Development and performances of a Japanese quail line homozygous for the diabetes insipidus (di) mutation

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Development and Performances of a Japanese Quail Line Homozygous for the Diabetes Insipidus (*di*) Mutation

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ABSTRACT A strain of Japanese quail with the polyuria disorder (excessive urination) was developed from founders that regurgitated water spontaneously. A backcross with a nonpolyuric quail line showed that the polyuric strain was fixed for an autosomal recessive mutation that also induced polydipsia (excessive drinking). Plasma levels and brain mRNA contents for avian Arg vasotocin were little affected by the mutation, but plasma avian Arg vasotocin was 13-fold higher and brain mRNA contents were significantly increased in both normal and mutant quail following a 24-h water deprivation. Affected and normal birds had similar performance traits (egg production and quality, feed intake, and gross carcass traits), but residual feed consumption was higher in polydipsic males. These results are consistent with the hypothesis that this strain was fixed for a mutation similar to the *di* gene described in the chicken and which induces nephrogenic diabetes insipidus. This new strain of Japanese quail might constitute a convenient model for the analysis of the underlying mechanisms of the disorder in birds and for comparative study with mammals.

Key words: Japanese quail, diabetes insipidus, di mutation, avian arginine vasotocin, performance

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INTRODUCTION

Only a limited number of mutations with a major effect have been reported in the Japanese quail (Cheng and Kimura, 1990). Most of them affect plumage color, and some, like the albino (Silversides and Mérat, 1991) and the lavender (Minvielle et al., 2002) mutations, are common and homologous in the quail and chicken. Some others have only been found in the quail so far, like the dominant fawn mutation used to tag commercial lines (Cheng and Kimura, 1990) and the sex-linked roux mutation, which makes it possible to sex crossbreds at hatching (Minvielle et al., 1999, 2000). Because of its small size and ease of raising, the Japanese quail is also used in biology and medicine (Minvielle, 2004). For example, the albino quail, which develops a glaucoma-like syndrome with age, has been extensively studied as an experimental model for human glaucoma (Dkhissi et al., 1994, 1996; Schrödl et al., 2005).

Nephrogenic diabetes insipidus is a metabolic disorder characterized by excessive drinking (polydipsia) and urination (polyuria) that has been thoroughly studied in humans (Maghnie, 2003) and mice (Lloyd et al., 2005). Its inherited autosomal form is determined by a mutation in the vasopressin receptor 2 or the aquaporin 2 genes, and a viable murine model of the disorder was only described recently (Lloyd et al., 2005). Adult chickens with a similar hereditary defect were reported earlier in 2 different locations (William and Buss, 1968; Obeidah et al., 1977), and the possible involvement of the avian antidiuretic hormone Arg vasotocin (**AVT**) in the defect was tested with infusions of AVT in *di* and normal chickens (Mühlbauer et al., 1992; Brummermann and Braun, 1995), because AVT plays a major role in the regulation of fluid balance in birds (Grossmann and Kisliuk, 1998). Up to now, however, no *di* Japanese quail line was available for medical or physiological studies, because this disorder had not been described in this species. The objectives of the present work were to develop the first Japanese quail line homozygous for the nephrogenic diabetes insipidus disorder, to study the association between the *di* mutation and avian AVT, and to estimate the effects of the mutation on quail performance traits.

MATERIALS AND METHODS

Birds and Husbandry

Japanese quail chicks were kept in group cages for 5 wk at a temperature which was decreased gradually from 37 to 25°C. There was artificial lighting for 24 h/d during the first week, and light was decreased gradually to 14

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h/d. Chicks received water and a mash starter diet (2,901 kcal of ME/kg, 11.5% moisture, 7% ash, 27% total protein, 8% fat, and 4% crude fiber) ad libitum. Males and females were separated at 3 to 4 wk of age. Then, quail were moved into cages of a 4-tier battery maintained at 22°C under artificial lighting for 14 h/d. They received a commercial layer diet (2,709 kcal of ME/kg, 11.5% moisture, 12% ash, 20% total protein, 4% fat, and 4% crude fiber), and feed and water were available ad libitum.

Development of the Polyuric Quail Line

A few healthy adult quail regurgitating water spontaneously when handled were spotted in a multipurpose experimental line maintained in our quail colony in Nouzilly. They were placed in individual cages for further inspection; the females demonstrated abnormally abundant and watery droppings, but the males were somewhat intermediate and more difficult to classify from this observation alone. The 8 most polyuric birds (2 males and 6 females) were chosen as founders (G_0) of the new line. Successive generations with a population size of 60 to 80 visually tested adults were obtained by selection and mating of the 20 to 30 birds with the most extreme polyuric phenotype. The process was continued until G_{20}, and all quail were clearly polyuric at that stage. The expression of the trait, however, still varied between quail and between sexes.

