the injection to the beginning of the minute scored. Heart period change scores were computed by subtracting pre-injection heart period from post-injection heart period. Note that this method of scoring inevitably produces a small scoring artifact because the pre-injection value is a mean of the period analyzed, but what is shown in the post-injection figure (Fig. 2) is an extreme of its period of analysis. The control injections of the dose response study provide an estimate of this value for each condition. In the autonomic blockade study, the graphs and statistical analyses were adjusted with the appropriate value for each condition.

Data are typically presented as means±standard error of the mean (SEM). Statistical analyses were performed using analysis of variance (ANOVA). A priori or follow-up post hoc tests were by *t* test or Tukey's Honestly Significant Difference (HSD), respectively. In some cases, only the *p* values for the *t* tests are reported to make reading easier. However, *t* tests were only performed in cases where an overall ANOVA showed a significant difference across groups.

3. Results

3.1. Dose response study

Baseline heart period for pups in the dose response study for PND 6 was 156.8±1.2 ms, and did not differ as a function of their experimental group ($F(6,35)=0.60$, ns). Changes in heart period in response to vasoactive drugs are illustrated in Fig. 1. At PND 6, there was no significant effect of nitroprusside dose on heart period change ($F(3,20)=1.19$, ns; see Fig. 1, panel B). That is, the responses to nitroprusside injection were no different than the responses to saline injection. Conversely, phenylephrine produced large and significant increases in heart period (F $(3,20)=7.26$, $p<0.01$; Fig. 1, panel A). At PND 14, baseline heart period for pups was 153.0±1.3 ms and did not differ by experimental group ($F(6,35=0.56$, ns). At this age, both nitroprusside and phenylephrine altered heart period significantly ($F(3,20)=5.68$, $p<.01$ and $F(3,20)=24.42$, $p<.001$, respectively; Fig. 1, panels C and D).

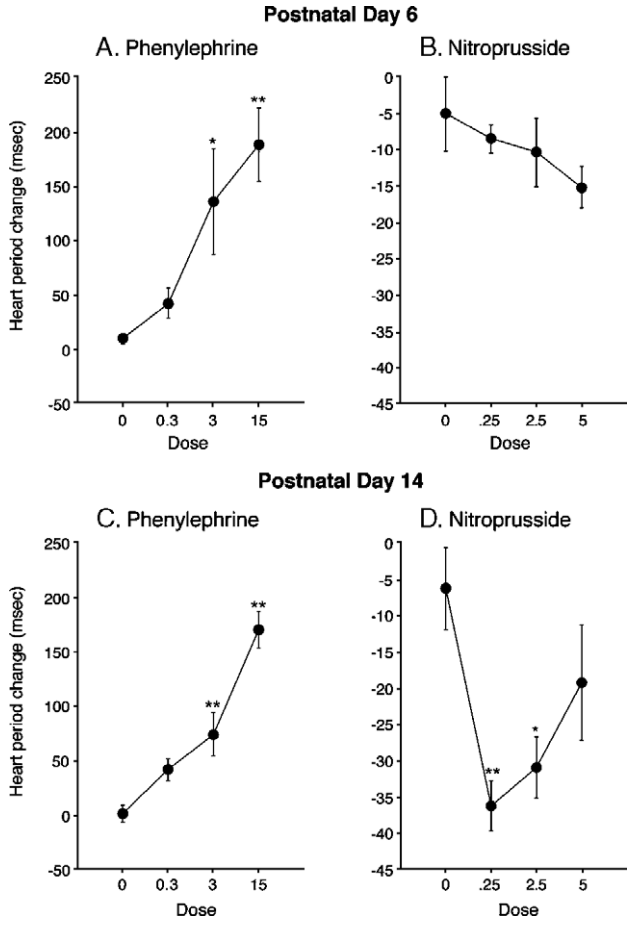

Fig. 1. Dose response data for heart period of PND 6 (panels A and B) or PND14 (panels C and D) pups given phenylephrine or nitroprusside injections ($n=6$ for each drug at each age). Values are means±SEM. Symbols indicate significant differences from the saline condition by post hoc Tukey HSD tests. * $p<.05$; ** $p<.01$.

Table 1
Effects of autonomic blockade on heart period in (milliseconds) in 6 and 14-day old rats

	Saline	Atropine	Atenolol	Dual blockade
PND 6	151.5 (3.2)	163.7 (3.7)	233.4 (5.2)**	227.2 (4.6)**
PND 14	143.9 (4.9)	147.8 (3.7)	187.2 (4.1)**	194.9 (3.1)**

Data shown are means and (SEM). Data from both animals given the blockade drug from each litter were used in the analyses (see Materials and methods).
** Significantly different from Saline control group using Tukey's HSD post hoc test, $p<.001$.

