Government of South Australia
SA Health

Central Adelaide Local Health Network Inc

Research Secretariat
Level 3 IMVS Building
North Terrace Campus
Adelaide SA 5000

Postal Address
PO Box 14
Rundle Mall SA 5000
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ResearchSecretariat@health.sa.gov.au

Ref: 1475

22 November 2012

Prof Karen L Jones
Discipline of Medicine
Centre of Clinical Research Excellence, Nutritional Physiology, Interventions and Outcomes
University of Adelaide
Royal Adelaide Hospital
Frome Road
Adelaide SA 5000

RE: RAH RESEARCH FOUNDATION 2013 PROJECT GRANTS

Congratulations on being awarded a 2013 RAH Research Fund Project Grant. Please read the attached terms and conditions carefully.

Please sign the attached document where indicated, advising your acceptance of these terms and return it to our office by **Mon 10 December 2012.**

Please note that funds will not be released until this office has received all required documentation including copies of any ethics approvals. Any research involving humans may now require a Site Specific Assessment, please refer to http://www.rah.sa.gov.au/rg/research-governance.php for further details.

Congratulations again on receiving this award.

Yours sincerely

Roy Sneddon
Grant Manager, Research Secretariat

Government of South Australia
SA Health

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Tel 08 8222 5650
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2013 Project Grant Terms and Conditions

Chief Investigator: Karen Jones

Funding: $49,989 (SPF)

Term: 1 year

Project: #1475 Postprandial hypotension in Parkinson's Disease – impact of gastric emptying and splanchnic blood flow

Conditions:

1. Grants are awarded for one year only. Funds must only be expended on direct research costs relating to this project as outlined in your original application. Any unexpected funds will be automatically reclaimed at the beginning of the following years unless prior written approval has been granted from the Research Committee.
2. Where appropriate, human and animal ethical clearance is required before commencement of the project. Human research may also require a site specific assessment.
3. Funds will be reimbursed in arrears, subject to the receipt of an approved tax invoice and/or reimbursement claim in accordance with SA Health procedures.
4. Recipients will be required to provide a written report detailing achievements of the research, publications resulting from the research conducted and whether any subsequent funding was achieved as a result of this award (within six months of the end of the funding period)
5. It is expected that the project will commence as soon as possible to 01 January 2013 and no later that 31 March 2013. Committee approval is required for projects to commence after 31 March 2013
6. The research is to be undertaken within departments and units of the Royal Adelaide Hospital, SA Pathology, the Hanson Institute, or affiliated University Departments operating on the Royal Adelaide Hospital Campus, and the researcher agrees to abide by all policies and procedures, confidentiality, OHS&W obligations of theses institutions as well as the Australian Research Code of Conduct.

This grant funding is accepted in accordance with the terms and conditions listed above

Chief Investigator: Signed: X _____ Date: 5 / 12 / 2012

Name: PROF KAREN JONES

Authorised Delegate: Signed: _____ Date: / /

Name: Simon Brennan, Director Research Branch

Organisation: University of Adelaide

RESEARCH GRANT ACCEPTANCE FORM

THE UNIVERSITY of ADELAIDE

RESEARCH BRANCH

This Grant Acceptance Form must be fully-completed and signed by the **first-named University of Adelaide investigator** and the **Head of School** (or delegate) and returned to the Research Branch as a pre-condition to establishing a project code. If you are using this form electronically use the tabs to guide you to each new field and use your space bar to X the boxes.

OFFICE USE ONLY	RM No.:		Funding Category:		UA Finance completed:	
	RMO:		Country of Grant Origin:		RB Data entry completed:	
	RB Portfolio:		Grant Transfer from:		Cat1 Fellow table updated:	

1A 1ST-NAMED CHIEF INVESTIGATOR

Family Name:	Given Name/s:	Title:
Jones	Karen	Prof
School:	**Faculty/Division:**	**Lead Organisation**
Medicine	Medicine	
Telephone Contact Number:	**Email Address:**	
82225394	Karen.jones@adelaide.edu.au	

All Other Named Investigators *(please include Title, Initials, Surname and Organisation: e.g. Prof AB Smith (UA), Ms CD Jones (CSIRO) & Dr EF Chan (Cambridge Uni)*

Dr Thomas Kimber (Royal Adelaide Hospital)

1B RESEARCH GRANT DETAILS

Project Title:	Total $ Funded
Postprandial hypotension in Parkinson's Disease – impact of gastric emptying and splanchnic blood flow	$49,989

Name of Funding Sponsor:	Name of Funding Scheme:		
RAH Research Foundation	RAH Research Foundation 2013 Project Grants		
Project ID:	**Date of Offer:**	**Commencement Date:**	**Completion Date:**
1475	22 November 2012	2 January 2013	2 January 2014

1C UNIVERSITY HONORARY TITLE HOLDERS ONLY

If the 1st-named Chief Investigator is an Honorary Title Holder of the University of Adelaide please complete all of the questions in this sub-Section below

- Which organisation is the 1st-named Chief Investigator employed by? Where is the research being conducted?
- Is the funding to be administered entirely by the Honorary Title Holder's organisation? ☐ **Yes** ☐ **No***

**If NO, please indicate below the UA School the project should be allocated to: (If funding is to be split between Schools, this should be negotiated at School level)*

University of Adelaide School to administer funding:

2 RESEARCH CLASSIFICATIONS DATA

You must nominate up to three (3) FOR and SEO Codes for your project, indicating their relative importance by providing percentages adding up to 100%. The list of FOR and SEO codes is available from http://www.adelaide.edu.au/rb/resources/codes.html The types of ABS R&D Activity must also be indicated as percentages adding up to 100%.

