Hormones and Behavior 106 (2018) 189–192

Contents lists available at ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh

Commentary

Comparative neuroendocrinology: A call for more study of reptiles!

David Kabelik[a,b,*], Hans A. Hofmann[c,d,e]

[a] Department of Biology, Rhodes College, Memphis, TN 38112, USA
[b] Program in Neuroscience, Rhodes College, Memphis, TN 38112, USA
[c] Department of Integrative Biology, University of Texas at Austin, Austin, TX 78712, USA
[d] Institute for Cellular and Molecular Biology, University of Texas at Austin, Austin, TX 78712, USA
[e] Institute for Neuroscience, University of Texas at Austin, Austin, TX 78712, USA

Squamate reptiles (lizards and snakes) are one of the most species-rich clades in the animal kingdom (Fig. 1). Together with turtles and crocodilians (and their long-extinct relatives, the dinosaurs), they comprise diverse life histories, morphological features, and behavior, which have fascinated humans for ages. Even though much research over the last few decades on the ecology, evolution, and systematics of reptiles has resulted in important insights into reptilian biology, reptiles have received surprisingly little attention from neuroscientists.

It is natural that as humans we gravitate toward mammalian research as we seek to understand the working of our own minds and bodies. And combined with long-standing funding priorities, it is thus not surprising that mammalian research, both human and non-human, well exceeds that of other vertebrate taxa. However, even beyond a focus on mammals, a superficial examination reveals a remarkable imbalance of research effort across other vertebrate taxa. For example, even though the number of behavioral neuroendocrinology publications involving non-human mammals, birds, and fish has been increasing over time since the late 1940s, the number of such studies involving reptiles, and amphibians, has only seen a modest increase (Fig. 2). Of course, to objectively assess the research effort for each taxonomic group it is more appropriate to calculate a ratio by dividing the number of research publication by the number of species present. This metric makes it even more evident that there is less research effort focused on the behavioral neuroendocrinology of reptiles than of any other vertebrate class (Fig. 3). This is similarly true for more general areas of research such as Neuroscience and Behavioral Neuroscience, and for unrelated research areas such as cardiovascular research and ecology (using the PubMed search engine). However, the results are most dramatic for behavioral neuroendocrinology where research effort for reptiles (0.018 publications/species) is nearly an order of magnitude below that of birds (0.148), and more than two orders of magnitude lower than that of mammals (4.778). In contrast, while research effort for birds is 8-fold higher than for reptiles in behavioral neuroendocrinology and behavioral neuroscience, it is only 5-fold higher for neuroscience and cardiovascular research, and 4-fold for ecology. Amphibians and fish also receive low research effort scores, the latter partly due to the very large number of extant fish species.

Amniotic vertebrates (mammals, birds, and reptiles) all evolved from reptilian ancestors (Fig. 1; Wade, 2005, Wilczynski et al., 2017) and it has been argued (Karten, 2015; Naumann et al., 2015) that modern day reptiles retain more ancestral characteristics than do mammals and birds. Thus, from an evolutionary and comparative perspective, this enormous discrepancy in research effort exposes a missed opportunity. Both mammalian and avian classes possess highly derived physiology and locomotion, as well as neural development and anatomy (Karten, 2015; Montiel et al., 2016; Nomura and Izawa, 2017). Furthermore, immense changes in locomotion, diet, and behavior are associated with endothermy (Lovegrove, 2017). Reptiles, in contrast, maintain ectothermy and much more limited telencephalic development (Cárdenas et al., 2018). Their behaviors are thus likely regulated to greater degree by basal forebrain and midbrain circuits, with less pallial input. Thus, reptilian brains may possess a more independently functioning social decision-making network (SDMN; see O'Connell and Hofmann, 2011,2012) than would be found in other amniote vertebrates, making them a highly important amniotic 'out group' for study. However, even the presence of a functional SDMN in reptiles, and anamniotic vertebrates, has been questioned (Goodson and Kingsbury, 2013).