Experiment 1

Design. To study the existence of an association between AVT and the polyuria disorder, 5 G_{17} males with a clear polyuric phenotype were selected, and each one was mated to 1 G_{17} female and to 1 (nonpolyuric) female from another line (DD). This was done to produce normal (from the DD dam) and polyuric (from the G_{17} dam) progeny within each sire family, assuming the disorder was determined by an autosomal recessive gene, like in the chicken. At 5 wk of age, quail were placed in individual cages of a 4-tier battery in such a way that each combination of sire origin and sex was equally represented in each tier and that all progeny of G_{17} dams were placed in the first 2 tiers and progeny of DD dams in the other 2. For a fully balanced design, 2 male and 2 female progeny per sire were needed in each of the 4 tiers. Feed was given ad libitum. At 8 wk of age, 1 tier housing progeny of G_{17} dams and 1 tier with progeny of DD dams were taken off drinking water for 24 h. The remaining part of the experiment was carried out on the 47 members of the 3 most complete sire families with the expected pattern of polyuric (from G_{17} dams) and normal (from DD dams) phenotypes. The design was then a $3 \times 2 \times 2 \times 2$ factorial experiment (3 sires, 2 levels of water deprivation, 2 polyuria phenotypes, and 2 sexes) with 2 quail (replicates) measured per combination of the 4 main effects, but 1 individual was missing.

Tissue and Blood Collection. All quail from the 3 sire families were decapitated, and trunk blood was collected at the end of the 24-h water deprivation treatment. Plasma was separated by centrifugation ($1,000 \times g$, 15 min, 4°C) and stored at –20°C until the analysis. The brains were removed immediately, frozen on dry ice, and kept at –80°C until the RNA study.

RNA Extraction. Total cellular RNA was extracted from individual tissues using the acid guanidinium thiocyanate-phenol-chloroform method (Chomczynski and Sacchi, 1987). Briefly, the tissues were homogenized in guanidinium thiocyanate solution, and the total RNA was isolated from homogenate by phenol-chloroform centrifugation. The resulting pellets of total RNA were dissolved in water, and the quantity and quality of total RNA were measured by a spectrophotometer at 260 nm.

Northern Blot Analysis. Northern blots were performed according to Sambrooks et al. (1989). Briefly, 20 μg of total RNA were fractionated by 1.5% formaldehyde-agarose gel electrophoresis at 60 V of constant voltage. After electrophoresis, the RNA was transferred to a nylon membrane (Hybond N^+, Amersham, Braunschweig, Germany) by capillary transfer. The membranes were prehybridized with hybridization buffer (45% formamide, 5 × standard Na citrate (**SSC**), 1 × Denhardt's solution, 25 μg/mL of salmon sperm DNA, and 10 × dextran sulfate) for 2 h at 42°C. After prehybridization, the membranes were incubated with hybridization buffer containing [α-^{32}P] deoxycytidine triphosphate-labeled DNA probe. The AVT cDNA insert, a 270-bp portion of the distal 3' glycopeptide domain of the AVT gene, was labeled with [α-^{32}P] deoxycytidine triphosphate (Amersham) by Megaprime labeling (Hamann et al., 1992; Mühlbauer et al., 1993). Blots were first hybridized with the specific radioactive cDNA probe. After hybridization, the blots were washed twice at 42°C for 30 min in 1 × SSC/0.1% (wt/vol) SDS. The final stringency wash was carried out for 15 min at 55°C in 0.2 × SSC/0.1% (wt/vol) SDS. After washing, the filters were exposed to phosphor screens. All the blots were later stripped and rehybridized to a randomly primed labeled pT7 RNA 18S template (Ambion Inc., Austin, TX). The quantitative analysis of hybridization signals was performed by phosphorimaging (Bio-Rad, Munich, Germany). Target mRNA signals were normalized via 18S ribosomal RNA signal intensities.