% of ABS R&D Activity:	MUST TOTAL 100% ↓	Field of Research (FOR) Six-Digit Codes	%	Socio-Economic Objective (SEO) Six-Digit Codes	%
Pure Basic Research					
Strategic Basic Research					
Applied Research	100	110399	100	920111	100
Experimental Development		MUST TOTAL 100% ↓		MUST TOTAL 100% ↓	

3 INTELLECTUAL PROPERTY DETAILS

Will a University Honorary Title Holder, that does not have employment elsewhere, be working on this project? ☐ **Yes*** ☒ **No**

**If YES a "Non-Salaried Project Participation Agreement" will need to be completed. Please contact the Research Branch to coordinate this agreement.*

Will an Honours/Higher Degree Research student be involved in this project? ☒ **Yes*** ☐ **No**

**If YES a "Student Project Participation Agreement" may need to be completed. Please contact the Adelaide Graduate Centre www.adelaide.edu.au/graduatecentre to coordinate this agreement.*

Is there the possibility that commercialisation issues may come out of this research? ☐ **Yes** ☒ **No**

Will this project involve the Intellectual Property or Intellectual input from non-University of Adelaide sources? ☐ **Yes** ☒ **No**

For Intellectual Property or confidential material enquiries please refer to the Adelaide Research and Innovation website at www.adelaide.edu.au/aripl/ and/or contact an ARI Commercial Development Manager on +61 8 8303 5020.

4 APPLICATION REFERENCE LIBRARY

We seek your approval to include your application in a reference library of successful applications to provide University staff with an opportunity to peruse successful application and strengthen the research base of the University.

☐ I give approval for my application to be used as a **reference** for University staff and allow applicants to have a **copy** of the application.

☒ I give approval for my application to be used as a **reference** for University staff, for **perusal only** (not to be copied).

☐ I do not wish to have my application used as a reference.

5 RESEARCH ETHICS, COMPLIANCE AND SAFETY APPROVAL REQUIREMENTS

PLEASE NOTE: Gaining research ethics, compliance and safety approvals is your responsibility. The project cannot commence until all required approvals and/or licences have been obtained.

- *For Research Ethics and Compliance Approval requirements please refer to* www.adelaide.edu.au/ethics
- *For Biohazard and Ionising Radiation safety / licensing requirements please refer to* www.adelaide.edu.au/hr/ohs

5A RESEARCH ETHICS AND COMPLIANCE APPROVALS

Please indicate whether this research project will involve the following research ethics or compliance issues:

- **Animal Research Ethics** ☐ Yes ☐ No
- **Human Research Ethics** ☒ Yes ☐ No
- **Gene Technology** ☐ Yes ☐ No
- **Quarantine** ☐ Yes ☐ No
- **Other** (please specify) _____

If "YES" to any of the above, please provide details of approvals below

Full Name of Approving Committee	Institution	Approval No.	Approval Date	Copy Attached?
Royal Adelaide Hospital Research Ethics Committee	Royal Adelaide Hospital	111223	13 January 2012	☒ Y ☐ N
				☐ Y ☐ N
				☐ Y ☐ N
				☐ Y ☐ N
				☐ Y ☐ N
				☐ Y ☐ N

5B BIOHAZARDS AND IONISING RADIATION REQUIREMENTS

Please indicate whether this research project will involve the use of biohazardous materials or ionising radiation

- **Biohazards**(including carcinogens or teratogens) ☐ Yes ☒ No
- **Ionising Radiation** ☒ Yes ☐ No

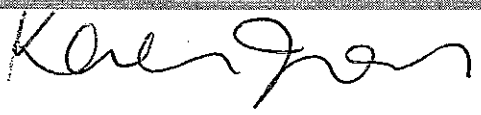
Please note the requirements of University Policies in relation to Chemical Safety Management (http://www.adelaide.edu.au/policies/1203/), Hazard Management (http://www.adelaide.edu.au/policies/2283/) & Radiation Safety (http://www.adelaide.edu.au/policies/619/) are included in the certifications below.