For all these reasons, we believe it is high time for reptiles to become more prominent as model systems in behavioral endocrinology! The diversity of reptiles with regards to social behavior (Fox et al., 2003), cognition (Northcutt, 2013), and life history strategies (reviewed in Kabelik and Crews, 2017) makes them powerful model systems for basic questions in behavioral neuroscience, especially with regards to neuroendocrine processes governing behavior. This was recognized already in the 1930s by Noble and Evans (reviewed by Crews and Moore, 2005). After a 40-year hiatus, this work was extended significantly by Greenberg (2002), Crews et al. (2006), Summers (2002), and Wade (2005), among others, including recent systematic examinations of various neuroendocrine signaling pathways by Kabelik and co-workers (Hartline et al., 2017; Kabelik et al., 2013, 2014; Kabelik and Magruder, 2014; Smith and Kabelik, 2017). Also, Wilczynski et al. (2017) systematically reviewed the function of arginine vasopressin in reptiles (and amphibians), in comparison to other

* Corresponding author at: Department of Biology, Rhodes College, 2000 N Parkway, Memphis, TN 38112, USA.

https://doi.org/10.1016/j.yhbeh.2018.10.005
Received 10 October 2018; Accepted 13 October 2018
Available online 09 November 2018
0018-506X/

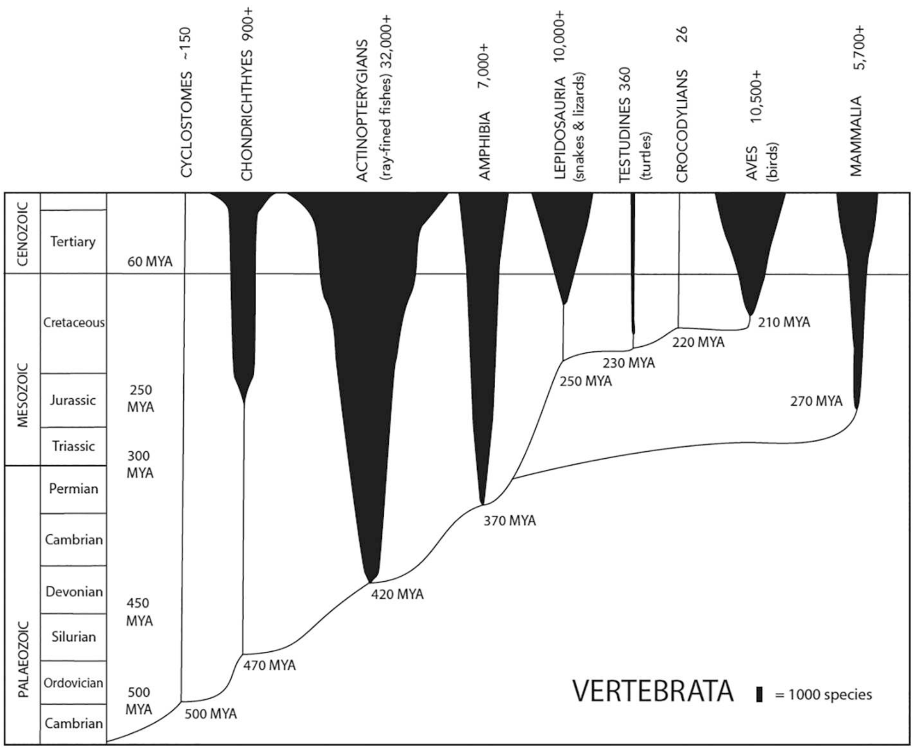

Fig. 1. Evolutionary history of vertebrates. The spindle diagram shows the relative diversity of the major groups through time, with the width indicating an estimate of species number (The World Conservation Union, 2014). Past expansions and extinction events are not shown for simplicity. The figure shows the Lepidosauria, which comprises both the Squamata and the single species of extant Rhynchocephalia, the tuatara.
Modified from Benton (2005).

