Hormesis and Its Potential Implications for the Pharmaceutical Industry

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Take Home Messages

- Hormesis is found not only in biochemistry, radiation biology and toxicology. There are many examples of hormesis across a wide range of biomedical science and clinical medicine

- The concept of hormesis could help the pharmaceutical industry address some of its major and frequently mentioned concerns, even though short-term it could add to its many challenges

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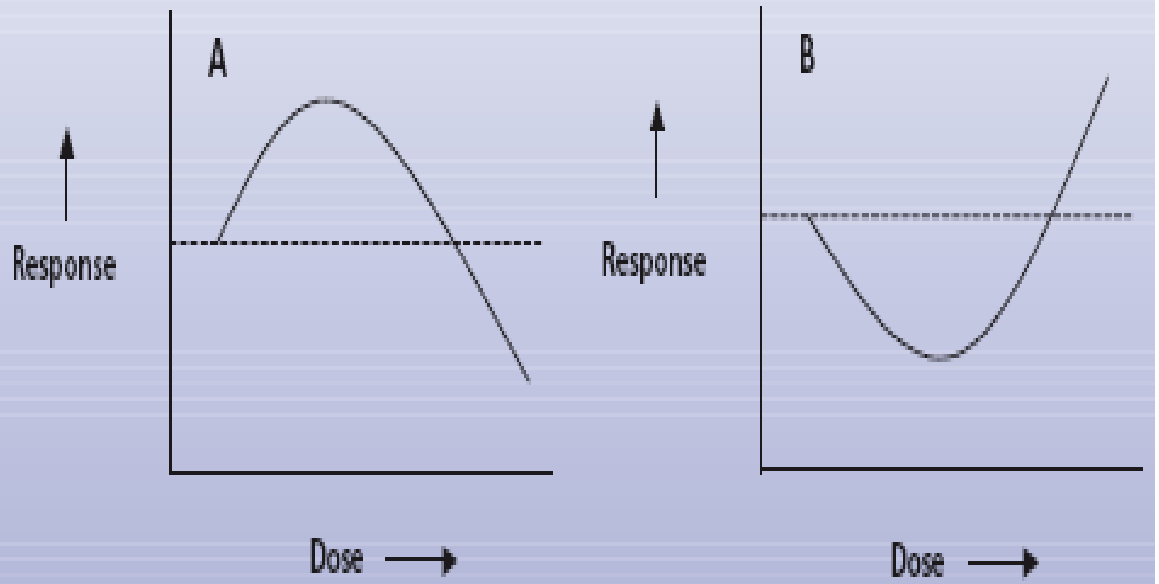
Hormesis – Traditional definition

Traditional definition

- Low-dose stimulation and high-dose inhibition or low-dose reduction and high-dose enhancement
- Confined to biochemistry, radiation biology and toxicology

Figure 1: (A) The most common form of the hormetic dose–response curve, depicting low-dose stimulatory and high-dose inhibitory response, the β- or inverted U-shaped curve. Endpoints displaying this curve include growth, fecundity and longevity. (B) The hormetic dose–response curve depicting low-dose reduction and high-dose enhancement of adverse effects. Endpoint displaying this curve include (J-shaped) carcinogenesis, mutagenesis and disease incidence.[1]



Calabrese, 2007, A dose of common sense. Good Clinical Practice Journal, July, pp12-16

Hormesis – Current revelation

Current experience based on the literature

- biphasic dose-response curves are not only confined to biochemistry, radiation biology and toxicology, but extend across many areas of biomedical science and clinical medicine

  - **"*including anxiety, seizure, memory, stroke, cancer chemotherapy, dermatological processes such as hair growth, osteoporosis, ocular diseases, including retinal detachment, statin effects on cardiovascular function and tumour development, benign prostate enlargement, male sexual behaviours/dysfunctions, and prion diseases*."**
    Calabrese, 2008, Br J Clin Pharm 66:594-617

  - **Neuroscience and Hormesis – Four special issues covering neuronal survival, neurite outgrowth, glial adaptive responses to neurotoxins, p-glycoprotein efflux transporter activity, anxiolytic drugs, traumatic brain injury, stroke, addiction, Alzheimer's Disease ….**
    Critical Reviews in Toxicology, 2008, Volume 38, Nos 4 – 7

  - **Aging, chemosensitization, oxidative stress, caloric restriction, cancer, memory and synaptic plasticity, drug binding, risk of stroke, cellular response (biochemical and physiological) ….**
    American Journal of Pharmacology and Toxicology, 2008, Volume 3, Issue 1