6 CERTIFICATIONS (NB these certifications arise from University and Funding Sponsor policies and requirements)

1st-NAMED CHIEF INVESTIGATOR CERTIFICATION

I hereby certify that on behalf of all named project investigators:

- I accept the award specified above including the terms and conditions of the Funding Agreement/s for the awarded project;
- I will ensure all necessary research ethics, compliance and safety approvals will be obtained before commencement of my project;
- I will ensure that if there is a non-salaried person working on this project or a Honours/Higher degree student involved in this project, they will complete a "Non-Salaried Project Participation Agreement" or "Student Project Participation Agreement" as appropriate;
- The conduct of the project will comply with all relevant University Policies and the *Australian Code for the Responsible Conduct of Research (see* www.adelaide.edu.au/rb/policies/resprac.html);
- To the best of my knowledge and belief, there are no actual or potential conflicts of interest in relation to the investigators and/or collaborating parties on this project;
- I will notify my Head of School and Research Branch if any material changes occur to the project; and
- In relation to a Category 1 Research Fellowship funded by this grant, I certify that the Fellow's level of appointment has been discussed with and agreed by the Head of School. Fellowship details are provided below:

Category 1 Fellow Name (if applicable):	**Yearly Sponsor Base Fellowship Salary + %on-costs**	**Agreed Level of Appointment** (e.g. B3)
	Base Salary $ p.a. + % on-costs	
NAME OF CHIEF INVESTIGATOR:	**SIGNED:**	**DATED:**
Professor Karen Jones		5 December 2012

HEAD OF SCHOOL CERTIFICATION (Honorary Title Holders should have Local Head of Division or Divisional Chief countersign)

I hereby certify that:

- I accept this grant on behalf of the School under the conditions specified in the application and Funding Agreement;
- The School will contribute the financial and in-kind resources to the project as detailed in the proposal, unless otherwise specified;
- The project is viable in terms of existing workloads, the School's/Division's resources and the funds awarded;
- The Chief Investigator will, prior to the commencement of the project, obtain the required research ethics, compliance and safety approvals for the project;
- The School will carry out all necessary risk assessments and have appropriate chemical registers, MSDS's and hazard management procedures in place; in relation to this project;
- The use of any ionising radiation will be carried out in a Radiation Registered Laboratory, by suitably licensed and registered personnel;
- The School will monitor adherence to University Policies and the *Australian Code for the Responsible Conduct of Research* in relation to this project; and
- The School will be responsible for managing any salary shortfalls that might occur in relation to staff to be employed from this grant, unless otherwise confirmed.

NAME OF HEAD OF SCHOOL:	**SIGNED:**	**DATED:**

Research Branch
Ph: +61 8 8303 5137
Fx: +61 8 8303 3700
rb@adelaide.edu.au
www.adelaide.edu.au/rb

ROYAL ADELAIDE HOSPITAL RESEARCH FOUNDATION

$50K CLINICAL PROJECT GRANT APPLICATION 2013

A. APPLICATION

1. Title of Proposal

Postprandial hypotension in Parkinson's Disease – impact of gastric emptying and splanchnic blood flow.

2. Applicant(s)

Prof Karen L Jones, DipAppSci(Nuc Med) PhD, NHMRC Senior CDA Research Fellow, Discipline of Medicine, Centre of Clinical Research Excellence, Nutritional Physiology, Interventions and Outcomes, University of Adelaide, Royal Adelaide Hospital, Frome Road, Adelaide, SA 5000, (08) 8222 5394, karen.jones@adelaide.edu.au.

Dr Thomas Kimber, MBBS (Hons), PhD, FRACP Neurologist and Director of Stroke Unit, Department of Neurology, Royal Adelaide Hospital; Ph: 8222 5298; email: Thomas.Kimber@health.sa.gov.au

Project details:

The project is to be conducted in the Department of Nuclear Medicine, Positron Emission Tomography and Bone Densitometry, Royal Adelaide Hospital and the Discipline of Medicine, Eleanor Harrald Building, Royal Adelaide Hospital.

Prof Jones will devote approximately 4 hours, and Dr Kimber approximately 3 hours, to the project per week.

3. Applications For Other Research Support Currently Pending

No funds are available to support the proposed study that represents a new collaboration between the two applicants. Prof Jones' research relating to postprandial hypotension has been supported by a NHMRC Project Grant ID: 627189 - Project title: *Gastric, small intestinal and cardiovascular mechanisms of postprandial hypotension.* Prof Jones returned to work in late February 2012 following maternity leave and, not surprisingly, it was not logistically feasible to formulate a further application to the NHMRC in 2012 for funding in 2013. – The proposed studies will strengthen an application to the NHMRC to be submitted in 2013 for funding to commence in 2014.

4. Current Research Support

Professor Karen Jones

2010 - 2012 **KL Jones**, Gentilcore D, Visvanathan R, Chapman I, Rayner C, Horowitz M - NHMRC - 627189 - Project title: *Gastric, small intestinal and cardiovascular mechanisms of postprandial hypotension* ($225,500 pa)

2010 - 2012 Rayner CK, Horowitz M, **KL Jones**, Feinle-Bisset C - NHMRC - 627139 - Project title: *Upper gastrointestinal function and glycaemic control in diabetes mellitus* ($251,167 pa)

2010 - 2013 **KL Jones** - NHMRC Senior Career Development Award (Level 2) - NHMRC - 627011 - Project title: *Gastric, small intestinal and cardiovascular mechanisms of postprandial hypotension in the elderly* ($104,250 pa)

2012 - 2017 M Horowitz, G Wittert, P Clifton, CK Rayner, IM Chapman, C Feinle-Bisset, **KL Jones**, M Noakes, M Chapman, N Nguyen. NHMRC – 1041687 – Title: *Centre of Research Excellence in Translating Science to Good Health* ($500,000 pa)

Dr Thomas Kimber has no current research support funding

5. Relationship Of This Application To Other Funding

As discussed under (3.) Prof Jones' research relating to postprandial hypotension is supported by a project grant provided by the NHMRC that terminates at the end of 2012. The proposed application will support ongoing work in this area and represents a novel initiative.