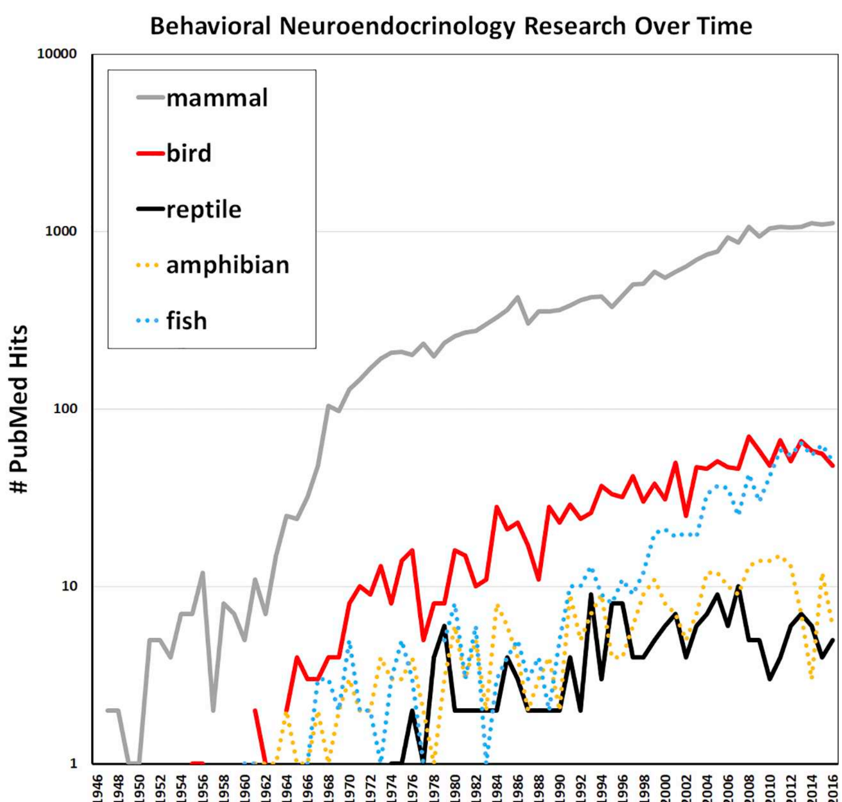

Fig. 2. Number of behavioral neuroendocrinology studies found in PubMed (pubmed.gov) per vertebrate class. Search parameters were: "(neural OR brain) AND (hormone or steroid or endocrine) AND behavior AND ___", with the blank representing either "mammal", "bird", "reptile", "amphibian", or "fish". The upper date cut-off was set to 12/31/2016 and no lower cut-off was employed. Only non-human mammals were included. A search including more broad search terms produced parallel results and so the above terms were used throughout for simplicity.

vertebrates, and spelled out concrete questions for future research. And a review by Naumann et al. (2015) introduced the reptilian brain to a broader audience. Maybe not entirely coincidentally, reptiles have lately also received considerable attention from systems neuroscientists based on the observation that due to its simpler structure, the reptilian cerebral cortex, which shares many functional attributes with mammals, lends itself to the identification of general algorithmic principles (Fournier et al., 2015; Reiter et al., 2017; Tosches et al., 2018).

In this issue, Kabelik et al. (2018) provide evidence for a functional SDMN in reptiles by demonstrating its involvement in the regulation of reproductive and agonistic behaviors. The authors find that although activation of the SDMN as a whole is largely unrelated to social behavioral output, activity at specific SDMN nodes does correlate with behavioral output and social environment. Furthermore, the interconnectedness of

