Two Dimensions of Value: Dopamine Neurons Represent Reward But Not Aversiveness

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Science **341**, 546 (2013);
DOI: 10.1126/science.1238699

Science (print ISSN 0036-8075; online ISSN 1095-9203) is published weekly, except the last week in December, by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005.

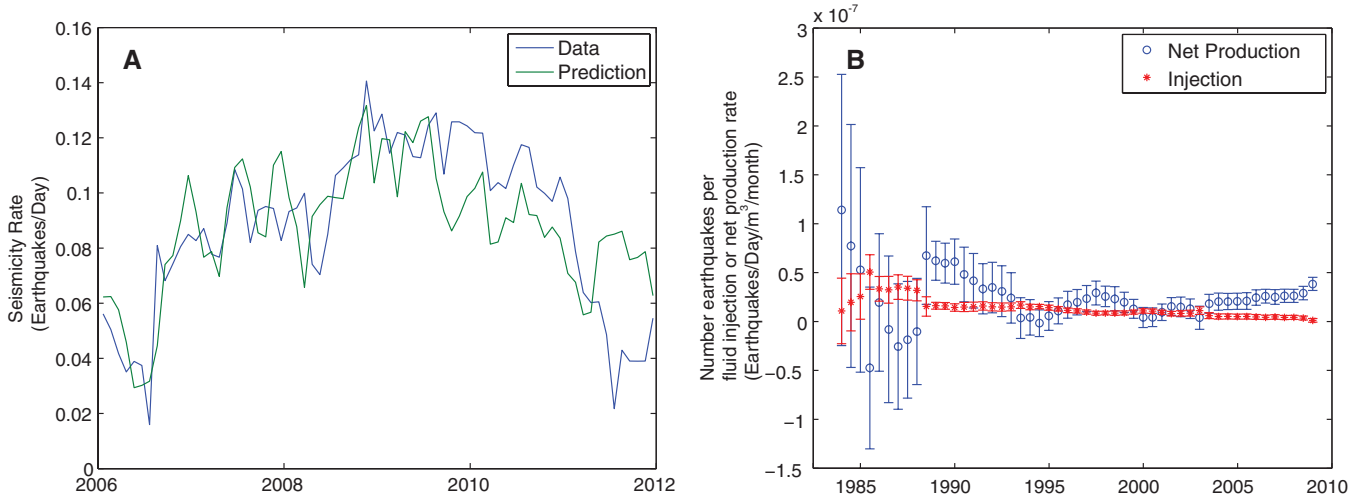

Figure 3. Results of linear model of seismicity based on a combination of injection and net production. (**A**) Sample seismicity rate and model prediction of seismicity rate using the observed fluid data and the best-fit linear model of Eq. 2. (**B**) Number of earthquakes per day triggered per rate of net volume of fluid extracted or total fluid injection. Symbols are best-fit coefficients for Eq. 2. The injection values are coefficient c_1 in Eq. 2, and net production values are c_2. Error bars are 2 SD of model estimates based on the linear regression.

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Acknowledgments: This work was funded in part by the Southern California Earthquake Center (SCEC contribution 1752). SCEC is funded by NSF Cooperative Agreement EAR-0106924 and U.S. Geological Survey Cooperative Agreement 02HQAG0008. Geothermal operation data are archived and distributed by the California Department of Conservation (www.conservation.ca.gov/dog/geothermal/manual/Pages/production.aspx) and seismic data are from the Southern California Seismic Network (www.data.scec.org/eq-catalogs). Comments from T. Lay, A. Shuler, P. Fulton, and M. Clapham improved the manuscript, and P. Fulton's assistance with figures is greatly appreciated.