RIA of Plasma AVT. The RIA was performed on plasma according to Gray and Simon (1983). Briefly, frozen plasma samples were thawed at room temperature, and AVT was extracted with 2 × volume acetone and centrifuged ($3,500 \times g$, 10 min, 4°C). The aqueous phase was extracted twice with 2 × volume petroleum ether and dried under vacuum in a SpeedVac concentrator (Savant Instruments Inc., Holbrook, NY). The pellet was dissolved in 0.2 mL of assay buffer (0.1 *M* Tris-HCl, pH 7.4, 2% wt/vol BSA, and 0.2% wt/vol Neomycin) and stored at –20°C until assayed. The intraassay variability was 7.1 ± 0.13%, and the interassay variability was 10.0 ± 0.19%. Invariably, duplicate measurements of AVT concentrations were taken using synthetic AVT as standard (Sigma Chemie GmbH, Deisenhofen, Germany). The AVT antiserum was kindly provided by D. Gray, Max Planck Insti-

Table 1. Effects of water deprivation and of the phenotype for polyuria on avian vasotocin (AVT) in tissues (mean ± SD) of Japanese quail[1] in experiment 1

	Water deprivation		Polyuria		Significance of main effect				Significance of interaction[3]			
Trait	Deprived	Not deprived	Polyuric	Normal	Water	Polyuria	Sex	Sire	P × sex	P × sire	W × sex	R^2
Brain AVT mRNA[2] (%)	109.6 ± 5.2	88.2 ± 6.9	98.5 ± 13.4	98.9 ± 11.7	***	NS	NS	NS	NS	*	NS	0.88
Plasma AVT (pg/mL)	38.0 ± 26.1	2.8 ± 4.2	24.2 ± 31.3	15.7 ± 17.3	***	NS	**	NS	*	NS	**	0.76

[1]Half-sib polyuric and normal females sired by polyuric males and polyuric females of the same line or females from another, nonpolyuric, line.
[2]Expressed as a deviation from the mRNA contents of the housekeeping gene.
[3]All 2-way interactions were tested, but nonsignificant ones are not shown; P = polyuria; W = water deprivation.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

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Experiment 2

Five G_{19} polyuric males were crossed to nonpolyuric females from another line (DD) to produce a F_1 progeny. Eighteen F_1 males were backcrossed to G_{19} females (single pair matings) to produce quail used for experiment 2 in a single hatch after a 3-wk egg collection.

Heredity of Observed Polyuria and Association with Polydipsia. At 5 wk of age, 95 females and 78 males from the 18 families were weighed and placed in individual cages. As the onset of visible polyuria varied among birds, droppings of quail were observed repeatedly starting at 7 wk of age, and each quail could be assigned to either 1 of 2 classes (polyuric or normal) by 20 wk of age. The BW and rectal body temperature were recorded at 33 wk of age. At the end of the experiment, a 100-mL beaker was fixed in each cage and filled manually with drinking water up to 3 times a day so that water was available at all time and spillage was avoided, whereas automatic water supply was discontinued. After a 1-wk training period, the amount of water provided daily was registered individually during 2 periods of 4 consecutive days to obtain the total water consumption of each female.

Feed Trial, Egg Quality, and Egg Production. A 4-wk feed trial was started at 17 and 22 wk of age in males and females, respectively. Individual feed intake (**FI**), BW at the start and the end of the trial, and egg mass (**EM**) laid by the females were collected to estimate residual FI (**RFI**). Egg quality was assessed by measuring weight and composition (yolk, albumen, and shell weights) of 3 normal eggs laid consecutively. Individual egg production was recorded for 13 mo, and age at first egg, total egg number, and clutch length were obtained for each female.

Gross Body Dissection. At 22 wk of age, 48 males from 12 different families were slaughtered and bled, and carcasses were kept overnight at 4°C before a gross dissection was carried out. Slaughter weight, abdominal fat weight, and weights of the left half breast meat and left leg were obtained.

Statistical Analyses

All analyses were carried out using SAS procedures (SAS Institute, 1999). A 4-way ANOVA was used to analyze AVT data. The linear model included sex (2 levels), water treatment (normal or deprived), polyuria phenotype (polyuric or normal), and sires (3 levels) as main fixed effects and their 2-way interactions.

Mendelian segregation of the putative *di* gene in the 95 females and 78 males of experiment 2 was analyzed by using the χ^2 test. All other traits, including water consumption, were analyzed by a 2-way ANOVA with the family (18 levels) and the polyuria phenotype (polyuric or normal) as fixed effects. In females, values of RFI were the residuals of the multiple regression of FI on BW gain (**BWG**), metabolic BW, and EM. The multiple regression fitted to the data ($R^2 = 0.53$) was FI = 143.26 + 1.73 BWG + 4.72 $BW^{0.75}$ + 1.061 EM. To estimate RFI in males, the multiple regression ($R^2 = 0.48$) was FI = 65.20 + 2.06 BWG + 8.00 $BW^{0.75}$.