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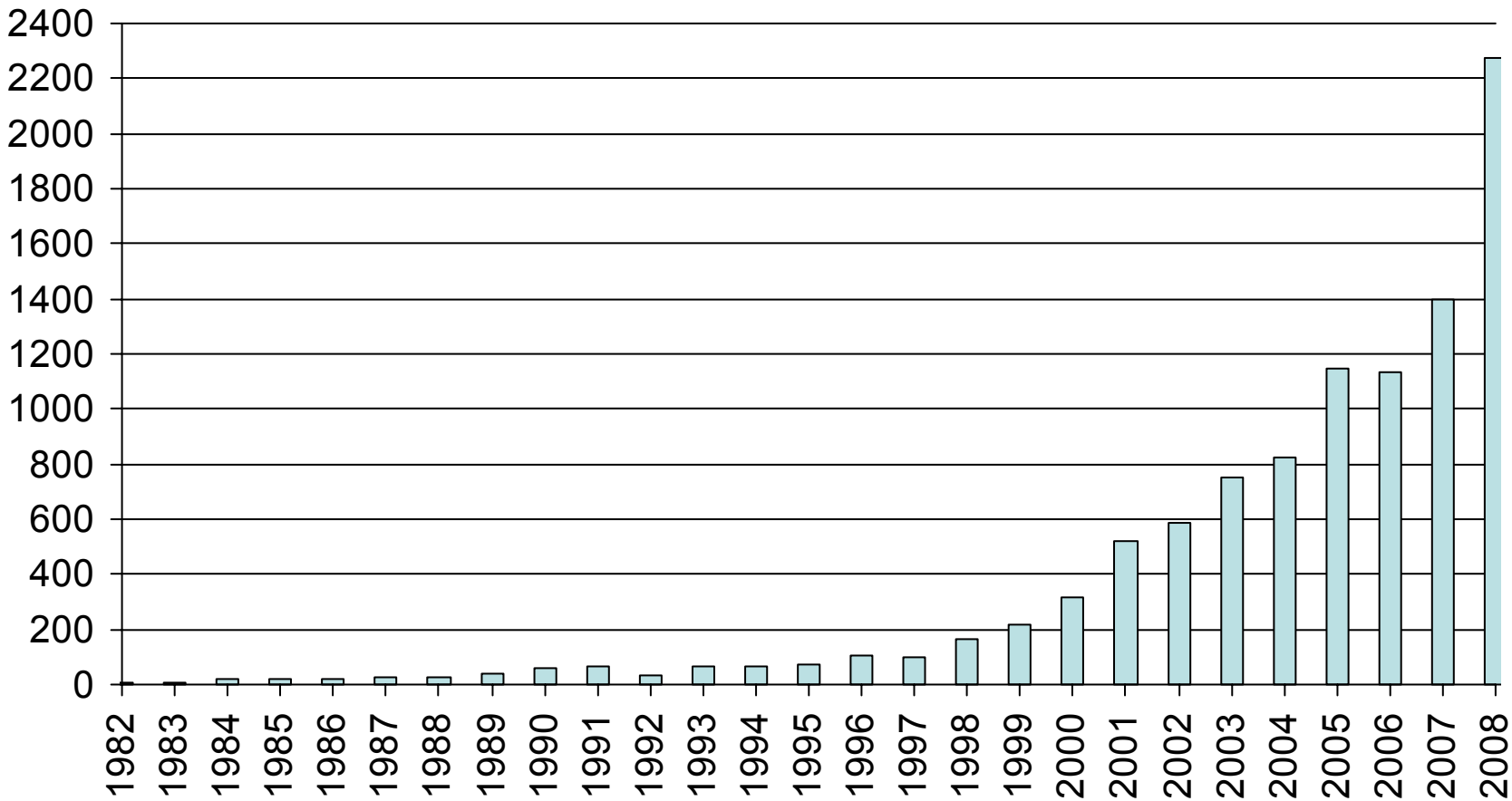
The Number of Publications Citing “Hormesis” or “Hormetic” in the Web of Science Data Base Has Increased Markedly



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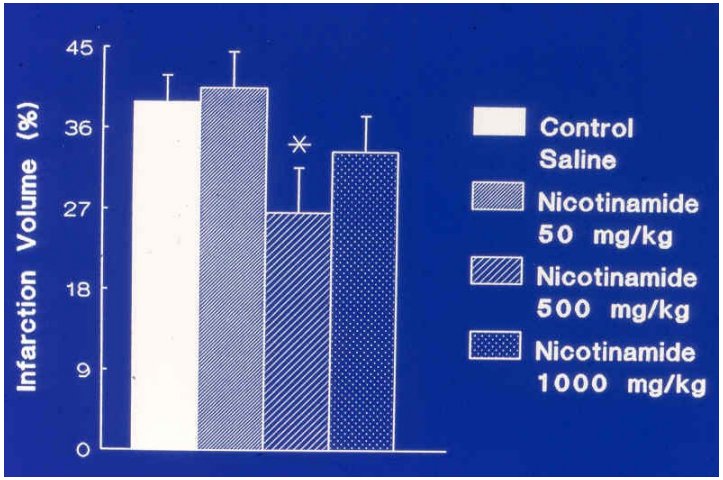
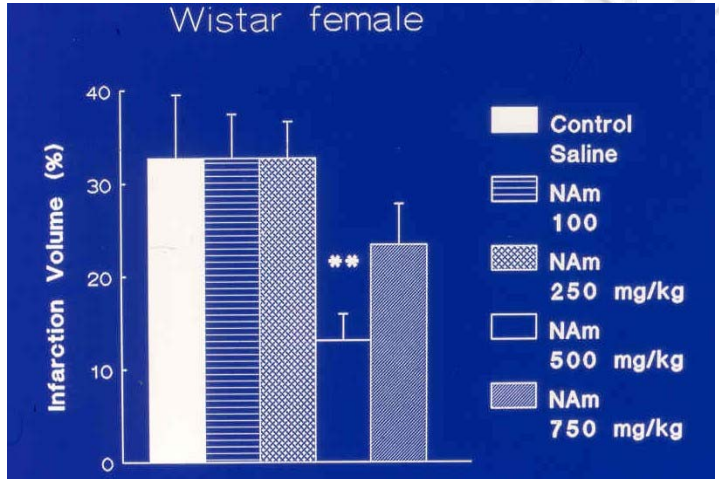
Courtesy Prof. Edward Calabrese

