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ORIGINAL PAPER

Replication of an experiment on extremely diluted thyroxine and highland amphibians

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Introduction: **The purpose of this study was to reproduce an experiment with diluted thyroxine and amphibians. A detailed account of the difficulties of this line of research has been published by the initial team (Endler and Scherer-Pongratz). One experiment which has been reported reproducible by the initial team and independent researchers is the effect of extremely diluted agitated thyroxine (T30x) *versus* analogously prepared water (W30x) in amphibians from biotopes above the tree line (highland amphibians).**

Methods: **(A) The author replicated the experiment. *Rana temporaria* were taken from an alpine biotope and the methods given in the original protocols were followed. Animals were treated from the 2-legged stage on. (B), the author reanalyzed the results reported by the initial team and by independent researchers (van Wijk, Lassnig, Zausner-Lukitsch, Bach, Harrer).**

Results: **(A) In the author's own experiment, there was a clear trend of T30x animals developing more slowly (i.e. up to 6 h within 3 days) than W30x animals. This is in line with the previous experiments. Due to small numbers of animals, the differences in the frequency of larvae reaching the 4-legged stage and the stage with reduced tail were not statistically significant ($p > 0.05$). The effect size was large ($d > 0.8$). (B) In the analysis of all available data with regard to the 4-legged stage, pooled T30x values from the initial team were 10.6% smaller than W30x values (100%) and pooled T30x values from the 5 independent researchers were 12.4% smaller ($p < 0.01$ and $d > 0.8$). Analogously, the number of animals entering the juvenile stage with reduced tail was smaller for T30x than for W30x.** *Homeopathy* (2013) **102**, 25–30.

Keywords: Homeopathy; High dilution; Thyroxine; Amphibians; Metamorphosis; Independent replication; Reproducibility

Introduction

Reproducibility of experiments is a key issue in science,[1,2] and thus a key issue in research in the field of complementary medicine.[3,4] In an earlier study at the Universitätsklinikum Benjamin Franklin (Steglitz), Free University Berlin, the author scrutinized experiments on life energy and came to the conclusion that previous results were either trivial, i.e. could be explained by classical physics, or probably due to a misinterpretation of observations.[5] Following Popper, failure to reproduce an experiment does not in itself mean that the original result was false positive.[6] Apart from random effects or publication bias, another possible explanation is that the initial outcome may have come about through superior handling know-how or technical details.

The purpose of this study was to investigate the reproducibility of an experiment with diluted thyroxine and amphibians.[7] A detailed account of the difficulties and pitfalls of this line of research has been published by the initial team.[8] One experiment in particular was subsequently reported by the initial team as well as by independent researchers to be reproducible, namely that on extremely diluted agitated thyroxine (T30x) tested *versus* analogously prepared water (W30x) in amphibians from biotopes above the tree line (highland amphibians). Animals were treated from the 2-legged stage on. Outcome parameters were the number of animals that had reached the 4-

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legged stage and the number that reached the stage with reduced tail. The author's attention was first drawn to this model when the results were published in the Berlin Journal on Research in Homeopathy,[7] edited by J Hornung of the Free University, Berlin in 1991, and again in 2002 results were published in the journal Perfusion,[9] and again when Lingg and Endler published a survey on their raw data and data recalculation, including results from 2010.[10] All three studies reported T30x-treated animals to metamorphose more slowly than W30x control animals.

The author confined himself to data from this type of experiment. Other types of experiments performed by the initial team were not considered: Experiments on *Rana temporaria* from lowland biotopes,[11] *Bufo bufo*,[12] on other application intervals continuous treatment through the walls of a sealed glass vial[13–15] and experiments with other dilutions (thyroxine 6x or 8x,[16,17] 'Q-potencies' [18]), experiments starting from another than the standardized 2-legged stage[19,20] and experiments with artificially hyperstimulated larvae[21,22] were excluded.

Thus, the author replicated the experiment, reanalyzed and combined the results of the initial team (Endler and Scherer-Pongratz[7,9,10]) and of independent researchers (R van Wijk, H Lassnig, C Zausner-Lukitsch and G Bach[7,9,23]) including his own results.

Methods

Replication experiment

The methods given in ref.[10] were followed as closely as possible. The only obvious deviation was that the animals were stored at dimmed daylight and a temperature of only 8°C for 3 days to prevent them from developing beyond the designated starting stage before the scheduled start of the experiment. All possible steps were taken to avoid any animal suffering and procedures followed the scientific and public authority guidelines for animal collection and experimentation.

