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Clinical research

Determination of Six Thyroid Hormones in the Brain and Thyroid Gland Using Isotope-Dilution Liquid Chromatography/Tandem Mass Spectrometry

Analytical Chemistry, **83**, 417-424 (2011)
Tatsuya Kunisue

Tags
SampliQ OPT, ZORBAX Eclipse XDB-C18, ZORBAX Eclipse XDB-C8, clinical research, disease research

Abstract
Thyroid hormones (THs) play critical roles in the regulation of growth and development, including brain development, in both humans and animals. Until recently, TH levels were assayed with measurements in serum, using immunoassay (IA)-based methods. IA methods are sensitive but are compromised by the lack of adequate specificity. Furthermore, measurements of TH levels in blood do not necessarily reflect the levels and profiles found in critical organs such as the brain. Measurement of TH levels in the brain is critical for studies that assess the effects of environmental contaminants on TH homeostasis. In this study, we developed a selective and sensitive method for the analysis of six THs, l-thyroxine (T4), 3,3′,5-triiodo-l-thyronine (T3), 3,3′,5′-triiodo-l-thyronine (rT3), 3,5-diiodo-l-thyronine (3,5-T2), 3,3′-diiodo-l-thyronine (3,3′-T2), and 3-iodo-l-thyronine (3-T1), in the brain and thyroid gland (TG) using isotope ([13C]T4)-dilution liquid chromatography (LC)/tandem mass spectrometry (MS/MS). Proteins in the (rat) brain and TG were digested by pronase, and THs were extracted with a solid-phase extraction method and analyzed by LC/MS/MS. The instrumental calibration range for each TH ranged from 0.5 to 200 ng/mL and showed excellent linearity ($r > 0.9995$). The instrumental detection limits for THs were in the range of 7.5–13.5 pg, in positive ion mode, and 13.5–16.5 pg, in negative ion mode. The optimized procedural recoveries for THs (except for 3-T1), spiked into a pig-brain matrix, were between 97.6% and 109%, with a coefficient of variation (CV) of 1.2–8.2%, for the brain, and between 96.4% and 101%, with a CV of 1.8–8.6%, for the TG. Concentrations of THs in the brain and TG of the five rats were 2.20–3.65 ng/g T4, 1.56–2.20 ng/g T3, and below the limit of detection (<LOD) for the other THs, in the brain, and 88.9–274 ng/mg T4, 14.1–49.1 ng/mg T3, 2.79–12.0 ng/mg rT3, 0.176–0.535 ng/mg 3,5-T2, 0.340–0.880 ng/mg 3,3′-T2, and <LOD for 3-T1, in the TG. This method can permit more comprehensive evaluation of TH homeostasis in the brain and other critical organs following exposure to environmental contaminants.

Modulation of septin and molecular motor recruitment in the microtubule environment of the Taxol-resistant human breast cancer cell line MDA-MB-231

Proteomics, **11**, 3877-3886 (2011)
Laurence Froidevaux-Klipfel *et al.*

Tags
ZORBAX 300SB-C18, ZORBAX Eclipse XDB-C8, 1200 Infinity Series, 6330 Ion Trap LC/MS, HPLC-Chip Cube MS Interface, clinical research, disease research

Abstract
Tryptic peptides were analyzed on an Agilent 1200 Infinity Series attached to an Agilent 6330 Ion Trap LC/MS with HPLC-Chip Cube MS Interface. Separation was accomplished using an Agilent ZORBAX 300SB-C18 column. Published by John Wiley & Sons Ltd.

Metabolites of Purine Nucleoside Phosphorylase (NP) in Serum Have the Potential to Delineate Pancreatic Adenocarcinoma

PLoS ONE, **6**, (2011)
Shaiju K. Vareed *et al.*

Tags
ZORBAX 300SB-C18, ZORBAX Eclipse XDB-C18, 1100 Series LC, HPLC-Chip Cube MS Interface, 6300 Series Ion Trap XCT Ultra, 6510 Q-TOF LC/MS, 6410 Triple Quadrupole MS, clinical research, disease research