RESULTS

Experiment 1

Water deprivation significantly increased ($P < 0.001$) brain AVT mRNA contents (Table 1), and a large propor-

Table 2. Effects of the phenotype for polyuria on 8-d water consumption, BW, and body temperature (mean ± SD) of female Japanese quail[1] in experiment 2

	Polyuria		Significance of effects		
Trait	Polyuric	Normal	Polyuria	Family	R^2
Total water consumption (g)	606 ± 187	443 ± 146	***	NS	0.41
BW (g)	268 ± 26	267 ± 33	NS	***	0.48
Body temperature (°C)	41.34 ± 0.31	41.31 ± 0.45	NS	NS	0.27

[1]Full-sib quail sired by F_1 males (crossbreds between the polyuric line and another, nonpolyuric, line) and females from the polyuric line.
***$P < 0.001$.

Table 3. Effects of the phenotype for polyuria on production performances (mean ± SD) of female Japanese quail[1] in experiment 2

	Polyuria		Significance of effects		
Trait	Polyuric	Normal	Polyuria	Family	R^2
BW at 5 wk of age (g)	199 ± 14	197 ± 18	NS	***	0.64
Daily feed intake (g)	25.4 ± 2.8	24.4 ± 3.2	NS	**	0.40
28-d residual feed intake (g)	5.1 ± 52	–4.7 ± 49	NS	**	0.41
Egg weight (g)	11.7 ± 0.95	11.4 ± 0.82	NS	***	0.50
Shell weight (g)	0.85 ± 0.11	0.87 ± 0.08	NS	*	0.33
Yolk weight (g)	4.0 ± 0.39	3.9 ± 0.30	NS	*	0.38
Yolk:albumen (%)	59.7 ± 4.9	59.5 ± 4.4	NS	NS	0.20
Age at first egg (d)	41.1 ± 3.4	41.7 ± 3.6	NS	**	0.35
Egg number	287.7 ± 56.3	295.7 ± 36.5	NS	NS	0.16
Clutch length (d)	7.4 ± 2.5	6.7 ± 2.1	NS	NS	0.22

[1]Full-sib quail sired by F_1 males (crossbreds between the polyuric line and another, nonpolyuric, line) and females from the polyuric line.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

tion ($R^2 = 0.88$) of the total variation was explained by the 4 factors in the model and their 2-way interactions. The polyuria × sire interaction was the only significant one ($P < 0.05$), however. It indicated that there was an association between polyuria and mRNA level, which varied among families, as shown by the respective mRNA least square means for polyuric and normal quail in the 3 sire families: 102.3 and 98.5, 96.2 and 104.1, and 96.9 and 95.7. Similarly, plasma AVT concentration was over 13-fold ($P < 0.001$) higher in water-deprived quail. It was also 2 times higher ($P < 0.05$) in females than in males. The polyuria × sex and water × sex interactions were significant ($P < 0.05$ and $P < 0.01$, respectively). Plasma AVT least square means of males and females were 12.0 and 36.3 in polyuric quail and 13.0 and 18.5 in normal ones, respectively. Similarly, they were 23.3 and 51.0 under water deprivation and 1.7 and 3.8 with ad libitum drinking water, respectively.

Experiment 2

Heredity of Observed Polyuria and Association with Polydipsia. Under the autosomal recessive mutation hypothesis for polyuria, half (n = 86.5) of the progeny of the crosses between crossbred F_1 sires and G_{19} dams were expected to be homozygous for the mutation. Only 79 quail out of 173, that is 42 females (out of 95) and 37 males (out of 78), were scored as polyuric. This apparent deficit in polyuric progeny was not significant, however, because the estimated χ^2 value was 1.3, smaller than χ^2_{1df} ($\alpha = 0.10$) = 2.7. Water consumption was significantly higher ($P < 0.001$) in polyuric females, and there was no difference in BW or in body temperature between polyuric and normal females (Table 2).

Feed Trial, Egg Quality, and Egg Production. Expected family effects were obtained for most production traits, but polyuria did not have any significant effect on performances of females (Table 3). In males, similar family effects were found, and polyuria was associated with higher ($P < 0.05$) RFI (Table 4).