6. Ethical Clearances

The proposed study has recently been approved by the Research Ethics Committee of the Royal Adelaide Hospital (RAH protocol #111223).

7. Certification

This application has been certified by the Head of Department that appropriate general facilities will be available to the investigator if successful and that the project will be carried out strictly in accordance with NHMRC Ethical and Scientific Practice Guidelines.

Prof Gary Wittert ..../...../.....

Head Discipline of Medicine

8. Scientific Referees

Professor Geoffrey Hebbard
Director of Gastroenterology
Royal Melbourne Hospital
Phone (03) 93427470
Fax (03) 93427848
Email: Geoff.Hebbard@mh.org.au

Professor Chris Mathias
Imperial College, School of Medicine, St Mary's Pickering Unit
St Mary's Hospital, Praed St, London, W2 1NY, United Kingdom
Phone: +44 20 7886 1468
Fax: +44 20 7886 1540
Email: c.mathias@imperial.ac.uk

Professor Richard McCallum
Texas Tech University Health Sciences Center
Paul L. Foster School of Medicine
4800 Alberta Ave, Elpaso Texas, USA
Phone: +1 915-545-6626x265
Fax: + 1 915-545-6634
Email: Richard.mccallum@ttuhsc.edu

B. RESEARCH PROPOSAL

1. Budget

a. Equipment:

All of the required equipment is available	$0

b. Maintenance & Consumables:

- Radiopharmaceuticals (^{99m}Tc-sulphur colloid):	$1500
- Biochemical screen:	$375
- Blood glucose (368 samples @ $5/sample):	$1840
- Plasma 3-OMG analysis (368 samples @ $20/sample):	$7360
- Plasma noradrenaline (147 samples @ $27/sample):	$3969

c. Salaries

Research assistant (PSP 3, FTE:0.5) for 12 months:	$34,945
TOTAL	**$49,989**

2. Justification of budget

The sum requested represents the minimum required to pursue the proposed studies effectively. Routine biochemical screens and measurements of blood glucose will be performed by the IMVS at a reduced rate. Measurements of plasma 3-OMG (chromatography) and noradrenaline are, unfortunately, expensive, but essential and analysis will be performed at the University of South Australia (3-OMG) and Queensland Pathology (noradrenaline). The number of samples is calculated on the basis of the number of subjects that will be studied. The proposed studies are technically demanding, lasting ~5 hours. 1 – 2 studies will be performed a week. A PhD student, Mr Laurence Trahair, will be involved, but the involvement of another experienced research assistant is essential. The research assistant will also play a major role in recruitment and data analysis.

3. Aims

To evaluate the blood pressure, heart rate and superior mesenteric artery blood flow responses to both oral and intraduodenal glucose in patients with Parkinson's disease. The primary **hypotheses** underlying the study are that in patients with Parkinson's disease, unselected for PPH: (i) gastric emptying will be related to the fall in blood pressure after a 75g oral glucose load and (ii) the fall in blood pressure induced by intraduodenal glucose infusion at 2 kcal/min will be greater than after oral glucose, greater than in healthy subjects, and related to splanchnic (superior mesenteric artery) blood flow.

4. Statement on Ethical Considerations

All aspects of the study will be discussed with each subject during a phone interview or screening visit. An information sheet will be provided, and each subject will be given the opportunity to seek medical advice or to discuss the study with friends or family prior to involvement. Each volunteer will give written, informed consent, in accordance with the attached form, and the subjects will be free to withdraw from the study at any time. This study will be performed in accordance with the Declaration of Helsinki.

5. Background and Research Plan

Postprandial hypotension (PPH), leading to syncope and falls, is now recognised as an important clinical problem, particularly in the elderly and in patients with autonomic dysfunction [1]. Postprandial hypotension occurs in 30 - 40% of nursing home residents, and is distinct from, and may occur more frequently than, orthostatic hypotension, representing a significant cause of morbidity and mortality [1]. PPH occurs in ≥ 50% of patients with Parkinson's disease (PD) [2] and has been attributed to the high prevalence of autonomic impairment [3, 4] and hypertension [5] in this group. It has been suggested that PPH may account for the increase in symptoms experienced by some patients with PD following meals [6]. The mechanisms mediating PPH are poorly understood. Gastric distension [7, 8], small intestinal nutrient delivery [9, 10] and neural and hormonal mechanisms [11], which may all modulate splanchnic blood flow [1] may be important. Current management is suboptimal [1].