Rana temporaria larvae were taken from a highland biotope (Western Alps, 1500 m above sea level). For preparation of the test solution T30x, a stock solution was prepared from tetra-iodo-thyronine sodium pentahydrate (T_4, Sigma), diluted 10^{-4} parts by weight in double distilled water and then further diluted with water in 26 steps of 1:10 and agitated after each step by banging the half-filled hardglass bottles 30 times against a rubber stop at intervals of approximately 0.5 s. The water control solution was prepared analogously. 3 μL of probe dilutions (T30x or W30x) were added per animal and 300 ml of basin water (chlorine-free tap water) at intervals of 48 h [see[10]]. For reasons of laboratory convenience (danger of cross-contamination) the author followed[7,9,10] and used only one bottle per substance.

The starting stage of treatment was defined as the point at which the hindlegs of the 2-legged tadpoles are such that they are just visible through the triangle formed by thigh, shank, and tail. This corresponds to Gosner's stage 31.[24] 4 white plastic basins were randomly assigned to each group (T30x and W30x). This gave a rectangle of 8 basins with identical treatment groups arranged diagonally adjacent to one another. The number of animals per basin was 20. A total of 80 + 80 animals were randomly assigned to the basins. The basins were exposed to indirect natural light. The tadpoles were fed with blanched lettuce *ad libitum*. Temperature was 23 ± 1°C. For the first part of the evaluation, the tadpoles were observed until their forelegs, which are preformed under the skin, broke through and the animals had thus entered the 4-legged stage. For the second part of evaluation, tadpoles were observed until their tails were reduced to a length shorter than their body. Development was monitored at intervals of 8 h. Counting results were documented photographically. The experiments were performed blind. Due to a handling error, two basins were cross-contaminated with the blinded substances and were excluded from the experiment. Thus, 60 + 60 animals in 3 + 3 basins were considered.

60 to 100 animals per group suffice to show a trend with a medium or large effect size ($d > 0.5$ or 0.8) but to reach statistical significance requires several hundred per group. Due to recent species protection legislation restricting the use of highland *Rana temporaria*, the author determined in advance that a clear trend would also be a worthwhile outcome to test for.

T30x and W30x groups were compared until about 70% of all animals had reached the 4-legged stage and 50% had reached the stage with reduced tail.[10] Means, standard deviations and effect sizes were calculated. Frequencies of 4-legged animals as well as animals with reduced tail in the T30x and W30x groups were compared by (Yates corrected) Chi square tests at the individual measuring points. The areas under the curve (AUCs) − as sum of separated trapezoids for each measuring point − were compared by means of a Chi square test on a 2 × 2-crosstab-design for the areas at both sides of both treatment curves. Frequencies were plotted and compared graphically. Apart from differences between frequencies (in percentage), differences were also expressed in % of control, i.e. W30x was set to 100%.

Comparison of results: initial team *versus* independent researchers

The PUBMED, HOMBREX and www.inter-uni.net research databases were screened for publications on experiments with highland *Rana temporaria* that underwent treatment with thyroxine 30x applied at 48-h intervals on entering the standardized 2-legged stage. The experiments were split into those performed by the initial researchers (PC Endler, Zoological Institute Graz University and Waltraud Scherer-Pongratz, Boltzmann Institute for Homeopathy, Graz: 15 experiments involving 60−100 animals per group subjected to either test or control treatment, total of 1290 animals per group); and those performed by 4 independent researchers (Roel van Wijk, Department for Molecular Cell Biology Utrecht University;[7] Haimo Lassnig, Federal Institute of Veterinary Medical Investigation, Graz;[9] Christa Zausner-Lukitsch, Zoological Institute Vienna University;[9] Gudrun Bach, KIKOM, Bern University;[10] 6 experiments involving 60−100 animals per group each, giving a total of 430 per group).

Some of the above-mentioned experiments had been continued until the animals reached the stage with reduced tail. The results of these follow-on experiments were split into those performed by the initial team (2 researchers, experiments total 390 animals per group[7]) and those performed by one independent researcher (experiments total 180 animals per group[7]).

For comparison of results, the author followed the suggestion given in ref.[10] of referring to standard measuring points in time where about 70% of all animals had reached the 4-legged stage and where about 50% had reached the stage with reduced tail. Apart from differences between frequencies, differences were also expressed in % of control.