Abstract
Pancreatic Adenocarcinoma (PDAC), the fourth highest cause of cancer related deaths in the United States, has the most aggressive presentation resulting in a very short median survival time for the affected patients. Early detection of PDAC is confounded by lack of specific markers that has motivated the use of high throughput molecular approaches to delineate potential biomarkers. To pursue identification of a distinct marker, this study profiled the secretory proteome in 16 PDAC, 2 carcinoma in situ (CIS) and 7 benign patients using label-free mass spectrometry coupled to 1D-SDS-PAGE and Strong Cation-Exchange Chromatography (SCX). A total of 431 proteins were detected of which 56 were found to be significantly elevated in PDAC. Included in this differential set were Parkinson disease autosomal recessive, early onset 7 (PARK 7) and Alpha Synuclein (aSyn), both of which are known to be pathognomonic to Parkinson's disease as well as metabolic enzymes like Purine Nucleoside Phosphorylase (NP) which has been exploited as therapeutic target in cancers. Tissue Microarray analysis confirmed higher expression of aSyn and NP in ductal epithelia of pancreatic tumors compared to benign ducts. Furthermore, extent of both aSyn and NP staining positively correlated with tumor stage and perineural invasion while their intensity of staining correlated with the existence of metastatic lesions in the PDAC tissues. From the biomarker perspective, NP protein levels were higher in PDAC sera and furthermore serum levels of its downstream metabolites guanosine and adenosine were able to distinguish PDAC from benign in an unsupervised hierarchical classification model. Overall, this study for the first time describes elevated levels of aSyn in PDAC as well as highlights the potential of evaluating NP protein expression and levels of its downstream metabolites to develop a multiplex panel for non-invasive detection of PDAC.

Energy and chemicals

Analysis of Hydraulic Fracturing Flowback and Produced Waters Using Accurate Mass: Identification of Ethoxylated Surfactants

Analytical Chemistry, **86**, 9653–9661
E. Michael Thurman *et al.*

Tags
ZORBAX Eclipse XDB-C8, 1290 Infinity LC, 6540 Accurate-Mass Quadrupole Time-of-Flight LC/MS, MassHunter, energy and chemicals

Abstract
Two series of ethylene oxide (EO) surfactants, polyethylene glycols (PEGs from EO3 to EO33) and linear alkyl ethoxylates (LAEs C-9 to C-15 with EO3–EO28), were identified in hydraulic fracturing flowback and produced water using a new application of the Kendrick mass defect and liquid chromatography/quadrupole-time-of-flight mass spectrometry. The Kendrick mass defect differentiates the proton, ammonium, and sodium adducts in both singly and doubly charged forms. A structural model of adduct formation is presented, and binding constants are calculated, which is based on a spherical cagelike conformation, where the central cation (NH_4^+ or Na^+) is coordinated with ether oxygens. A major purpose of the study was the identification of the ethylene oxide (EO) surfactants and the construction of a database with accurate masses and retention times in order to unravel the mass spectral complexity of surfactant mixtures used in hydraulic fracturing fluids. For example, over 500 accurate mass assignments are made in a few seconds of computer time, which then is used as a fingerprint chromatogram of the water samples. This technique is applied to a series of flowback and produced water samples to illustrate the usefulness of ethoxylate "fingerprinting", in a first application to monitor water quality that results from fluids used in hydraulic fracturing.

Environmental

Determination of pesticides originating from golf courses by solid-phase extraction and liquid chromatography-tandem mass spectrometry

International Journal of Environmental Analytical Chemistry, **93**, 858-871 (2013)
Miho Shinomiya *et al.*

Tags
Bond Elut PPL, EnvirElut, ZORBAX Eclipse XDB-C18, environmental, water analysis

Abstract
A multi-residue method using liquid chromatography coupled to triple quadrupole tandem mass spectrometry (LC-MS/MS), associated with solid-phase extraction (SPE), was developed for the determination of 21 pesticides in water samples. The compounds investigated are used for the maintenance of golf courses and ordinarily measured by gas chromatography-mass spectrometry (GC-MS). Electrospray ionisation (ESI) was applied to all compounds, and LC and MS conditions were optimised to measure them under SRM mode. This method showed excellent linearity ranges for all pesticides, with correlation coefficients greater than 0.996. Two kinds of extraction cartridges, namely, styrene divinylbenzene polymer (Sep-Pak PS-2) and divinylbenzene-N-vinylpyrrolidone copolymer (Oasis HLB), were tested and the extraction conditions were optimised. All the pesticides were determined using acetonitrile and ethyl acetate as eluents in both cartridges, and good recoveries (>77%) and repeatability with low relative standard deviations (RSDs, <12%) were achieved from ultra-pure water. In addition, satisfactory recoveries (>76%) and low intra-day and inter-day RSDs (<15%) of all pesticides were also obtained with the Sep-Pak PS-2 cartridge when using river water. The method limits of detection (LODs) ranged between 0.068 (diazinon) and 3.9 (triclopyrbutoxyethyl) ng L^{-1}. The analytical method was successfully applied for the determination of pesticides in surface river water.