At the highest dose of nitroprusside, animals were frequently active throughout much of the post-injection period. At the highest dose of phenylephrine, animals became pale and in some cases, nearly expired. Thus, phenylephrine at 3.0 mg kg^{-1} and nitroprusside at either 0.25 or 2.5 mg kg^{-1} were used in the autonomic blockade study. Also, these doses were shown in our anesthetized animals to produce moderate changes in arterial pressure with subcutaneous administration (see Materials and methods).

3.2. Autonomic blockade study

3.2.1. Effects of autonomic blockades on basal heart period

In recordings prior to injection, PND 6 rats had longer resting basal heart periods than PND 14 rats (PND 6: 157.8±3.8 ms; PND 14: 145.8±2.4, $F(1,10)=8.42$, $p<.02$), which replicates previous studies (Quigley et al., 1996; Tucker and Johnson, 1984). Vehicle injection did not cause a significant change in HP at either age (compare with saline figures, Table 1). Blocking agents demonstrated that autonomic control of basal heart period was primarily adrenergic at both PND 6 and 14, again consistent with prior work (Hofer and Reiser, 1969; Tucker, 1985; Tucker and Johnson, 1984). This finding was demonstrated by separate 2 Age × 4 Blockade Drug ANOVAs for each age group on post-autonomic blockade baseline heart period which indicated a significant main effect of blockade drug type at both PND 6 and 14 (PND 6: $F(3,44)=99.15$, $p<.001$; PND 14: $F(3,44)=43.64$, $p<.001$, respectively). Post hoc comparisons revealed that only groups with adrenergic blockade (i.e., atenolol and dual blockade) were significantly different from the saline controls (see Table 1).

3.2.2. Effects of vasoactive drugs on heart period after saline pre-treatment

In PND 6 animals pretreated with saline, a paired sample t test indicated a significant effect of the vasoconstrictor phenylephrine on heart period ($t=5.72$, df=5, $p<.01$ see the saline bar, panel A, Fig. 2). The vasodilator nitroprusside had no significant effect at the younger age ($t=0.14$, ns, saline bar, panel B). At PND 14, both phenylephrine and nitroprusside were effective in altering heart period in saline pretreated pups ($t=8.07$, df=5, $p<.001$; $t=2.40$, df= 5, $p=.06$, respectively; saline bars in panels C and D).

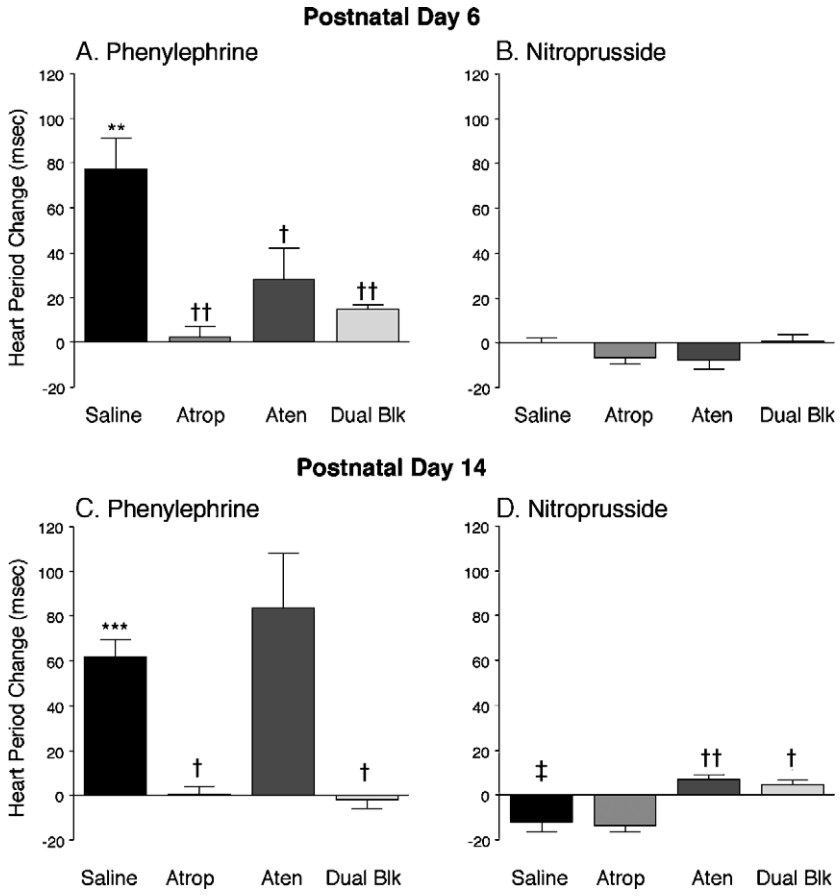

Fig. 2. Maximal changes in mean heart period from baseline in response to phenylephrine or nitroprusside injections for each of the autonomic blockade pre-treatments for rat pups at PND 6 (panels A and B) and PND 14 (panels C and D). Values are means ± SEM ($n = 6$ for each condition at each age). Asterisks or ‡ over the saline bars indicate a significant change in heart period from the baseline by paired-sample t tests caused by injection of phenylephrine or nitroprusside (see Materials and methods for details on how peaks and troughs were determined). Daggers indicate a significant effect of blockade on effects of the vasoactive drugs by comparisons by paired t tests to the saline injected pups (littermates treated as pairs). ‡ $p = .06$; ** $p < .01$; *** $p < .001$; † $p < .05$; †† $p < .01$.

