Could bromide (Br^-) be a thyroid hormone (THR) disruptor?

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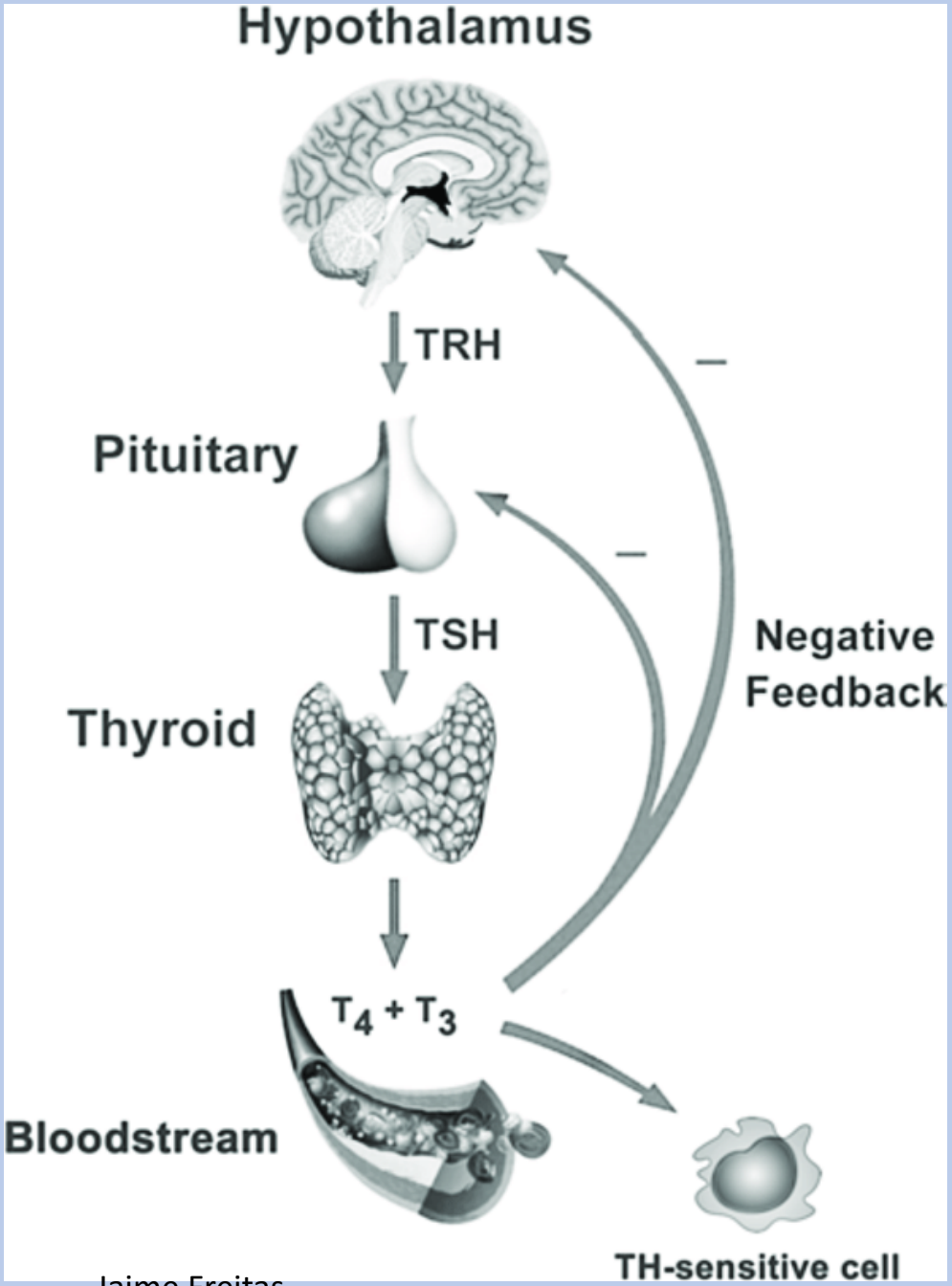
The project began as an investigation of water quality constituents in ground water in extensive livestock producing regions of South Africa



Why could Br^- be a TDC?