Our recent studies have established in healthy older subjects and in type 2 diabetes patients [9] that the magnitude of the fall in blood pressure (BP) induced by oral glucose is greater when gastric emptying (GE) is relatively more rapid. More rapid GE is also associated with a greater postprandial rise in blood glucose in this group [9] as a result of more rapid intestinal glucose absorption which can be measured using plasma concentrations of 3-OMG, a non-metabolized glucose analogue [12-14]. When glucose is infused intraduodenally in healthy 'older' subjects at 1, 2 and 3 kcal/min- rates which span the normal range of GE of glucose or saline, the 1 kcal/min load had no effect on BP or heart rate (HR), while the 2 and 3 kcal/min loads induced comparable, and substantial, falls in BP, although the increase in HR was greater with the 3 kcal/min infusion [16]. In contrast to the effect of small intestinal nutrients, gastric distension, possibly with volumes as low as 100mL, attenuates the fall in BP in response to both oral [8] and intraduodenal (ID) [17, 18] glucose. Gastrointestinal (GI) dysfunction and GI symptoms are common at all stages of PD [19], and there is a high prevalence of delayed GE [19] which may compromise the absorption of dopamine replacement therapy [20, 21]. Drugs such as *levodopa*, slow GE in both healthy subjects and PD, despite having a beneficial effect on symptoms in the latter group [22]. Somewhat surprisingly, only one study hitherto evaluated the impact of GE on postprandial BP in patients with Parkinson's disease and, given that the cohort studied comprised only 12 patients, it is not surprising that no relationship was evident [23]. Previous studies have also examined the BP response to oral, but not ID, nutrients [5, 6], compromising interpretation given the effect of gastric distension to attenuate the fall in BP [7, 8, 17]. Meal ingestion is associated with splanchnic blood pooling and a reduction in venous return to the heart [1]. In healthy young and older individuals, with intact baroreflex mechanisms, these changes induce a rise in HR, stroke volume and cardiac output, leading to a compensatory rise in BP [1]. However, in patients with PPH, this response is inadequate to maintain BP [1]. The increase in postprandial blood flow through the superior mesenteric artery (SMA) can be measured by duplex ultrasonography [24], and may correlate with changes in BP [25]. There is no information about SMA flow in patients with PD and how this may related to changes in postprandial BP.

Participants

25 subjects with Parkinson's disease will be studied; the effects of ID glucose will be evaluated in 12 of these. Subjects will be recruited from existing databases and by using advertisements placed in the Royal Adelaide Hospital. The Parkinson's Association of South Australia will be approached to assist in advertisement. The number of subjects to be studied is based on our previous studies [18, 25] to detect a significant difference in BP between study days; e.g. a minimum of 8 subjects would result in an 80% power ($\mu = 0.05$) to detect a significant difference in BP between the two study days.

Subject selection criteria

Inclusion criteria

Male or female subjects aged between 18 – 80 years with Body Mass Index (BMI) 19 - 30 kg/m². Subjects with a diagnosis of idiopathic Parkinson's disease according to the UK brain bank criteria of mild disease (Hoehn and Yahr Staging of 1 – 2.5). Subjects taking short-acting anti-Parkinsonian drugs who are able to withdraw from this medication overnight, and subjects who are taking long-acting anti-Parkinsonian drugs and are able to withdraw from this medication for 24 hours prior to the study.

Exclusion criteria

Subjects with a history of diabetes, severe respiratory, cardiovascular, GI (unrelated to PD) and/or renal disease, regular medication that may affect BP of GI function (apart from anti-Parkinsonian therapy) chronic alcohol abuse or epilepsy, smoking >10 cigarettes/day, alcohol consumption >20 g/day, pregnancy or breastfeeding or if iron status, or liver function tests are abnormal. Subjects requiring medication that may influence BP or gastrointestinal function, beyond the abovementioned anti-Parkinsonian therapy.

Withdrawal criteria

Subjects who experience severe symptoms, as a result of PPH e.g. fainting and falls

Study Plan and Design

Each subject will attend the Discipline of Medicine, Royal Adelaide Hospital at approximately 0830h on four occasions after an overnight fast. On the first occasion, subjects will have a blood sample (10mL) collected for the assessment of liver function, creatinine, fasting blood glucose and biochemistry and undergo physical examination by a Neurologist (TK). Pre menopausal women will undergo a pregnancy test. Subjects who meet the selection criteria will be included in the study and will be invited to attend for the remaining study days.