Determination of Priority Polybrominated Diphenyl Ethers by Isotope Dilution Gas Chromatography(Electron Ionization)MS Using 81Br-Labeled Standards

Analytical Chemistry, **83**, 3024-3032 (2011)
Adriana González-Gago *et al.*

Tags
DB-5ms Ultra Inert, ZORBAX Eclipse XDB-C18, 6890 GC, 1100 LC, environmental, soil, sludges and sediments

Abstract
A mixture of 81Br-labeled polybrominated diphenyl ethers (PBDEs), previously synthesized in our laboratory, was separated by liquid chromatography for the individual isolation of different 81Br-labeled PBDEs containing from 3 to 6 bromine atoms. The different fractions were collected, and a mixed labeled standard was then prepared adequate for the determination of priority PBDEs (congeners 28, 47, 99, 100, 153, and 154) in environmental samples. The spike mixture was then characterized using gas chromatography(electron ionization)MS (GC(EI)MS) both in isotope composition and concentration in combination with multiple least-squares. Contamination from natural abundance BDEs 153 and 154 was detected in the spike mixture, and a new isotope dilution equation was developed to take into account the natural abundance contribution from the spike. The spike mixture was shown to be stable during at least 4 months, and no isotope exchange between natural abundance and labeled PBDEs was detected during this period of time. Finally, the 81Br-labeled PBDEs standard was used for the determination of congeners 28 (+33), 47, 49, 99, 100, 153, and 154 in a standard reference material (Lake Michigan fish tissue SRM 1947) using three different sample to spike ratios. No methodological calibration needed to be prepared, as no isotopic effects were detected using this labeling mode. Concentrations found were in agreement with the certified concentrations (recoveries between 89% and 116%), and reproducibility was always below 7% RSD. Kragten procedure was used to calculate expanded uncertainties. Very low limits of detection were obtained for all compounds (between 0.02 and 0.9 ng·g−1) using the procedure developed here. Reprinted with permission from Analytical Chemistry.

Food testing and agriculture

HT-2 Toxin 4-Glucuronide as New T-2 Toxin Metabolite: Enzymatic Synthesis, Analysis, and Species Specific Formation of T-2 and HT-2 Toxin Glucuronides by Rat, Mouse, Pig, and Human Liver Microsomes

Journal of Agricultural and Food Chemistry, **60**, 10170-10178 (2012)
Tanja Welsch, Hans-Ulrich Humpf

Tags
Bond Elut Plexa, ZORBAX Eclipse XDB-C18, food testing and agriculture, mycotoxins and biotoxins

Abstract
Glucuronides of the mycotoxin T-2 toxin and its phase I metabolite HT-2 toxin are important phase II metabolites under in vivo and in vitro conditions. Since standard substances are essential for the direct quantitation of these glucuronides, a method for the enzymatic synthesis of T-2 and HT-2 toxin glucuronides employing liver microsomes was optimized. Structure elucidation by nuclear magnetic resonance spectroscopy (NMR) and mass spectrometry revealed that besides T-2 toxin glucuronide and HT-2 toxin 3-glucuronide also the newly identified isomer HT-2 toxin 4-glucuronide was formed. Glucuronidation of T-2 and HT-2 toxin in liver microsomes of rat, mouse, pig, and human was compared and metabolites were analyzed directly by liquid chromatography coupled with tandem mass spectrometry (LC–MS/MS). A distinct, species specific pattern of glucuronidation of T-2 and HT-2 toxin was observed with interesting interindividual differences. Until recently, glucuronides have frequently been analyzed indirectly by quantitation of the aglycone after enzymatic cleavage of the glucuronides by β-glucuronidase. Therefore, the hydrolysis efficiencies of T-2 and HT-2 toxin glucuronides using β-glucuronidases from Helix pomatia, bovine liver, and *Escherichia coli* were compared. Reprinted with permission from the Journal of Agricultural and Food Chemistry

Monitoring and risk assessment of pesticide residues in yuza fruits (*Citrus junos* Sieb. ex Tanaka) and yuza tea samples produced in Korea

Food Chemistry, **135**, 2930-2933 (2012)
Kwang-Geun Lee, Suk-Kyung Lee

Tags
DB-5, DB-5ms, ZORBAX Eclipse XDB, 6890N GC, 7683 Autosampler, food testing and agriculture, pesticides

Abstract
An optimized method was developed for the analysis of seven pesticides in yuza and yuza tea using Agilent J&W GC columns and an Agilent ZORBAX Eclipse XDB LC column. Published by Elsevier B. V.