3.2.3. Effects of vasoactive drugs on heart period after autonomic blockade pretreatment

3.2.3.1. PND 6. A one-way ANOVA of blockade drug on heart period change scores after the vasoconstrictor phenylephrine at PND 6 indicated a significant effect of autonomic blockade ($F(3,20) = 15.40$, $p < .001$). A priori comparisons by t test showed significantly smaller heart period changes after atropine, atenolol and dual blockade than after saline ($p < .01$, $p < .05$, $p < .01$, respectively; Fig. 2, panel A). A one-way ANOVA of blockade drug on heart period change scores for PND 6 animals after nitroprusside revealed no significant effect of autonomic blockade ($F(3,20) = 1.95$, ns; Fig. 2, panel B).

3.2.3.2. PND 14. A one-way ANOVA of blockade drug on heart period change at PND 14 also indicated a significant effect of autonomic blockade on response to phenylephrine injection ($F(3,20) = 11.05$, $p < .001$; Fig. 2, panel C). A priori t tests demonstrated that although the heart period change after both atropine and dual blockade was significantly smaller than after saline (both ps $< .05$), there was no significant difference between the unblocked (i.e., saline) heart period response to phenylephrine and that following atenolol. An ANOVA of blockade drug on heart period change scores for PND 14 animals in response to nitroprusside demonstrated a significant effect of autonomic blockade ($F(3,20) = 10.23$, $p < .001$; Fig. 2, panel D). T test comparisons showed that although there was no significant difference between the nitroprusside-induced decrease in heart period after atropine relative to saline, there were significantly smaller responses after both atenolol and dual blockade ($p < .01$ and $p < .05$, respectively) compared to the saline pre-treatment.

3.2.4. Effects of autonomic blockade on the latency to maximal effect of vasoactive drugs

As expected, the latency to maximal response to nitroprusside injection was shorter than the response to phenylephrine (see Table 2). The latency data for three of 4 conditions (2 Ages × 2 Vasoactive drugs) matched the findings of changes in mean heart period. In PND 6 pups there was no significant effect of autonomic blockade on the latencies to maximal effect of nitroprusside, presumably

Table 2
Mean latency in (seconds) to reach maximal change in heart period in response to phenylephrine or nitroprusside injections for each of the autonomic blockade pre-treatments for rat pups at PND 6 and PND 14

		Saline	Atropine	Atenolol	Dual block
PND 6	PHE	217.5 (24.4)	172.5 (20.0)	185.0 (31.6)	52.5 (31.6)**
	NP	65.0 (22.5)	87.5 (15.7)	65.0 (19.2)	52.5 (15.8)
PND14	PHE	230.0 (22.5)	127.5 (20.0)**	232.5 (16.8)	152.5 (34.3)*
	NP	77.5 (23.7)	37.5 (10.1)	30.0 (6.7)*	25.0 (7.4)*

Values are means and (SEM). $N=6$ for each condition at each age.
Asterisks indicate significant differences from Saline control group using Tukey's HSD post hoc test, * $p<.05$, ** $p<.01$.

because there was no nitroprusside effect. In response to nitroprusside injections at PND 14, post hoc comparisons showed that the latencies for the atenolol and dual blockade conditions were significantly shorter than after saline. For the 14-day old phenylephrine injected pups, pretreatment with atropine or the dual blockade yielded a significantly shorter latency relative to the response in the saline pretreated controls. The data for the phenylephrine injected pups at PND 6 was less orderly. Dual blockade significantly shortened the response latency and to the greatest extent of any pretreatment, just as it caused the greatest change in the mean heart period response. However, the latency data for atropine or atenolol pretreatment were not statistically different from the saline condition, in contrast to the mean heart period response.