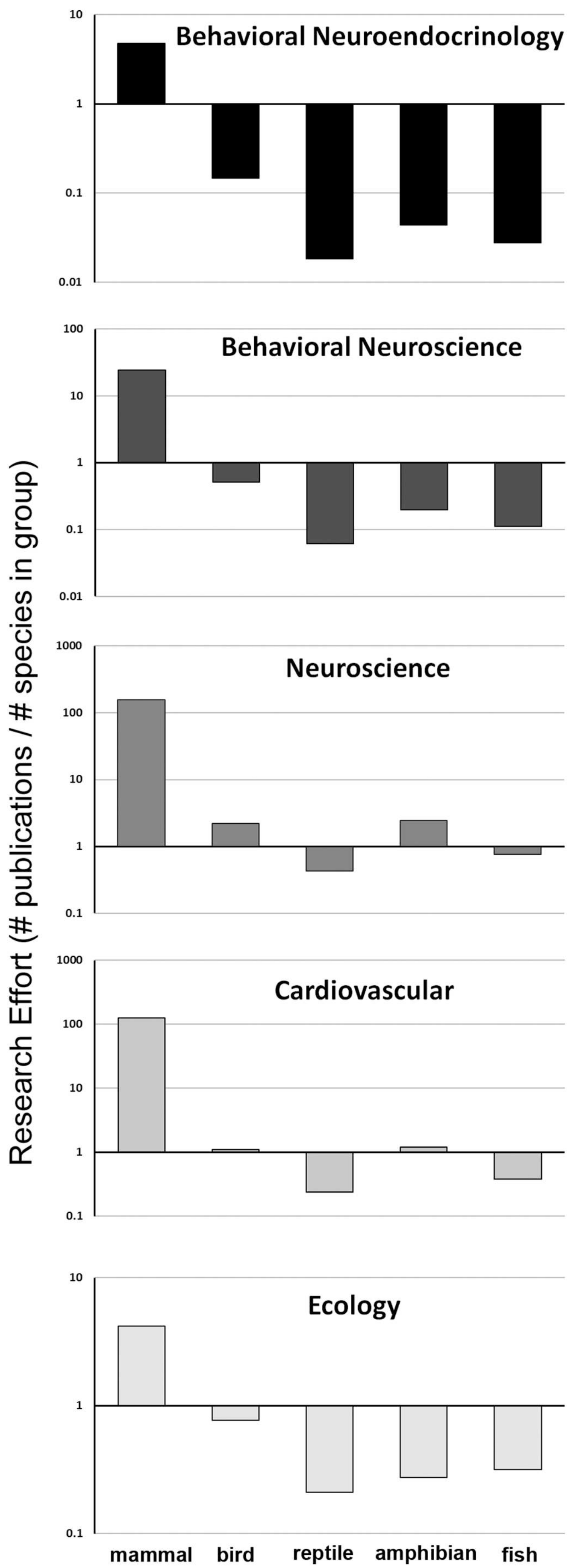

Fig. 3. Research effort per vertebrate class and field of research. Research effort is calculated as the number of PubMed hits divided by the number of species in that vertebrate class. Search parameters for behavioral neuroendocrinology were as in Fig. 2. Search parameters for other fields were adjusted to: "(neural OR brain) AND behavior AND ___", "(neural OR brain) AND ___", "(cardiovascular or cardiac or artery or vein or blood vessel) AND ______", and "ecology AND ______", respectively. Even though PubMed indexes only a subset of ecology publications, we used it for consistency; performing the search through Google Scholar also found reptiles to have the lowest research effort across vertebrate classes.

SDMN nodes – their functional connectivity – increases in social compared to asocial contexts, suggesting further involvement in processing of social decision making. Finally, the authors find that activity of various neurotransmitter and neuropeptide 'source nodes' relates to SDMN 'target' node activity, as well as behavioral output.

The Kabelik et al. (2018) study was performed on brown anole lizards (*Anolis sagrei*). Lizards, snakes, and the amphisbaenians (worm lizards) form the Squamata, the most species-rich order of reptiles, with an estimated 6451, 3691, and 194 species respectively (The Reptile Database, 2018). It is thus unsurprising that the bulk of behavioral neuroendocrinology research in reptiles has been carried out on Squamata. Of the other reptilian clades, Testudines (turtles and tortoises) constitute 350 species and a distinct phylogenetic lineage. Crocodylia (crocodiles, alligators, gavials, and caimans) comprise 24 species and are more closely related to birds than they are to other reptilian lineages. Finally, there is only one extant species of Rhynchocephalia, the tuatara. Even though there are few studies of reptiles outside of lizards and snakes, we found that research effort is actually lowest among the Squamata due to their species richness among non-avian reptiles. However, even though dividing by species number results in relatively higher research effort scores in other reptile groups, the actual number of studies is very small. For instance, the search terms behavioral neuroendocrinology resulted in only 13 hits for Testudines, 1 for Crocodylia, and 0 for Rhynchocephalia. These results highlight the relative paucity of research on several very interesting and poorly understood groups of reptiles. For instance, Crocodilians, like birds, are known to exhibit parental care and both Crocodilians and Turtles exhibit vocal communication (Chabert et al., 2015; Giles et al., 2009; Vergne et al., 2009), but we know of no neuroendocrine studies of these behaviors. And reptiles in general, like birds, exhibit high levels of adult neurogenesis, making them excellent models for research investigating structure-function remodeling of neural circuitry following behavioral and endocrine changes (Balthazart and Ball, 2016; Paredes et al., 2016).

Although we have placed great emphasis in this commentary on the lack of research involving reptiles, it must be noted that amphibians and fishes are similarly underrepresented in behavioral neuroendocrinology research relative to mammals and birds. Just like reptiles, these groups of organisms also provide fascinating opportunities for the study of hormone-brain-behavior relationships.

In conclusion, the behavioral diversity of reptiles, along with our increasing understanding of brain homologies, calls for a substantial increase in behavioral neuroendocrinology research in reptiles. Such work, placed within a phylogenetic comparative framework, can take advantage of the simpler, yet highly conserved, features of the reptilian brain. In this way, the brain and behavior of reptiles may prove indispensable for solving fundamental questions of behavioral neuroendocrinology.