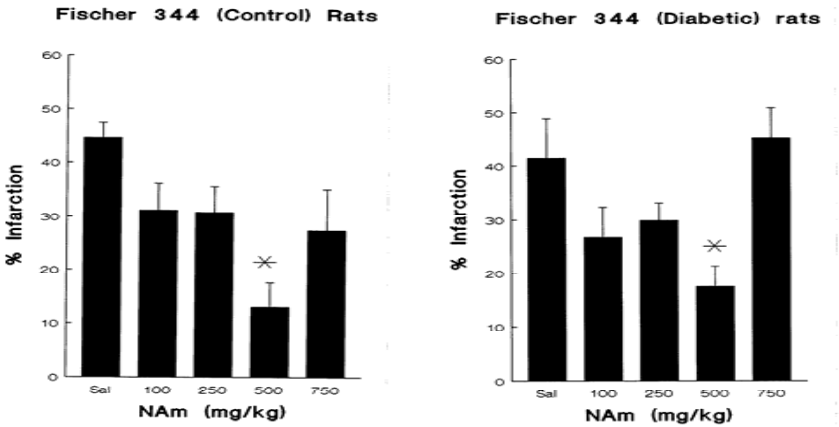
U-Shaped Dose Response Curves Consistently Seen With Nicotinamide in Different Models of Ischemic Stroke in Rats



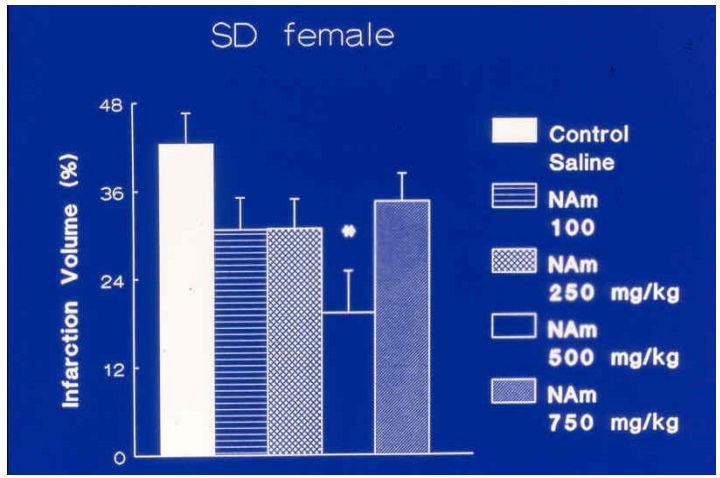
Ayoub et al., Neurosci Lett, 1999;259:21-24



Sakakibara et al., Neurosci Lett, 2000;281:111-114



Sakakibara et al., Brain Res., 2002;931:68-73



Sakakibara et al., Neurosci Lett, 2000;281:111-114

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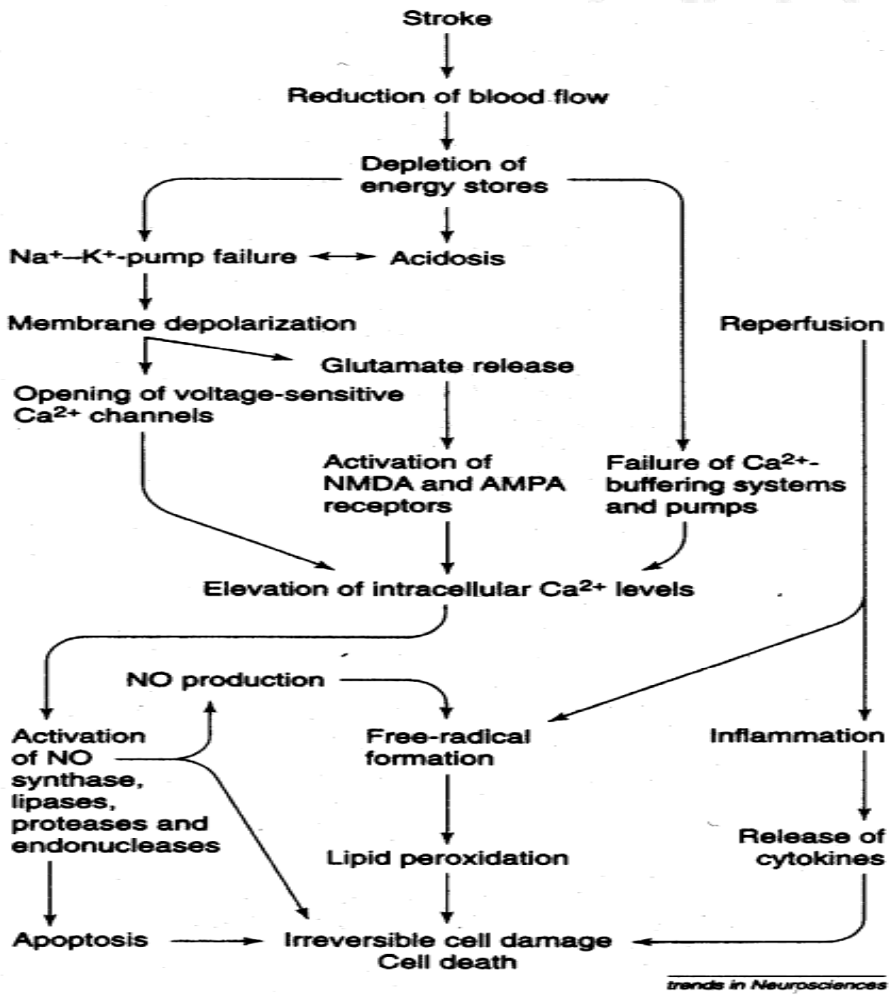
Proposed Mechanism Underlying Hormetic Dose-Response for Neuroprotection by Nicotinamide