4. Discussion

Our data confirm, in unanesthetized animals, the work of Kasparov and Paton demonstrating that one branch of the baroreflex functions during the first week of life (Kasparov and Paton, 1997), in contradiction to an earlier report (Bartolome et al., 1980). In PND 6 animals pretreated with saline, there was a significant effect of the vasoconstrictor phenylephrine on heart period. The lack of an effect of nitroprusside in PND 6 animals and emergence of a response to nitroprusside by PND 14 is also consistent with previous findings showing initial appearance of adrenergically mediated cardioacceleration in response to vasodilation during the second week of life (Bartolome et al., 1980; Seidler and Slotkin, 1981). Indeed, at PND 14, both phenylephrine and nitroprusside were effective in altering heart period in saline pretreated pups as previously observed (Bartolome et al., 1980; Kasparov and Paton, 1997).

We used the effect of pretreatment with blocking agents on the response to phenylephrine and nitroprusside to determine whether the heart period changes were mediated by baroreflex-driven autonomic changes. The phenylephrine data revealed a significant effect of autonomic blockade on the response to this vasoconstrictor at both PND 6 and 14. Dual autonomic blockade eliminated the cardiodecelerator response to phenylephrine injection at both PND 6 and 14 strongly suggesting that the effects of phenylephrine are autonomically mediated, and not due to direct α_1-adrenergic effects on the myocardium. Another issue concerns whether the minimal phenylephrine response under dual blockade occurred because atenolol greatly lengthened heart period which then may have limited further heart period lengthening by phenylephrine. As can be seen in Table 1, this problem was most critical at PND 6. Our dose response data from PND 6 suggest that this was not the case because the highest dose of phenylephrine produced a heart period response more than 40% greater than the effect of phenylephrine under atenolol.

Although significant cardiodecelerator responses occurred with phenylephrine at both PND 6 and 14, the autonomic mediation of these effects shifted over this age range. At PND 6, the cardiodecelerator response was reduced, but not eliminated by either adrenergic or parasympathetic blockade. Moreover, the deceleration was eliminated by dual autonomic blockade together suggesting that both adrenergic withdrawal and parasympathetic activation contributed to the heart period slowing induced by phenylephrine. This is notable because Kasparov and Paton observed a different mode of autonomic control in their anesthetized rats where the phenylephrine effect at PND 6 was purely parasympathetically mediated (Kasparov and Paton, 1997). The disparate results suggest that the extent of underlying autonomic tone affects the autonomic response to a baroreflex stimulus and that anesthesia results in substantial sympathetic withdrawal which limits further sympathetic decreases. In contrast, atropine blockade alone was sufficient to eliminate the cardiodeceleration induced by phenylephrine at PND 14. These results suggest that at PND 14, the chronotropic response to increases in blood pressure were mediated almost exclusively by parasympathetic activation in the awake animal. It is not clear to us why phenylephrine at PND 14 would result only in parasympathetic activation, and not sympathetic withdrawal since the atenolol effect on basal heart period suggests the presence of basal sympathetic tone. Although we cannot explain these data, they are consistent with other findings in awake, behaving rat pups in the second week of life where a startle-induced increase in heart period (Richardson, Wang and Campbell, 1996), a conditioned increase in heart period (Hunt, Richardson, Hess and Campbell, 1997), and the heart period response to aversive white noise (Kurtz and Campbell, 1994) also were blocked completely by atropine and unchanged by atenolol. Together with our results, these data suggest a prominent parasympathetic mediation of cardiodecelerator responses at two weeks of age with virtually no involvement of sympathetic withdrawal, despite the presence of sympathetic tone.

At PND 14, there was a robust response to nitroprusside. The shortened heart period was eliminated by both adrenergic and dual autonomic blockades, and was unaltered by parasympathetic blockade alone consistent with sympathetic mediation of this change in heart period. At PND 6, there was no effect of nitroprusside injection on

heart period, replicating the findings of the dose response study. These data are consistent with previous findings demonstrating the appearance of adrenergically-mediated cardioacceleration with vasodilation by the second week of life (Bartolome et al., 1980; Seidler and Slotkin, 1981). Although atenolol does not cross the blood brain barrier, the possibility of central effects of atropine methyl nitrate especially on animals this young has not been ruled out (Moore et al., 1992). Even if such effects exist, the current pattern of results can be explained by peripheral effects alone. However, further work on this issue is warranted.

In conclusion, these results show that autonomically mediated baroreflex responses to increases in blood pressure are evident within the first postnatal week in awake, freely moving rats. The data provide further support for the idea of an asymmetrical development of the autonomic nervous system such that decreases in blood pressure in rat pups do not alter heart period before the second week of life, whereas increases in blood pressure are effective and potent stimulators of heart period change as early as the first week of life. In addition, together with the results of Kasparov and Paton (Kasparov and Paton, 1997), these data indicate that although the mode of autonomic control evoked by a vasoconstrictor baroreflex stimulus in early life may be parasympathetic under anesthesia (due to withdrawal of sympathetic tone), the same stimulus in the awake rat evokes both parasympathetic activation and sympathetic withdrawal in the first week of life, with a shift to parasympathetic mediation in the second postnatal week.

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