(1) Effects of oral glucose

On the second occasion, 25 subjects will undergo concurrent measurements of GE by scintigraphy [9, 26], BP, HR and SMA blood flow by Doppler ultrasound [17, 18, 25], blood glucose [9, 17, 18, 25-31], plasma 3-OMG and catecholamines [25]. On arrival, an intravenous cannula will be inserted into an antecubital vein for blood sampling [9, 17, 18, 25-27] and subjects will be walked to the Department of Nuclear Medicine, Positron Emission Tomography and Bone Densitometry, Royal Adelaide Hospital. The subject will be seated with their back against a gamma camera [9, 26] with an automated blood pressure cuff placed around the opposite arm for measurement of BP (systolic, diastolic and mean arterial pressure) and heart rate [9, 17, 18, 25-27]. Subjects will also be attached to a Finometer Pro (Finapress Medical Systems, Amsterdam, The Netherlands) on one finger of one hand to allow continuous measurement of cardiac output, stroke volume, vascular resistance and baroreflex sensitivity. The subject will then be given a drink (t = 0 minutes) comprising 75g glucose and 5g 3-OMG labelled with 20 MBq 99mTc-sulphur colloid, made up to 300ml water [9, 26]. GE, blood glucose, BP, HR and cardiac parameters will be monitored for 180 minutes after ingestion of the drink. On study days, BP and HR will be measured (DINAMAP ProCare 100, GE Medical Systems, Milwaukee, WI, USA) at 3 minute intervals for 9 minutes (i.e. t = -9, -6 and -3 minutes) prior to the ingestion of the drink and the average of these measurements will be taken to represent 'baseline', and then again at 3 minutes from t = 0 - 180 minutes [9, 17, 18, 25-27]. Measurements of cardiac parameters with the Finometer Pro will occur continuously from t = -9 minutes through to t = 180 minutes. Blood samples (19 ml) will be obtained prior to the ingestion of the drink and then at t = 15, 30, 45, 60, 90, 120 and 180 minutes for measurement of blood glucose [9, 17, 18, 25-27], plasma 3-OMG and noradrenaline [25]. Samples will be stored at -70°C until analysed. Blood glucose concentrations will also be immediately determined using a portable blood glucose meter (MediSense Companion 2 Meter; MediSense Inc., Waltham, MA) [9, 17, 18, 25-27]. SMA blood flow will be assessed using a Logiq™ 9 ultrasound system (GE Medical Systems. SMA blood flow will be measured immediately prior to the ingestion of the drink (t = -3 minutes) and then at t = 15, 30, 45, 60, 90, 120 and 180 minutes [17, 18, 25]. Sensations relating to appetite, PPH, PD and other GI symptoms will be evaluated using a visual analogue scale immediately prior to the ingestion of the drink (t = -3 minutes) and then at t = 15, 30, 45, 60, 90, 120 and 180 minutes [9, 17, 26]. GE curves (expressed as % of the maximum content of the total stomach) will be derived and the content of the total stomach at t = 0 and every 15 minutes until t = 180 minutes will be calculated [9, 26]. The 50% emptying time (T50) will also be obtained [9, 26]. At t = 180 minutes, subjects will be offered a light lunch and a final blood glucose measurement will be taken and the intravenous cannulae will then be removed and the subject's BP monitored until it has returned to

baseline levels. Prior to the subject's departure from the laboratory, autonomic nerve function will be assessed using standardised cardiovascular reflex tests [9, 17, 18, 25-27]. Parasympathetic function will be calculated by the variation (R - R interval) of the HR during deep breathing and the immediate HR response to standing ("30:15" ratio). Sympathetic function will be assessed by the fall in systolic BP in response to standing.

(2) Effects of intraduodenal glucose

In 12 of the 25 subjects (selected at random) on the remaining two occasions, subjects will undergo concurrent measurements of BP, HR [9, 17, 18, 25-27] and SMA blood flow by Doppler ultrasound [17, 18, 25], blood glucose [9, 17, 18, 25-27], plasma 3-OMG and noradrenaline [25] during intraduodenal infusion, under randomised, double-blind fashion. On each study day, subjects will attend the Discipline of Medicine, Royal Adelaide Hospital at approximately 0830h. On arrival, a silicone rubber ID catheter (~ 4mm in diameter) incorporating a duodenal infusion port will be introduced into the stomach via an anaesthetised nostril [10, 17, 25, 27]. With the subject supine, the tip of the tube will be allowed to pass into the duodenum by peristalsis. A subcutaneous saline-filled reference electrode (20-guage intravenous cannula) will be inserted into the left forearm to measure antroduodenal transmucosal potential difference (TMPD) across the stomach and duodenum, so that the position of the tube can be monitored continuously [10, 17, 25, 27]. An intravenous cannula will then be inserted into an antecubital vein for blood sampling [9, 17, 18, 25-27] and an automated BP cuff placed around the opposite arm for measurement of BP (systolic, diastolic and mean arterial pressure) and heart rate [9, 17, 18, 25-27]. Subjects will also be attached to a Finometer Pro (Finapress Medical Systems, Amsterdam, The Netherlands) on one finger of one hand to allow continuous measurement of cardiac output, stroke volume, vascular resistance and baroreflex sensitivity. When the catheter has been positioned correctly, each subject will be given an infusion intraduodenally of either (0.9%) saline or glucose at a load of 2 kcal/min with 5g 3-OMG for 60 minutes (t = 0 – 60 minutes) followed immediately by an infusion of (0.9%) saline for a further 60 minutes (t = 60 – 120 minutes) [10, 25]. On each of the study days, BP and HR will be measured (DINAMAP ProCare 100, GE Medical Systems, Milwaukee, WI, USA) at 3 minute intervals for 9 minutes (i.e. t = -9, -6 and -3 minutes) prior to the commencement of the ID infusion and the average of these measurements will be taken to represent 'baseline', and then again at 3 minute from t = 0 - 120 minutes [9, 17, 18, 25-27]. Measurements of cardiac parameters with the Finometer Pro will occur continuously from t = -9 minutes through to t = 120 minutes. Blood samples (19 ml) will be obtained prior to the commencement of the ID infusion and then again at t = 15, 30, 45, 60, 90 and 120 minutes for measurement of blood glucose [9, 17, 18, 25-27], plasma 3-OMG and noradrenaline [25]. Samples will be stored at -70°C until analysed. Blood glucose concentrations will also be immediately determined using a portable blood glucose meter (MediSense Companion 2 Meter; MediSense Inc., Waltham, MA). SMA blood flow will be assessed using a Logiq™9 ultrasound system (GE Medical Systems). SMA blood flow will be measured immediately prior to the commencement of the ID infusion (t = -3 minutes) and then at t = 15, 30, 45, 60, 90 and 120 minutes [17, 18, 25]. Sensations relating to appetite, PPH, PD and other GI symptoms will be evaluated using a visual analogue scale immediately prior to the commencement of the ID infusion (t = -3 minutes) and then at t = 15, 30, 45, 60, 90 and 120 minutes [9, 17, 26]. At t = 120 minutes, the silicone-rubber catheter will be removed and subjects will be offered a light lunch. A final blood glucose measurement will be taken and the intravenous cannula will then be removed and the subject's BP monitored until it has returned to baseline levels prior to the subject's departure.