Results

Replication experiment

Transition to the 4-legged stage: Figure 1 shows the frequencies of 4-legged animals for the T30x group (60 animals) and W30x group (60 animals) over time (8-h intervals). A clear trend was observed of T30x animals being slower than W30x animals. This trend was most marked after 32 h, where the difference between T30x and W30x values was 10% points; in other words when W30x was set to 100%, the T30x value was 25% of W30x. This means a delay in development of the T30x group of about 5 h. Due to the small numbers of animals however, these differences are not statistically significant ($p > 0.05$).

Transition to the stage with reduced tail: Figure 2 shows the frequencies of animals with reduced tail for the W30x group (60 animals) and the T30x group (60 animals). The same trend as above is observed. It was most marked after 56 h, where the difference between T30x and W30x values was 11.7% points; in other words when W30x was set to 100%, the T30x value was 53,3% of W30x. This means a delay in development of the T30x group of about 6 h. Due to the small numbers of animals, these dif-ferences are not statistically significant ($p > 0.05$).

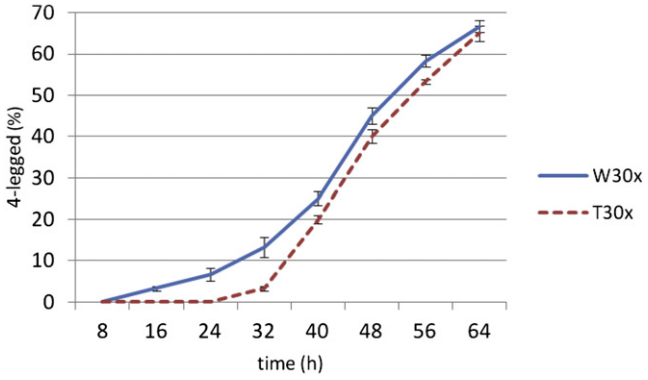

Figure 1 Results of the author's own independent replication experiment on the influence of extremely diluted agitated thyroxine (T30x) tested *versus* analogously prepared water (W30x) on highland amphibians up to the 4-legged stage. *N* = 60 per group. Ordinate = cumulative frequency of 4-legged tadpoles in %. Bars: S.E.M. Abscissa = time in hours. For further explanation, see text.

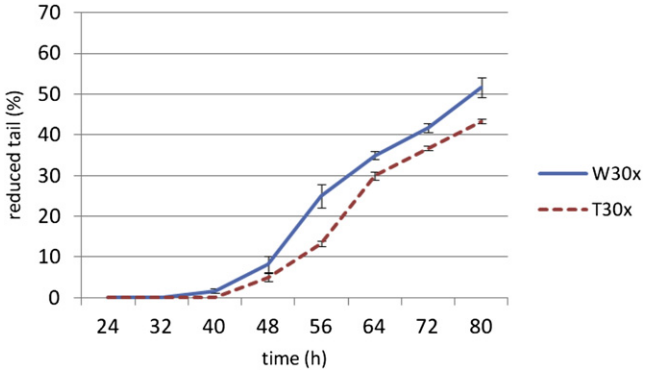

Figure 2 Results of the author's experiment on highland amphibians at the reduced tail stage. *N* = 60 per group. Ordinate = cumulative frequency of tadpoles with reduced tail in %. Abscissa = time in hours. For further explanation, see text.

Comparison of results: initial team *versus* independent researchers

Dark columns in Figure 3 refer to the transition to the 4-legged stage and show the relative differences between W30x and T30x groups at the predefined measuring point for experiments performed by the initial team (above, results from 15 experiments each involving 60−100 animals per group) and by 5 independent researchers (below, 7 experiments each involving 60−100 animals per group). In most of the experiments (with the exception of two experiments performed and reported by the initial team), a trend was found of T30x animals being slower than W30x animals. The differences in the individual sub-experiments were mostly not statistically significant ($p > 0.05$). After pooling, the difference at the predefined measuring point was statistically significant both for the results of the initial team and for those of the independent researchers ($p < 0.01$ in either case); T30x values were 10.1% smaller than (i.e. equal to 89.4%) W30x values (100%) for the initial team and 12.4% smaller for the independent researchers. The Cohen's D effect size was >0.8 (large) in either case.