Nicotinamide is a poly-ADP ribose polymerase (PARP) inhibitor and other PARP inhibitors exhibit U-shaped neuroprotection

- PARP activation contributes to neuronal damage
- Ischemic infarction reduced in PARP-null mice
- BUT, excessive PARP activation leads to augmentation of NO- and glutamate-induced excitotoxicity and depleted ATP

Nicotinamide (and 3-aminobenzamide) increase choline release which may be

- neuroprotective or
- exacerbate hypoxic or glutamate-induced injury



Ayoub et al., Neurosci Lett, 1999;259:21-24

De Keyser et al., TINS 1999;22:535-540

…. But U-Shaped Dose Response Curves Are Seen With Neuroprotective Agents Acting By Various Mechanisms

Nimodipine	L-type - Ca2+ channel antagonist	EJP 1999;364:99
NAAG	Glutamate precursor	EJP 2000;408:233
Ebselen	Antioxidant & Anti-inflammatory	BJP 1997;122:1251
L-NAME	NOS inhibitor	BJP 1997;120:160
Nicotinamide	NAD^+ precursor, PARP, etc.	Neurosci. Lett. 1999;259:21
BW619C89	Glutamate release inhibitor	Stroke 1993;24:1063
DPQ	PARP inhibitor	JCBFM 1997;17:1137
Progesterone	Reproductive hormone (steroid), ERK?	JNS 1999;171:24
MDL 28170	Calpain inhibitor	Stroke 1998;29:152
PNQX	AMPA (glutamate) receptor antagonist	Stroke 1999;30:1472
Dextrorphan	NMDA antagonist	J Neurotrauma 1996;13:215
Heparin	Anti-coagulant	Brain Res 2001;902:30
Aspirin	Anti-platelet	Neurosci Lett 1998;249:159
SNX-912	Anti-apoptotic agent	PSDE 29 Jan, 2001
GP-683	Adenosine kinase inhibitor	Stroke 1998;29:1952

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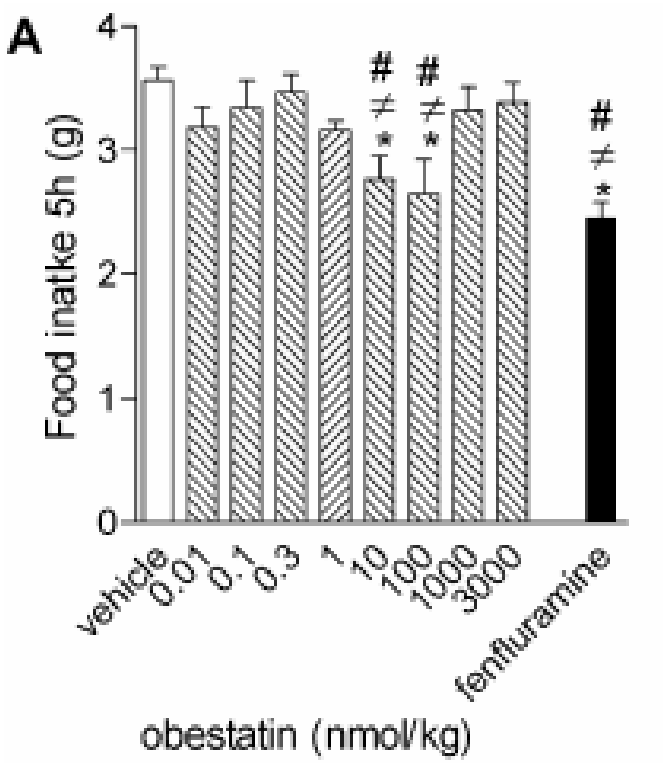
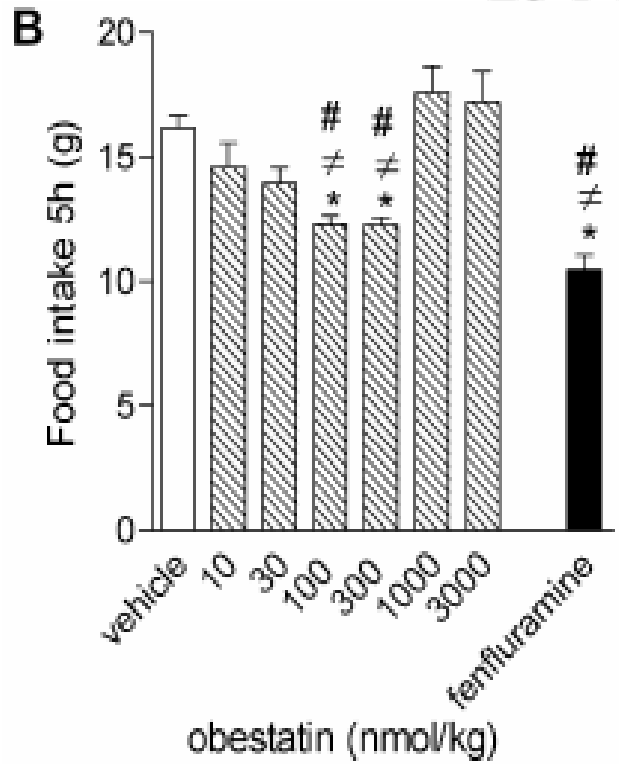
Dose-response relationship for obestatin's effect on food intake in mice and rats over 5 h