Key meat flavour compounds formation mechanism in a glutathione–xylose Maillard reaction

Food Chemistry, **131**, 280-285 (2012)
Ran Wang, Chao Yang, Huanlu Song

Tags
DB-5ms Ultra Inert, ZORBAX SB-C18, ZORBAX Eclipse XDB-C18, 7890A GC, 7000B Triple Quadrupole MS, 6210 TOF-MS, 1200 Infinity Series, food testing and agriculture, food authenticity, fish and meat

Abstract
Meat flavor volatiles were assessed using an Agilent J&W DB-5ms UI GC column fitted to an Agilent 7890A/7000B Triple Quadrupole GC/MS. Non-volatile components were measured using Agilent 6210 TOF-MS and Agilent 1200 Series HPLC, with an Agilent ZORBAX Eclipse XDB-C18 LC column. DKP was quantified with a ZORBAX SB-C18 LC column. Published by Elsevier B.V.

Analytical strategies to determine antibiotic residues in fish

Journal of Separation Science, **30**, 2549-2569 (2007)
Victoria F. Samanidou, Evaggelia N. Evaggelopoulou

Tags
Bond Elut ENV, Bond Elut C18, ZORBAX Eclipse XDB-Phenyl, food testing and agriculture, pesticides

Abstract
This article is an extended and comprehensive review of recent analytical methods for antibiotic residues in fish, mentioning Agilent Bond Elut ENV and Bond Elut C18 cartridges for cleanup, with ZORBAX Eclipse XDB-Phenyl columns for HPLC analysis. Published by John Wiley and Sons.

Direct Chiral Determination of Acephate and Its Metabolite Methamidophos in Vegetables Using QuEChERS by Gas Chromatography–Tandem Mass Spectrometry

Food Analysis Methods, **6**, 133-140 (2013)
Xiangyun Wang *et al.*

Tags
Bond Elut QuEChERS, SampliQ, ZORBAX Eclipse XDB, 1200 Infinity Series, 6460 Triple Quadrupole LC/MS, food testing and agriculture, pesticides

Abstract
In an investigation of acephate enantiomers and its metabolite methamidophos, Agilent Bond Elut QuEChERS was used for extraction, followed by LC/MS using an Agilent ZORBAX Eclipse XDB LC column fitted to an Agent 1200 Infinity with 6460 Triple Quadrupole MS. Published by Springer.

Identification of Anthocyanins in the Liver, Eye, and Brain of Blueberry-Fed Pigs

Journal of Agricultural and Food Chemistry, **56**, 705-712 (2008)
Wilhelmina Kalt *et al.*

Tags
Bond Elut NEXUS, ZORBAX Eclipse XDB-C18, ZORBAX SB-C18, 1100 Series LC, food testing and agriculture

Abstract
Dietary intervention with anthocyanins may confer benefits in brain function, including vision. Research to date indicates that animals have only a limited capacity to absorb anthocyanins, compared to other types of flavonoids. Pigs, which are a suitable model for human digestive absorption, were used to examine the deposition of anthocyanins in tissues including the liver, eye, and brain tissue. Pigs were fed diets supplemented with 0, 1, 2, or 4% w/w blueberries (*Vaccinium corymbosum* L. 'Jersey') for 4 weeks. Prior to euthanasia, pigs were fasted for 18–21 h. Although no anthocyanins were detected in the plasma or urine of the fasted animals, intact anthocyanins were detected in all tissues where they were sought. LC-MS/MS results are presented for the relative concentration of 11 intact anthocyanins in the liver, eye, cortex, and cerebellum. The results suggest that anthocyanins can accumulate in tissues, including tissues beyond the blood-brain barrier. Reprinted with permission from the Journal of Agricultural and Food Chemistry.

Direct Chiral Determination of Acephate and Its Metabolite Methamidophos in Vegetables Using QuEChERS by Gas Chromatography–Tandem Mass Spectrometry

Food Analytical Methods **6**, 133–140 (2013)
Xiangyun Wang *et al.*

Tags
Bond Elut QuEChERS dispersive kit, CP-Chirasil Dex CB, HP-Chiral B, ZORBAX Eclipse XDB, 1200 Infinity LC, food testing and agriculture, pesticides

Abstract
Methamidophos residues were analyzed using Agilent GC and LC columns or systems, with sample extraction provided by Agilent Bond Elut QuEChERS SPE. Published by Springer.