- Hypothalamus – Pituitary – Thyroid axis (HPT)
- Growth hormone
- Reproductive hormones
- Implications?

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Functions of TH

- Development (differentiation and growth)
  - Embryo/Foetus
  - Post-natal

- General metabolic processes
  - Neonate
  - Growing animal
  - Reproductive
  - Older - maintenance

Where does Br^- occur and why is it an element of concern?

- Br^- occurs naturally in groundwater in combination with other ions such as chloride (Cl^-) (Davis et al., 2004)
- Range in SA groundwater: 0 - 132 mg/L

  (Casey and Meyer, 2001; Casey et al., 2001; Meyer, 2005;

  Casey and Meyer, 2006; Korsten et al., 2016)
- Potential of high exposure – both chronic and acute
- Br^- in a dissociated anionic form, has chemical properties similar to other halides, I^- and Cl^-
- This appears to present the potential problem

Competitive

- Halides share transport channels
  - Halide pool in the body – body processes do not discriminate between Br^-, I^-, Cl^-
- Site of interaction: Thyroid
  - T_4 production
  - Deiodination: $T_4 \leftrightarrow T_3$
- Hypothesis: Disruption of TH synthesis
  - Disruption of negative feedback loop by Br^-
  - ↓ T_4 production; ↓T_4 pool available → low T_3
  - Hypothyroidism → Compensation mechanisms → Thyroid gland hypertrophy (goiter)

Br^- dynamics in biological systems

- Br^- moves freely in body water spaces
  - ^{82}Br for body water compartments: ECF + ICF (Yartsev, 2015)
  - ^{36}Cl + ^{82}Br distributed in approximately same volume (Mørkeberg et al., 1991)
- Hypothyroidism + secondary I^- deficiency (Loeber et al., 1983)
- Hypothyroidism response brought on by Br^- manifests as decreased serum T_4 (Loeber et al., 1983; Pavelka et al., 2002)

Br^- half-life

- ~14 days in sheep (administered p.o.) (Quast et al., 2015)
- ~12 days in humans (Olszowy et al., 1998)

- Whole-body Br^- depends on:
  - Intake
  - Normal dietary Cl^- levels
    - NaCl supplementation could alleviate Br^- effects
  - Physiological state of animal
    - Metabolic state - young growing; lactating; heat stress; hypothyroidism →female body condition → reproduction (Doufas & Mastorakos, 2000)
  - Target organ

Organ	Relative bromide proportion
Thyroid	1.000
Blood (ECF)	0.602
Kidney	0.536
Liver	0.394
Brain	0.131

(Jolles, 1966)

Our evidence of Br- risk

- NOAEL: WQG – 0.01 mg/L as NOAEL (Lucht et al., 2019)
- Differential development: Organs in chicken embryos (Lucht et al., 2019)
- Decreased survivability: Chicken embryos (Lucht et al., 2019)
- Weak chicks at hatch (Lucht et al., 2019 anecdotal evidence)
- Commercial broilers: Thyroid pathology (Meyer et al., 2005)
- Broiler performance: Poor growth and depressed feed intake (Du Toit & Casey, 2010; 2012)
- Organ accumulation: Br in liver and kidneys (Mamobolo et al., 2009)

Br risk cont.

- Excretion: Decreased excretion with increasing Br^- treatment – threshold value (Reijnders et al., in progress)
- Reproduction: Sows - poor reproduction; indications of neuropathology; in extreme cases death (Meyer, Lucht & Casey, water quality case study on commercial farm)
- Transplacental transfer probability is high because of Br^- permeability (Finken & Robertson, 1963; Pleasure & Blackburn, 1975)
  - Future research in livestock

Conclusion

- Shown that Br^{-1} can be a THDC
- Conditions:
  - Acute with high exposure
  - Chronic with low exposure rates can exceed the threshold value
    - EG Acute exposure to 0,01 and 0,05 mg/L in early chicken embryo development ->
      - Indications of hypertrophic heart and hypotrophic liver and brain.
  - NaCl (excretion) and I (assimilation) homeostasis electrolyte balance
  - Consequence of THDC is that TH homeostasis can be disrupted.

- Thank you for your attention