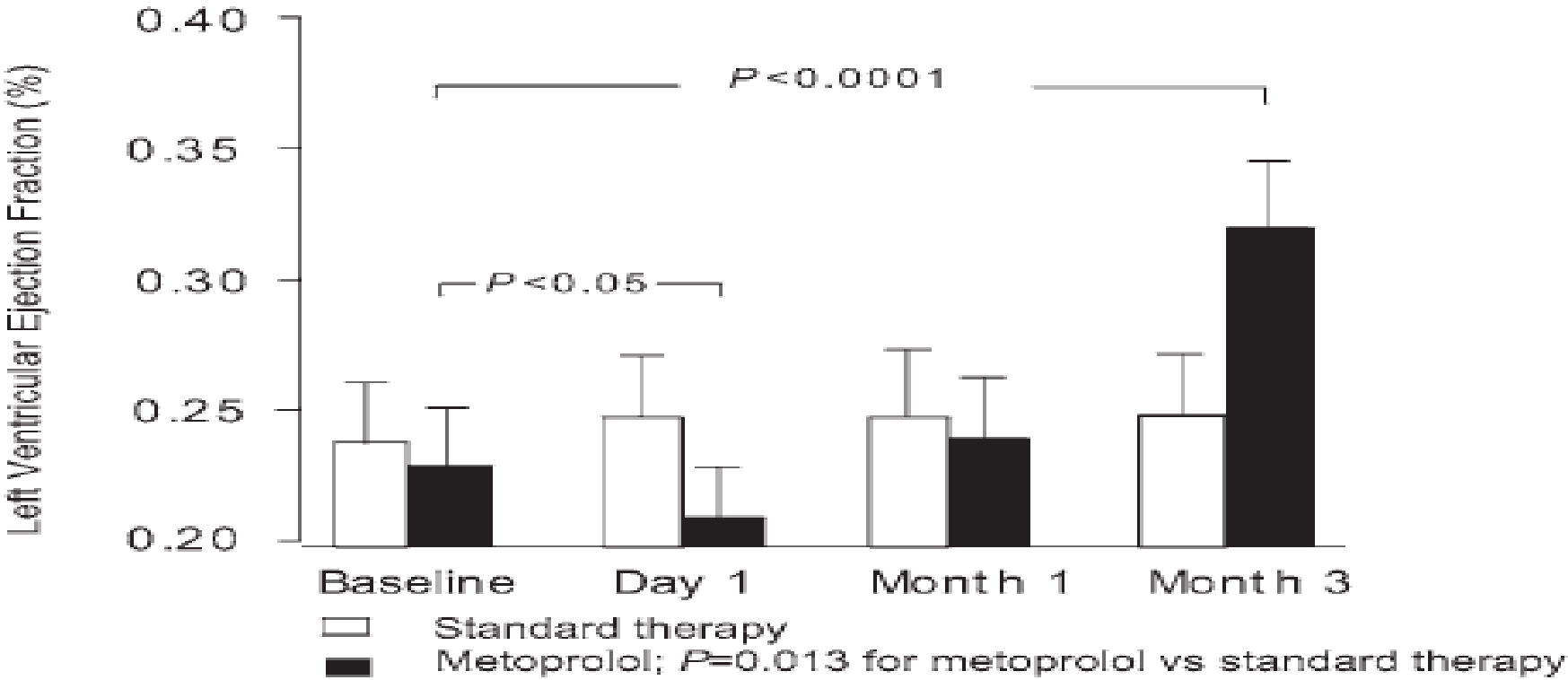
(A) Food intake in vehicle-treated mice (first column) or mice treated with different doses i.p of obestatin (0.1 nmol/kg to 3 µmol/kg). The final column shows the response to 18 µmol/kg fenfluramine i.p. n = 4–5. (means ±SEM).



(B) Food intake in vehicle-treated rats (first column) or rats treated with 10 nmol/kg3 µmol/kg obestatin i.p. n = 6–12. The final column shows the response to 18 µmol/kg fenfluramine i.p. n = 3. *p < 0.05 compared to vehicle control; ≠p < 0.05 compared to 1 µmol/kg dose of obestatin; #p < 0.05 compared to 3 µmol/kg dose of obestatin. (means ± SEM)