Gross Body Dissection. Family had a significant effect on all 4 slaughter traits (Table 4). Moreover, there was no effect of the polyuria status of the birds on carcass traits.

DISCUSSION

In the present work, the inheritance of the polyuria disorder in experiments 1 and 2 was compatible with the hypothesis of a recessive autosomal mutation. Moreover, the association observed between polyuria and polydipsia is a well-established characteristic of nephrogenic diabetes insipidus induced by the recessive *di* mutation in

Table 4. Effects of the phenotype for polyuria on production performances (mean ± SD) of male Japanese quail[1] in experiment 2

	Polyuria		Significance of effects		
Trait (g)	Polyuric	Normal	Polyuria	Family	R^2
BW at 5 wk of age	178 ± 13	174 ± 14	NS	***	0.51
Daily feed intake	19.4 ± 2.3	17.9 ± 2.4	NS	**	0.47
28-d residual feed intake	12.0 ± 51.8	–11.7 ± 41.2	*	**	0.42
Slaughter weight	223 ± 26	223 ± 25	NS	***	0.54
Abdominal adipose tissue	11.2 ± 6.3	10.9 ± 5.0	NS	**	0.49
Breast muscle	19.6 ± 1.8	20.1 ± 1.9	NS	*	0.45
Leg weight	17.1 ± 1.9	17.2 ± 2.1	NS	*	0.41

[1]Full-sib quail sired by F_1 males (crossbreds between the polyuric line and another, nonpolyuric, line) and females from the polyuric line.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

mammals (Maghnie, 2003) and domestic fowl (William and Buss, 1968; Dunson et al., 1972; Bordas et al., 1978). This disorder is not associated with a change in plasma contents of the Arg vasopressin hormone in humans (Lloyd et al., 2005). In the present experiment, the interaction between sex and polyuria indicated that, among affected quail, plasma AVT contents were only altered in females. Moreover, plasma AVT increased more in females after water deprivation, but to a similar extent in affected and control quail, as it did in normal domestic fowl and chickens from a strain with a mutation for nephrogenic diabetes insipidus after the same treatment (Braun and Stallone, 1989; Roberts, 1991). The effect of the gender on plasma AVT did not seem to have been studied in other studies on the *di* mutation. Overall, these results are strong indications, however, that the new Japanese line was fixed for the *di* gene. The mutation has not yet been mapped in birds, but the high degree of synteny conservation between quail and chicken (Kayang et al., 2006) should help determine if the same locus is responsible for nephrogenic diabetes insipidus in the 2 Phasianidae species.

Preliminary investigations on AVT mRNA in the new Japanese quail line confirmed the previous observation made on normal quail (Mühlbauer et al., 1992; Seth et al., 2004) that AVT transcripts in the hypothalamus increased after water deprivation, but the presence of an interaction between sire family and polyuria found in the present work for the level of mRNA showed that other genes might also be involved in the response to water deprivation. The fact, however, that the mutation was not associated with consistent changes in brain AVT mRNA and in AVT plasma contents indicated that its effect should be studied also at the level of the kidney where reabsorbtion of fluids might be impaired. This hypothesis is consistent with the implication of genes from the aquaporin family (Agre, 2000) coding for renal water channel, which are sensitive to vasopressin in humans (Deen et al., 1994) and to AVT in quail (Yang et al., 2004).

Globally, the *di* mutation had little detrimental effect on performances. The RFI, however, was higher in *didi* quail but not significantly so in females, whereas increased RFI was reported in *didi* chicken layers (Bordas et al., 1978). The authors who studied RFI on females suggested that more energy was spent to increase ingested water to body temperature in *didi* birds, but the difference between sexes found in the present study indicates that the relationship might be more complicated. As in the present work, very marginal (Obeidah et al., 1977) or no (Bordas et al., 1978) *di*-related difference could be found in chicken for egg production and quality, but the dissection traits were not examined in *didi* chicken. The few production results obtained on *didi* birds concurred, however, and the *di* mutation did not seem to have any major detrimental effect on production traits. This absence of effect may explain the remaining presence of *di* in quail lines, because this mutation does not seem to be under marked systematic artificial (or even natural) selection.

In conclusion, polyuria, polydipsia, AVT-related characteristics, production performances, and the heredity of the disorder in the Japanese quail line developed by phenotypic mass selection have shown that it was a new genetic model for nephrogenic diabetes insipidus. The mechanisms behind this phenotype, however, remain to be studied in comparison with the homologous ones in mammals, but also in chickens.

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