Acknowledgements

We thank Dr. Rebecca Young Brim for critically reading this manuscript. DK' is supported by Rhodes College, US and Dr. Charles and Mrs. Patricia Robertson. HAH is supported by National Science Foundation, US grants DEB 1638861, IOS 1601734, IOS 1501704 and IOS 1354942.

References

Balthazart, J., Ball, G.F., 2016. Endocrine and social regulation of adult neurogenesis in songbirds. Front. Neuroendocrinol. 41, 3–22. https://doi.org/10.1016/j.yfrne.2016.03.003.

Benton, M.J., 2005. Vertebrate Palaeontology, 3rd edition. Blackwell Science Ltd, Oxford, UK, pp. 35.

Cárdenas, A., Villalba, A., de Juan Romero, C., Picó, E., Kyrousi, C., Tzika, A.C., Tessier-Lavigne, M., Ma, L., Drukker, M., Cappello, S., Borrell, V., 2018. Evolution of cortical neurogenesis in amniotes controlled by robo signaling levels. Cell. https://doi.org/10.1016/j.cell.2018.06.007.

Chabert, T., Colin, A., Aubin, T., Shacks, V., Bourquin, S.L., Elsey, R.M., Acosta, J.G., Mathevon, N., 2015. Size does matter: crocodile mothers react more to the voice of smaller offspring. Sci. Rep. 5, 15547. https://doi.org/10.1038/srep15547.

Crews, D., Moore, M.C., 2005. Historical contributions of research on reptiles to behavioral neuroendocrinology. Horm. Behav. 48, 384–394. https://doi.org/10.1016/j.yhbeh.2005.04.003.

Crews, D., Lou, W., Fleming, A., Ogawa, S., 2006. From gene networks underlying sex determination and gonadal differentiation to the development of neural networks regulating sociosexual behavior. Brain Res. 1126, 109–121. https://doi.org/10.1016/j.brainres.2006.07.031.

Fournier, J., Müller, C.M., Laurent, G., 2015. Looking for the roots of cortical sensory computation in three-layered cortices. Curr. Opin. Neurobiol. 31, 119–126. https://doi.org/10.1016/j.conb.2014.09.006.

Fox, S.F., McCoy, J.K., Baird, T.A., 2003. Lizard Social Behavior. JHU Press.

Giles, J.C., Davis, J.A., McCauley, R.D., Kuchling, G., 2009. Voice of the turtle: the underwater acoustic repertoire of the long-necked freshwater turtle, Chelodina oblonga. J. Acoust. Soc. Am. 126, 434–443. https://doi.org/10.1121/1.3148209.

Goodson, J.L., Kingsbury, M.A., 2013. What's in a name? Considerations of homologies and nomenclature for vertebrate social behavior networks. Horm. Behav. 64, 103–112. https://doi.org/10.1016/j.yhbeh.2013.05.006.

Greenberg, N., 2002. Ethological aspects of stress in a model lizard, *Anolis carolinensis*. Integr. Comp. Biol. 42, 526–540. https://doi.org/10.1093/icb/42.3.526.

Hartline, J.T., Smith, A.N., Kabelik, D., 2017. Serotonergic activation during courtship and aggression in the brown anole, *Anolis sagrei*. PeerJ 5, e3331. https://doi.org/10.7717/peerj.3331.

Kabelik, D., Crews, D., 2017. In: Pfaff, D.W., Joëls, M. (Eds.), Hormones, Brain, and Behavior, 3rd ed. Vol 2. Academic Press, Oxford, pp. 171–213 (editors-in-chief).

Kabelik, D., Magruder, D.S., 2014. Involvement of different mesotocin (oxytocin homologue) populations in sexual and aggressive behaviours of the brown anole. Biol. Lett. 10https://doi.org/10.1098/rsbl.2014.0566. (20140566-).

Kabelik, D., Alix, V.C., Burford, E.R., Singh, L.J., 2013. Aggression- and sex-induced neural activity across vasotocin populations in the brown anole. Horm. Behav. 63, 437–446. https://doi.org/10.1016/j.yhbeh.2012.11.016.

Kabelik, D., Alix, V.C., Singh, L.J., Johnson, A.L., Choudhury, S.C., Elbaum, C.C., Scott, M.R., 2014. Neural activity in catecholaminergic populations following sexual and aggressive interactions in the brown anole, *Anolis sagrei*. Brain Res. 1553, 41–58. https://doi.org/10.1016/j.brainres.2014.01.026.