Statistical analysis

Data will be analysed using standardised, non-parametric statistical methods (e.g. using repeated measures ANOVA). Relationships between variables will be assessed by linear regression analysis. The data will be prepared for publication in a peer-reviewed journal.

Future plans

The outcome of this study will strengthen a planned application for an NHMRC project grant to be submitted in 2013.

6. References

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27. Gentilcore, D, et al. *Effects of intraduodenal glucose concentration on blood pressure and heart rate in healthy older subjects.* Dig Dis Sci 2006;51:652-6.

C. PREVIOUS RESEARCH ACTIVITY AND ACHIEVEMENTS

1. Curriculum Vitae of Co-ordinating Chief Investigator

(attached)

2. Previous research support (last 5 years – 2008-2012)

Professor Karen Jones

2003 - 2008 **KL Jones** - NHMRC/Diabetes Australia Career Development Award - 250453 - Project title: *Gastroduodenal motility and glycaemic control in diabetes mellitus* ($417,500)

2007 - 2009 **KL Jones**, M Horowitz, IM Chapman, C Feinle-Bisset, CK Rayner - NHMRC - 453650 - Project title: *Pathophysiology of postprandial hypotension in the elderly - role of "gastric" and "small intestinal" mechanisms* ($450,813)

2007 - 2009 M Horowitz, **KL Jones**, CK Rayner, C Feinle-Bisset, AJPM Smout, M Samsom - NHMRC - 453647 - Project title: *Upper gastrointestinal motility and glycaemic control in diabetes mellitus* ($522,000)

2008 M Horowitz, **KL Jones**, D Gentilcore, C Rayner, C Feinle-Bisset - Rebecca Cooper Medical Research Foundation - Project title: *Measurement of autonomic nerve function in patients with or without postprandial hypotension* ($20,000)

***2008** D Gentilcore, **KL Jones**, M Horowitz, C Rayner - Royal Adelaide Hospital Project Grant - Project title: *Effects of the oligosaccharide, alpha - cyclodextrin, on postprandial blood pressure in healthy older subjects – relationships to gastric emptying, glycaemia and superior mesenteric blood flow* ($15,000)

***2008** C Feinle-Bisset, **KL Jones**, M Horowitz - Royal Adelaide Hospital Project Grant - Project title: *Characterisation of day-to-day variations in energy intake in healthy men and women, and the effect of the menstrual cycle in women - relationships with gastric emptying, intragastric meal distribution and gastrointestinal and reproductive hormones* ($15,000)

2008 CK Rayner, R Fraser, M Horowitz, G Wittert, C Feinle-Bisset, **KL Jones,** P Clifton - University of Adelaide, Faculty of Health Science - Project title: *Equipment for concurrent impedence, manometry and barostat recordings in nutritional physiology studies* ($10,000)

2008 CK Rayner, R Fraser, M Horowitz, G Wittert, C Feinle-Bisset, **KL Jones,** P Clifton, - NHMRC - 520946 - Project title: *Equipment for concurrent impedence, manometry and barostat recrdings in nutritional physiology studies* ($42,000)

2009 M Horowitz, C Rayner, P Clifton, **KL Jones**, C Feinle-Bisset, G Wittert - Rebecca Cooper Medical Research Foundation - Project title: *Measurement of endothelial function and arterial stiffness in diabetes* ($20,000)

2009 M Horowitz, R Fraser, **KL Jones**, C Rayner - Vera Ramaciotti Research Foundation - Project title: *Equipment grant for a Portable Scintillation Camera (Digirad 2020tc)* ($30,000)

2010 **KL Jones**, Horowitz M, Chapman IM, Feinle-Bisset C, Rayner CK, Clifton PM, Sanders P, Wittert G, Fraser R, Atlantis E - NHMRC Equipment Grant - 640305 - Project title: *Measurement of autonomic nerve function in patients with diabetes, obesity, the elderly, atrial fibrillation and the critically ill* ($34,000)