Lagaud et al., BBRC 2007;357:264-269

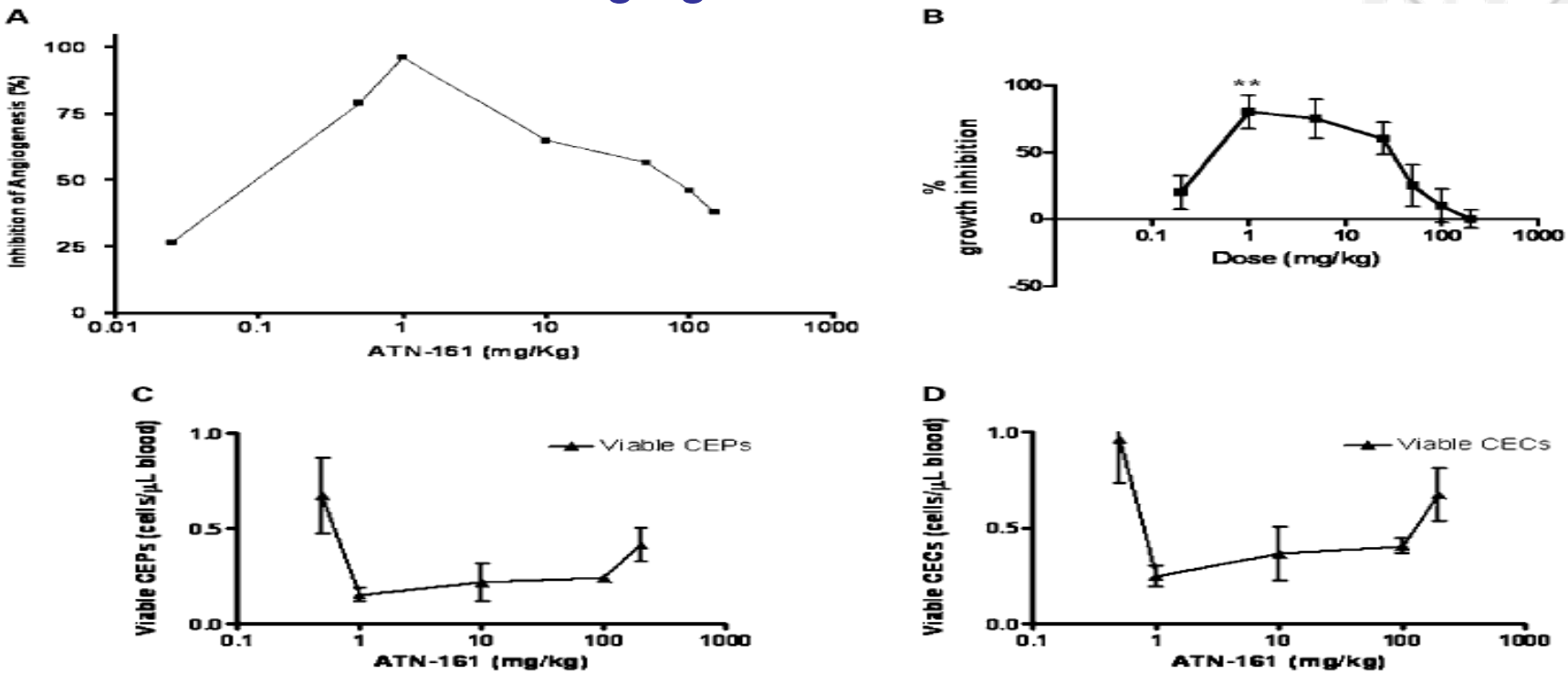
Negative acute effect of metoprolol on a measure of chronic heart failure replaced by beneficial effects with chronic administration



The left ventricular ejection fraction was measured using echocardiograph. Changes in the left ventricular ejection fraction from baseline to day 1, month 1 and month 3 in the metoprolol and standard therapy groups were recorded. The standard therapy was a long term angiotensin converting enzyme inhibitor except in two patients who received isosorbide dinitrate/hydralazine. Ejection fraction decreased about 25% on day 1 with acute metoprolol administration and increased only after 1 month of metoprolol therapy. By the 3rd month the metoprolol treated patients showed a significant increase in the left ventricular ejection fraction. (Reprinted with permission from JACC)

Dudekula et al., Dose Response 2005;3:414-424

Pharmacology of the Novel Antiangiogenic Peptide ATN-161: Observation of a U-Shaped Dose-Response Curve in Several Preclinical Models of Angiogenesis and Tumor Growth



A - The Matrigel plug model of angiogenesis was used to evaluate the effects of ATN-161 (i.v., 0.025-150 mg/kg). Each dose was tested in duplicate, and the experiment was repeated thrice with similar results. The curve presented is representative of these three experiments.

B - Dose-response (DR) curve obtained in the 3LL model of s.c. tumor growth. 3LL cells (1x 10^{-6} cells in 100 µL) were injected s.c. in C57/bl mice. Treatment with ATN-161was initiated the day after tumor cell inoculation. Tumor volumes were measured just before euthanasia. The ratio of tumor volume in treated mice to control mice was calculated to determine treated versus control; **, P = 0.001 (dose at 1mg/kg compared with 0.2 mg/kg).

C - ATN-161 exhibits a U-shaped DR curve in the percentage of viable CEPs. The optimal dose range is between 1 and 10 mg/kg, consistent with the results observed in the angiogenesis and tumor growth models.

D - ATN-161 exhibits a U-shaped DR curve in the percentage of viable CECs in MDA-MB-231 tumor-bearing mice.

Donate et al., Clin Can Res 2008;14:2137-2144

Hormesis [Biological Effects of Low Level Exposure, (B.E.L.L.E.)] and Dermatology

“Hormesis appears to be a common phenomenon in dermatology. Better understanding of this phenomenon will likely lead to different strategies for risk assessment process employed in the fields of dermatologic toxicology and pharmacology.”