Forensics

Establishing a universal swabbing and clean-up protocol for the combined recovery of organic and inorganic explosive residues

Forensic Science International, **223**, 136-147 (2012)
Nopporn Song-im, Sarah Benson, Chris Lennard

Tags
Bond Elut ENV, Bond Elut NEXUS, ZORBAX Eclipse XDB-C18, 1100 Series LC, forensics and toxicology, criminalistics

Abstract
Pre-conditioned Agilent Bond Elut NEXUS was chosen as the preferred SPE technology in the development of a cleanup protocol for explosives. An Agilent ZORBAX Eclipse XDB-C18 LC column was used for the final analysis. Published by Elsevier B.V.

Synthesis, characterisation, and mass spectrometric detection of a pegylated EPO-mimetic peptide for sports drug testing purposes

Rapid Communications in Mass Spectrometry, **25**, 2115-2123 (2011)
Ines Möller *et al.*

Tags
ZORBAX 300SB-C18, ZORBAX Eclipse XDB-C8, 1100 Series LC, forensics and toxicology, doping control

Abstract
Peptide dimer was purified by HPLC on an Agilent 1100 Series LC equipped with an Agilent ZORBAX Eclipse XDB-C8 column. LC/MS/MS was achieved on the same LC fitted with an Agilent ZORBAX 300SB-C18 column. Published by John Wiley & Sons Ltd.

Small molecule pharmaceuticals

NMR Spectroscopic Studies on the *in Vitro* Acyl Glucuronide Migration Kinetics of Ibuprofen ((±)-(R,S)-2-(4-Isobutylphenyl) Propanoic Acid), Its Metabolites, and Analogues

Analytical Chemistry, **79**, 8720-8727 (2007)
Caroline H. Johnson *et al.*

Tags
Bond Elut SPEC Disk SPE,
ZORBAX Eclipse XDB-C18, 1100 Series LC, small molecule pharmaceuticals

Abstract
Carboxylic acid-containing drugs are often metabolized to 1-β-O-acyl glucuronides (AGs). These can undergo an internal chemical rearrangement, and the resulting reactive positional isomers can bind to endogenous proteins, with clear potential for adverse effects. Additionally any 1-β-O-acyl-glucuronidated phase I metabolite of the drug can also show this propensity, and investigation of the adverse effect potential of a drug also needs to consider such metabolites. Here the transacylation of the common drug ibuprofen and two of its metabolites is investigated in vitro. 1-β-O-Acyl (S)-ibuprofen glucuronide was isolated from human urine and also synthesized by selective acylation. Urine was also used as a source of the (R)-ibuprofen, (S)-2-hydroxyibuprofen, and (S,S)-carboxyibuprofen AGs. The degradation rates (a combination of transacylation and hydrolysis) were measured using 1H NMR spectroscopy, and the measured decrease in the 1-β anomer over time was used to derive half-lives for the glucuronides. The biosynthetic and chemically synthesized (S)-ibuprofen AGs had half-lives of 3.68 and 3.76 h, respectively. (R)-Ibuprofen AG had a half-life of 1.79 h, a value approximately half that of the (S)-diastereoisomer, consistent with results from other 2-aryl propionic acid drug AGs. The 2-hydroxyibuprofen and carboxyibuprofen AGs gave half-lives of 5.03 and 4.80 h, considerably longer than that of either of the parent drug glucuronides. In addition, two (S)-ibuprofen glucuronides were synthesized with the glucuronide carboxyl function esterified with either ethyl or allyl groups. The (S)-ibuprofen AG ethyl ester and (S)-ibuprofen AG allyl esters were determined to have half-lives of 7.24 and 9.35 h, respectively. In order to construct useful structure–reactivity relationships, it is necessary to evaluate transacylation and hydrolysis separately, and here it is shown that the (R)- and (S)-ibuprofen AGs have different transacylation properties. The implications of these findings are discussed in terms of structure–activity relationships.

Amphotericin B/Sterol Co-loaded PEG-Phospholipid Micelles: Effects of Sterols on Aggregation State and Hemolytic Activity of Amphotericin B

Pharmaceutical Research, **29**, 1737-1744 (2011)
Thomas A. Diezi, Glen Kwon

Tags
ZORBAX 300SB-C18, ZORBAX Eclipse XDB-C8, small molecule pharmaceuticals, drug development

Abstract
Amphotericin B/sterol was detected on an Agilent ZORBAX Eclipse XDB-C8 LC column, while a ZORBAX 300SB-C18 column was used for quantification. Published by Springer.

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