2010 **KL Jones**, Horowitz M, Chapman IM, Feinle-Bisset C, Rayner CK, Clifton PM, Sanders P, Wittert G, Fraser R, Atlantis E - University of Adelaide, Faculty of Health

Science - Project title: *Measurement of autonomic nerve function in patients with diabetes, obesity, the elderly, atrial fibrillation and the critically ill* ($6,000)

2010 M Horowitz, **KL Jones**, CK Rayner - Rebecca L Cooper Medical Research Foundation - Project title: *Measurement of blood pressure in patients with diabetes with or without postprandial hypotension* - ($20,000)

2007 - 2011 M Horowitz, PM Clifton, GA Wittert, IM Chapman, Fraser RJ, CK Rayner, C Feinle-Bisset, **KL Jones** - NHMRC - 453557 - Project title: *CCRE in Nutritional Physiology, Interventions and Outcomes* ($2,000,000)

2009 - 2011 C Feinle-Bisset, M Horowitz, PM Clifton, **KL Jones**, CK Rayner - NHMRC - 565311 - Project title: *Effects of the fatty acid, lauric acid, on energy intake, and gut motor and hormonal function in health and obesity* ($714,000)

2009 - 2011 C Feinle-Bisset, PM Clifton, M Horowitz, **KL Jones**, GA Wittert - NHMRC - 565312 - Project title: *Modifications in energy intake and gastrointestinal regulation of appetite - implications for weight loss in obesity* ($714,000)

2011 M Horowitz, **KL Jones**, D Gentilcore, CK Rayner - Rebecca L Cooper Medical Research Foundation - Project title: *Measurement of superior mesenteric artery (SMA) blood flow in patients with diabetes with and without postprandial hypotension* - ($22,000)

***2011** **KL Jones**, D Gentilcore, R Visvanathan, IM Chapman, CK Rayner, A Deane, M Horowitz – Hanson Institute, Royal Adelaide Hospital Equipment Grant - Project title: *Assessment of splanchnic blood flow in humans* - ($65,000)

Dr Thomas Kimber

Nil over the past 5 years.

3. Publication History

Professor Karen Jones

1. Gentilcore D, Bryant B, Wishart JM, Morris HA, Horowitz M, **Jones KL**. Acarbose attenuates the hypotensive response to sucrose and slows gastric emptying in the elderly. Am J Med 2005;118:1289.e5-1289.e11.
2. Gentilcore D, Doran S, Meyer JH, Horowitz M, **Jones KL**. Effects of intraduodenal glucose concentration on blood pressure and heart rate in healthy older subjects. Dig Dis Sci 2006;51:652-656.
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5. Vanis L, Gentilcore D, Hausken T, Pilichiewicz, Lange K, Rayner CK, Feinle-Bisset C, Meyer JH, Horowitz M, **Jones KL**. Effects of gastric distension on blood pressure and superior mesenteric artery blood flow responses to intraduodenal glucose in healthy older subjects. Am J Physiol Regul Integr Comp Physiol 2010;299:R960-7.
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7. Trahair LG, Vanis L, Gentilcore D, Lange K, Rayner CK, Horowitz M, **Jones KL**. Effects of variations in duodenal glucose load on blood pressure, heart rate, superior mesenteric artery blood flow and plasma noradrenaline in healthy young and older subjects. Clin Sci (Lond). 2012;122:271-9.

8. Vanis L, Gentilcore D, Lange K, Gilja OH, Rigda RS, Trahair LG, Rayner CK, Horowitz M, **Jones KL**. Effects of variations in intragastric volume on blood pressure and splanchnic blood flow during intraduodenal glucose infusion in healthy older subjects. Am J Physiol Regul Integr Comp Physiol 2012;302:R391-9.

Dr Thomas Kimber

1. Kleinig TJ. **Kimber TE**. Thompson PD. Stroke prevention and stroke thrombolysis: quantifying the potential benefits of best practice therapies. *Medical Journal of Australia* 2009;190(12):678-82.

2. Kleinig TJ, **Kimber TE**, Thompson PD. Convexity subarachnoid haemorrhage associated with bilateral internal carotid artery stenoses. *J Neurol* 2009; 256(4):669-71.

3. Fung V, Hayes M, **Kimber T**, O'Sullivan J. Current concepts in the management of Parkinson's disease. *Medical Journal of Australia* 2010;192:144-149.

4. Todd G, **Kimber TE**, Ridding MC, Semmler JG. Reduced motor cortex plasticity following inhibitory rTMS in older adults. *Clin Neurophys* 2010;121:441-447.

5. **Kimber TE**. An Update on Tourette syndrome. *Current Neurology and Neuroscience Reports* 2010;10:286-291.

6. Thani NB, Bala A, **Kimber TE**, Lind CR. High frequency pallidal stimulation for camptocormia in Parkinson's disease. Neurosurgery 2011; 4 Feb (EPub ahead of print).

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8. **Kimber TE**, Thompson PD. Practical Neurology series: the patient with tremor. *Med J Aust* 2012;196:447-451.