White columns in Figure 3 refer to the transition to the stage with reduced tail in experiments performed by the initial team (above, 2 experiments with 115 and 103 animals per group) and by 2 independent researchers (below, 2 experiments each involving 180 and 60 animals per group). In all of the experiments, a trend was found of T30x animals being slower than W30x animals. The difference at the predefined measuring point was statistically significant both for the results of the initial team ($p < 0.01$) and for those of the independent researchers ($p < 0.05$); T30x values were 23% smaller than W30x values (100%) for the initial team and 15.3% for the independent researchers. The effect size was >0.8 (large) in either case.

Discussion

In his own independent replication of the experiment[7,9,10] on extremely diluted thyroxine and highland amphibians, the author followed the methods given in the original protocol.[8] *Rana temporaria* were taken from a biotope in the Western Alps for one experiment with 60 + 60

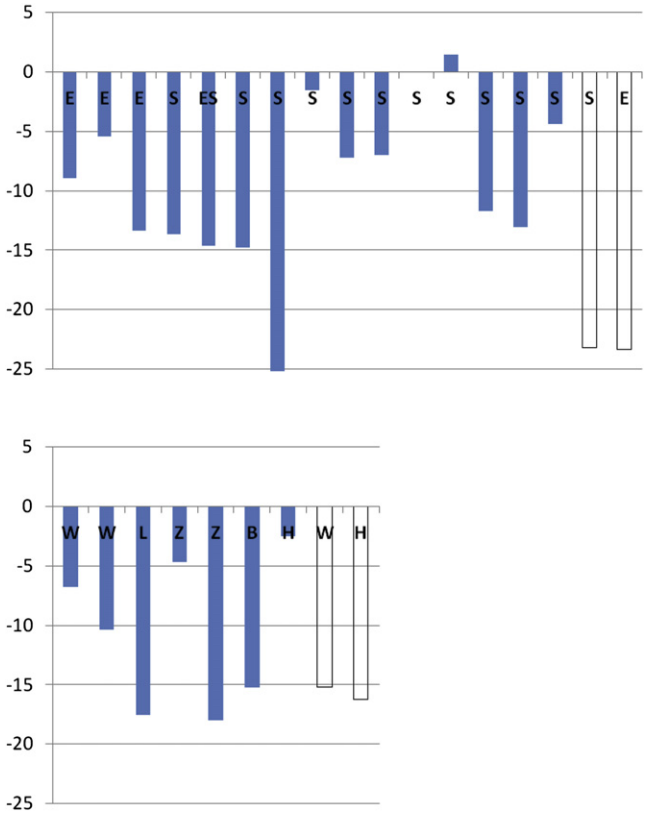

Figure 3 Results of sub-experiments on the influence of T30x on highland amphibians, comparison of the results of the initial team with those of independent researchers. Ordinate, 0 = reference W30x (set to 100%), bars = differences between W30x and T30x groups in % of W30x. Abscissa above, researchers of the initial team: E = PC Endler, Zoological Institute Graz University; S = Waltraud Scherer-Pongratz, Boltzmann Institute for Homeopathy, Graz; below, independent researchers: W = Roel van Wijk, Department for Molecular Cell Biology Utrecht University; L = Haimo Lassnig, Federal Institute of Veterinary Medical Investigation, Graz; Z = Christa Zausner-Lukitsch, Zoological Institute Vienna University; B = Gudrun Bach, Cooperative Office for Complementary Medicine, Bern University; H = Bernhard Harrer, Patienteninformation fuer Naturheilkunde, Berlin. Dark columns refer to the transition to the 4-legged stage, white columns to the transition to the stage with reduced tail. For further explanation, see text.

2-legged larvae. A clear trend towards the effect described in previous publications[7,9,10] was found, with the number of 4-legged T30x animals lagging behind up to 10% over the course of metamorphosis. In the course of metamorphosis from the 4-legged stage up to the stage with reduced tail, T30x animals lagged behind up by to 11.7%. Differences are not statistically significant ($p > 0.05$), but effect sizes are large (>0.8) at some measuring points, regardless of whether the 4-legged stage or the reduced tail stage is considered as outcome criterion.