Kabelik, D., Weitekamp, C.A., Choudhury, S.C., Hartline, J.T., Smith, A.N., Hofmann, H.A., 2018. Neural activity in the social decision-making network of the brown anole during reproductive and agonistic encounters. Horm. Behav. https://doi.org/10.1016/j.yhbeh.2018.06.013.

Karten, H.J., 2015. Vertebrate brains and evolutionary connectomics: on the origins of the mammalian ‘neocortex’. Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 370. https://doi.org/10.1098/rstb.2015.0060.

Lovegrove, B.G., 2017. A phenology of the evolution of endothermy in birds and mammals: evolution of endothermy. Biol. Rev. 92, 1213–1240. https://doi.org/10.1111/brv.12280.

Montiel, J.F., Vasistha, N.A., Garcia-Moreno, F., Molnár, Z., 2016. From Sauropsids to Mammals and back: new approaches to comparative cortical development: from Sauropsids to Mammals and back. J. Comp. Neurol. 524, 630–645. https://doi.org/10.1002/cne.23871.

Naumann, R.K., Ondracek, J.M., Reiter, S., Shein-Idelson, M., Tosches, M.A., Yamawaki, T.M., Laurent, G., 2015. The reptilian brain. Curr. Biol. 25, R317–R321. https://doi.org/10.1016/j.cub.2015.02.049.

Nomura, T., Izawa, E.-I., 2017. Avian brains: insights from development, behaviors and evolution. Develop. Growth Differ. 59, 244–257. https://doi.org/10.1111/dgd.12362.

Northcutt, R.G., 2013. Variation in Reptilian Brains and Cognition. Brain. Behav. Evol. 82, 45–54.

O'Connell, L.A., Hofmann, H.A., 2011. The vertebrate mesolimbic reward system and social behavior network: A comparative synthesis. J. Comp. Neurol. 519, 3599–3639. https://doi.org/10.1002/cne.22735.

O'Connell, L.A., Hofmann, H.A., 2012. Evolution of a vertebrate social decision-making network. Science 336, 1154–1157. https://doi.org/10.1126/science.1218889. (80-.).

Paredes, M.F., Sorrells, S.F., Garcia-Verdugo, J.M., Alvarez-Buylla, A., 2016. Brain size and limits to adult neurogenesis: brain size and limits to adult neurogenesis. J. Comp. Neurol. 524, 646–664. https://doi.org/10.1002/cne.23896.

Reiter, S., Liaw, H.-P., Yamawaki, T.M., Naumann, R.K., Laurent, G., 2017. On the value of reptilian brains to map the evolution of the hippocampal formation. Brain Behav. Evol. 90, 41–52. https://doi.org/10.1159/000478693.

Smith, A.N., Kabelik, D., 2017. The effects of dopamine receptor 1 and 2 agonists and antagonists on sexual and aggressive behaviors in male green anoles. PLoS One 12, 1–10. https://doi.org/10.1371/journal.pone.0172041.

Summers, C.H., 2002. Social interaction over time, implications for stress responsiveness1. Integr. Comp. Biol. 42, 591–599. https://doi.org/10.1093/icb/42.3.591.

The Reptile Database, 2018. http://www.reptile-database.org/db-info/SpeciesStat.html, Accessed date: 28 June 2018.

The World Conservation Union, 2014. IUCN red list of threatened species, 2014.3. In: Summary Statistics for Globally Threatened Species. Table 1: Numbers of Threatened Species by Major Groups of Organisms (1996–2014).

Tosches, M.A., Yamawaki, T.M., Naumann, R.K., Jacobi, A.A., Tushev, G., Laurent, G., 2018. Evolution of pallium, hippocampus, and cortical cell types revealed by single-cell transcriptomics in reptiles. Science 360, 881–888. https://doi.org/10.1126/science.aar4237.

Vergne, A.L., Pritz, M.B., Mathevon, N., 2009. Acoustic communication in crocodilians: from behaviour to brain. Biol. Rev. 84, 391–411. https://doi.org/10.1111/j.1469-185X.2009.00079.x.

Wade, J., 2005. Current research on the behavioral neuroendocrinology of reptiles. Horm. Behav. 48, 451–460. https://doi.org/10.1016/j.yhbeh.2005.02.006.

Wilczynski, W., Quispe, M., Muñoz, M.I., Penna, M., 2017. Arginine Vasotocin, the social neuropeptide of amphibians and reptiles. Front. Endocrinol. 8, 186. https://doi.org/10.3389/fendo.2017.00186.