Thong and Maibach (2007) call for a redirection of focus

- **from looking only at adverse effects at high levels of exposure**
- **to characterizing the complex biological effects, both adverse and beneficial, at low levels of exposure.**

(Thong and Maibach, 2007, Cut Ocul Tox 26:329-341)

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Hormesis [Biological Effects of Low Level Exposure, (B.E.L.L.E.)] and Dermatology (cont'd)

Low-dose toxicology and pharmacology will not only provide a significant research challenge but should also contribute to better methods for low-dose risk assessment for complex mixtures of chemical compounds. ***This refocusing from high- to low-dose effects will shift the focus in the field of toxicology from emphasizing on adverse effects into studying the biological effects of chemical compounds on living organisms***, taking into account the realization that the ultimate biological effect of a chemical may vary with its dose, the endpoint, the target organ considered, the interaction with other cell types/systems, and or the combined exposure with other chemicals. (Thong and Maibach, 2007, Cut Ocul Tox 26:329-341)

Hormesis appears to be a common phenomenon in *in–vitro* skin biology. However, in vivo data are lacking and the clinical relevance of hormesis has yet to be determined (Thong and Maibach, 2008, Dose Response 6:1-15)

Hormesis – Current revelation

Based on the literature

- biphasic dose-response curves are not only confined to biochemistry, radiation biology and toxicology, but are related to efficacy and extend across many areas of biomedical science and clinical medicine

Challenges for the Pharmaceutical Industry

- Lack of preclinical systems that accurately predict clinical outcome
  - **toxicity**
  - **therapeutic efficacy**
- High failure rate at all stages of research and development (R&D)
  - **How many projects have been stopped because of**
    - **inappropriate target - Discovery**
    - **toxicity - Preclinical**
    - **lack of efficacy - Clinical**
- Ever increasing costs
- Longer timelines from bench to bedside
- Increasing complexity of testing and developing molecularly targeted drugs/biologics and advanced technologies
- Increasing hurdles of regulatory agencies and payers

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Common Problems in Drug Discovery

Reduce the cost and time – sample large chemical libraries

- **Assume linear or threshold concentration-response relationship**
- **Narrow concentration ranges examined, or reduce sampling across a large range in vitro**
- **In vivo - Study narrow dose-ranges and less doses in animal models (e.g., 1, 2 or 3 doses)**

More emphasis on “First-in-class” drugs

- **Yes, but there is more risk because little is understood about the basic chemical biology surrounding these drugs**
  - Fewer data points – less confidence about extrapolation and more risk which could lead to termination of R&D projects at later and more costly stages

Common Failures in Drug Development

- Inaccurate dose selection
- Inappropriate selection of target population
- Poor protocol
  - Lack of an appropriate control group
  - Inappropriate or unspecified endpoints
  - Inappropriate or unspecified statistical analysis
    - Detecting statistical, but not clinical significance
- Incorrect length of study
- Unrepresentative sampling with high attrition rates

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Hormesis: Implications for the Pharmaceutical Industry

Hormesis:- beyond toxicology ….. impacts efficacy

- Numerous examples across biomedical science and clinical medicine in the literature

Drug R&D

- Do not assume linear or threshold dose-response relationship for safety or efficacy
- Need to study a large range of concentrations/doses with increased sampling

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FDA Guideline for Industry
Dose-Response Information to Support Drug Registration

- ***Identify reasonable, response-guided titration steps, and the interval at which they should be taken***, again with appropriate adjustments for patient characteristics. ***These steps would be based either on the shape of the typical individual's dose-effect curves (for both desirable and undesirable effects)*** …. and the time needed to detect a change in these effects.

- Dose-response data for both beneficial and undesirable effects ***may provide information that allows approval of a range of doses that encompass an appropriate benefit-to-risk ratio***. A well-controlled dose-response study is also a study that can serve as primary evidence of effectiveness.

ICH-E4 November 1994

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FDA Guideline for Industry
Dose-Response Information to Support Drug Registration (cont'd)

- ***Several dose levels are needed, at least two in addition to placebo, but in general, study of more than the minimum number of doses is desirable***. A single dose level of drug versus placebo allows a test of the null hypothesis of no difference between drug and placebo, but cannot define the dose-response relationship. Similarly, although a linear relationship can be derived from the response to two active doses (without placebo), this approximation is usually not sufficiently informative. ***Study designs usually should emphasize elucidation of the dose-response function, not individual pair-wise comparisons.***

- ***Dose-response data should be explored for possible differences in subsets*** based on demographic characteristics, ***such as age, gender, or race.***

Post-approval dose adjustments by the FDA

- 1 in 5 drugs approved by the FDA between 1980 and 1999 had dosage adjustments post-approval
  - 20% of these had the dose increased
  - 80% of these had the dose decreased
- Following the guidelines more closely may lead to fewer post-approval adjustments

Cross et al., 2002, Post-marketing drug dosage changes of 499 FDA-approved new molecular entities, 1980 – 1999 Pharmacoepidemiology and Drug Safety, 11:439-446

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Challenges in the pharmaceutical industry
Impact of hormesis: Some Solutions

Discovery

- High through-put screening

Preclinical

- Microdosing/Phase 0

Phase I

- Pharmacometrics

Phase II/III

- Adaptive trial design

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Challenges in the pharmaceutical industry - Impact of hormesis
Some Solutions – High through-put screening in Discovery