When the results of the initial team (Endler and Scherer-Pongratz[7,9,10]) and by independent researchers (R van Wijk, H Lassnig, C Zausner-Lukitsch and G Bach[7,9,23]) were compared, in most of the experiments (with the exception of two experiments by the initial team), a trend was found of T30x animals being slower than W30x animals. The differences in the individual sub-experiments (comprising 60−100 animals per group each) were mostly not statistically significant ($p > 0.05$). With regard to the 22 experiments using the 4-legged stage as outcome criterion, pooled T30x values were 10.6% smaller than (i.e. equal to 89.4% of) W30x values (100%) for the initial team and 12.4% smaller for the 5 independent researchers including the author ($p < 0.01$ and $d > 0.8$ in either case). With regard to the 4 experiments using the reduced tail stage as outcome criterion, pooled T30x values were 23% smaller than W30x values (100%) for the initial team and 15.3% for the independent researchers. The effect size was >0.8 (large) in either case.

The author's conclusion is that the results of his own replication experiment, though not statistically significant, are in line with those of the initial team and with those obtained by the other independent researchers.

One issue deserving discussion was that in the author's own experiment, although the methods given in the protocols[7,9,10] were followed as closely as possible, there was a deviation in that the animals were stored at dimmed daylight and a temperature of 8°C for 3 days to prevent them from developing beyond the designated starting stage before the scheduled start of the experiment. The experiment itself was then performed at 23 ± 1°C. This pre-treatment slightly delayed the onset of the transition from the 2-legged stage onwards, as can be seen from the incline of the curves in Figure 1 when compared to previous curves [[12], Figure 1; [10]], and may have influenced the sensitivity of the larvae to the T30x probe. However, Figure 2 suggests that the outcome cannot just be accounted for by the variability of the biological model itself. In other words, and in keeping with Popper's falsifiability paradigm,[6] the majority of experiments showed a decrease in metamorphosis speed under treatment with T30x, a dilution with a theoretical molarity beyond Avogadro's number prepared according to homeopathic method. This includes 15 experiments performed by the initial team and 6 by 4 independent researchers between 1990 and 2010 and one by an independent researcher in 2011.

A biological pathway of the action of T30x was suggested by Guedes *et al.*[25,26] who studied the influence of homeopathic high dilutions prepared from thyroid glands. This Brazilian group found a decrease of metamorphosis speed as well as histological changes during tail absorption evidenced by higher rates of programmed cell death (apoptosis) in the test group. One of the pathways of highly diluted homeopathic drugs may be the modulation of signal proteins at gene regulatory level.[27]

Sensitivity of amphibian larvae to highly diluted agitated substances (i.e. metal salts) prepared according to homeopathic/anthroposophic tradition was first reported by Koenig in Prague in 1927.[28] The team that initiated modern research on amphibians and diluted thyroxine (Endler and Scherer-Pongratz) themselves have provided detailed information on difficulties and pitfalls of their research.[8] Experiments on *Rana temporaria* from lowland biotopes, *Bufo bufo*, or experiments on further intervals of application (8 h or continuously through the wall of a sealed glass

vial) as well as experiments with further dilutions (thyroxine 6x or 8x) or starting from other than the standardized 2-legged stage were not considered here.

Despite the interesting findings it has produced, the highland amphibian model can be recommended for further research only within limits because the animals are not available from breeders but have to be collected in the field after procuring permits for animal collection and experimentation from the public authorities. Besides this, the diversity of alpine biotopes could be associated with hitherto unexamined differences in experimental material. It goes without saying that professional expertise and experience are required not only for the experiment itself but also for the animals' collection, transport and handling prior to the experiment.

Conclusion

The results of the author's replication experiment with extremely diluted thyroxine and highland amphibians are in line with those of the initial researcher team and with those of the 4 previous independent researchers involved in these studies between 1990 and 2010. A hormone diluted beyond Avogadro's limit, of theoretical 0-molarity, by a process derived from homeopathy produced a clear trend of inhibiting metamorphosis in most of 22 experiments. With regard to the 4-legged stage, pooled T30x values were 10.1% smaller than control for the initial team ($p < 0.01$ and $d > 0.8$) and 12.4% smaller for the 5 inde-pendent researchers including the author ($p < 0.01$ and $d > 0.8$). Reproducibility of experiments is a key issue in science, and thus a key issue in research in the field of complementary medicine and homeopathy. The findings have an impact on the scientific foundations of homeopathy, even if the underlying mechanisms remain to be explored.

Conflict of interest

Patienteninformation fuer Naturheilkunde e.V. (Patients Information Center for Natural Medicine) is an independent not-for-profit organisation doing research, documentation and consulting for patients in the field of natural and holistic medicine since 1997. The funds for this study were provided by the author himself out of personal interest in the subject. There are no conflicts of interest.

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