High through-put screening

- cellular and biochemical assays are conducted in 1,536-well and 2,080-well plate formats
- provides statistical hit-identification/confirmation, IC_{50} profiling, secondary testing, structural verification of the hit-compounds and SAR analyses

Large chemical libraries

- But increase the range and frequency of concentrations tested in *in vitro* assays, i.e., sample widely and often

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Challenges in the pharmaceutical industry - Impact of hormesis
Some Solutions – Microdosing in Phase 0

Microdosing (EU) or Phase 0 (US)

- studies drug behavior in humans at ultra-low (100 µg) doses unlikely to produce whole-body effects, but allows the study of cellular response
- helps predict whether a drug is viable for phase I testing
- aims to reduce resources (i) non-viable drugs and (ii) animal testing

"*Microdosing also directly addresses the ethical problems of administering full human doses of a drug or biologic to healthy volunteers based only on available animal and in vitro data, as well as the extreme inaccuracy of predicting humans doses based on animal data, as has been the standard procedure until now.*"

Graul, 2008, Drug News Perspect 21:36-43

" *…a better understanding is needed for those properties of a drug that might lead to significant nonlinearities in the pharmacokinetics seen between a microdose and a therapeutic dose.*"

Lappin and Garner, 2008, Expert Opin Drug Metab Toxicol 4:1499-1506

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Challenges in the pharmaceutical industry - Impact of hormesis
Some Solutions – Microdosing (cont'd)

- Ultra-low (100 µg) doses unlikely to produce whole-body effects, but allows the study of cellular response
  - Improving knowledge in humans about toxicity *and efficacy*
- Therapeutic Index (Margin of Safety)
  - Receptors may be highly homologous across species, but
  - Animal models are frequently not highly predictive of the clinical outcome ("biomarkers" versus "surrogate endpoints")
  - Animal → extrapolation of dose-response data to humans may not be obvious and may require confirmation in humans

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Challenges in the pharmaceutical industry - Impact of hormesis
Some Solutions – Pharmacometrics in Phase I

Pharmacometrics

- Pharmacometrics is an emerging science that quantifies drug, disease and trial information to aid efficient drug development and/or regulatory decisions. Drug models describe the relationship between exposure (or pharmacokinetics [PK]), response (or pharmacodynamics [PD]) for both desired and undesired effects, and individual patient characteristics
- Typical focus of pharmacometrics has been on drug models, also referred to by terms such as: concentration-effect, dose-response, PKPD relationships
- The single-most important strength of such analyses is its ability to integrate knowledge across the development program, compounds, and biology
  - Dose-response data should be explored for possible differences in subsets based on demographic characteristics, such as age, gender, or race. – (FDA Guidance)

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Adaptive Trial Design (ATD)

- ATD is defined as a study that includes a sequence of interim analyses to enable modification of the course of the clinical trial dynamically (e.g., used by DMCs to stop trials early due to overwhelming evidence of efficacy)
- Possible adaptation of late phase clinical trials includes sample size re-estimation by dropping or adding treatment arms (e.g., different doses)
- Although the complexity of an adaptive trial will be higher than a traditional trial it permits multiple objectives to be addressed in a single trial, e.g., identifying the dose-range as well as the patient population likely to get the maximum drug benefit, and potentially reducing the overall costs
- No formal guidelines from the FDA as yet, although their Critical Path Opportunities List highlights ATD as one way of speeding up drug development while reducing costs

Phillips and Du Mond, Pharmaceutical Executive July 2007, Vol 5, Iss 5

Overcoming the Challenges in the Pharmaceutical Industry
Impact of hormesis

Define the concentration-response relationship *in vitro*

- **Do not assume a linear or sigmoidal dose-response relationship**
- **It could be J-shaped, U-shaped or bell-shaped**
- **Sample widely and often**

Identify optimal dose, not necessarily maximal dose

- **Expand the dose-range and sampling of doses studied**
  - in animal models
  - in clinical trials, especially phase II

Define the therapeutic index - Get the safety and efficacy doses right

- **Do not assume that higher/est doses = greater toxicity**
- **Do not assume that the maximal tolerated dose = optimal dose with maximal efficacy**

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Overcoming the Challenges in the Pharmaceutical Industry
Impact of hormesis – cont'd

Safety

- **Challenges our mindset about toxic concentrations/doses**

Efficacy

- **Provide more robust data and confidence for moving forward in a therapeutic area**

Resources

- **Validation and targeted use of existing tools and techniques can help to ensure that drugs with better safety and efficacy do not necessarily add more to the cost of drug R&D**

Re-examination of past failures

- **It is possible that development was stopped in some areas not because the target was incorrect or the mechanism was invalid, but simply because we chose the wrong dose assuming a linear or threshold dose-response relationship**

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Challenges in academia
Impact of hormesis

Drug R&D is about science, medicine and creating drugs to help people. Consequently, the impact of hormesis on pharma also applies to academic research

- Drug discovery and development
- Elucidation of basic mechanisms of action

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Take Home Messages

- Hormesis is found not only in biochemistry, radiation biology and toxicology. There are many examples of hormesis across a wide range of biomedical science and clinical medicine

- The concept of hormesis could help the pharmaceutical industry address some of its major and frequently mentioned concerns, even though short-term it could add to its many challenges

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