Supplementary Materials

www.sciencemag.org/cgi/content/full/science.1239213/DC1
Methods
Figs. S1 to S7
Table S1
References (*28*–*36*)

16 April 2013; accepted 1 July 2013
Published online 11 July 2013;
10.1126/science.1239213

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Whereas reward (appetitiveness) and aversiveness (punishment) have been distinguished as two discrete dimensions within psychology and behavior, physiological and computational models of their neural representation have treated them as opposite sides of a single continuous dimension of "value." Here, I show that although dopamine neurons of the primate ventral midbrain are activated by evidence for reward and suppressed by evidence against reward, they are insensitive to aversiveness. This indicates that reward and aversiveness are represented independently as two dimensions, even by neurons that are closely related to motor function. Because theory and experiment support the existence of opponent neural representations for value, the present results imply four types of value-sensitive neurons corresponding to reward-ON (dopamine), reward-OFF, aversive-ON, and aversive-OFF.

In our common use of language, we typically treat "reward" and "punishment" as two qualitatively discrete categories. Many sensory stimuli can be readily classified as either appetitive or aversive, and we distinguish between a less-than-expected punishment and a greater-than-expected reward. Likewise, reward and punishment have often been considered as two distinct dimensions within the study of psychology and behavior, with appetitive and aversive stimuli eliciting approach and avoidance behaviors, respectively (*1*). If they constitute two distinct categories, then reward and punishment are not opposites of one another. However, to decide on motor outputs, the brain must effectively evaluate actions on a common scale in which evidence of good is counterbalanced by evidence of bad. Simple and elegant models have been based on neurons that represent both good and bad along a single continuum of value, analogous to light and dark on the single dimension of light intensity. Most previous work on the physiology and computational function of dopamine (*2*–*10*) and other value-sensitive neurons (*11*–*15*) has proposed,

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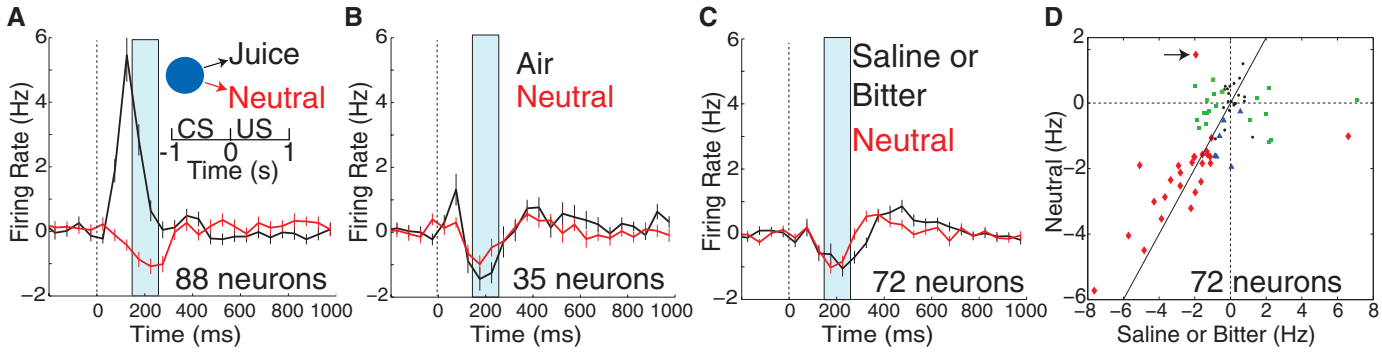

Fig. 1. Dopamine neurons are not activated by omission of an expected aversive stimulus. Monkeys were conditioned with audiovisual Pavlovian stimuli to expect a stimulus (after a 1.0-s delay) that was either neutral sound or had appetitive or aversive value [(A) inset and fig. S1A). (**A**) Juice (black) and its absence (red) caused an increase and decrease in average firing rate, respectively, across a population of 88 neurons. Neuronal discrimination of value was best at 150 to 250 ms after stimulus onset (shaded region) (*16*). All peri-stimulus time histograms (bin size, 50 ms) are averages across all recorded neurons, some of which were unresponsive. (**B**) Both air (black) and its absence (red) caused suppression. Unlike (A), (C), and (D), data are only from monkey F. (**C**) Both saline or bitter (black) and its absence (red) caused suppression. (**D**) Firing rates (150 to 250 ms, baseline rates subtracted) of each neuron to saline (or bitter) and neutral outcomes. The arrow indicates a single neuron in which the neutral stimulus caused activation, which is consistent with the single-dimension hypothesis. Symbols indicate results of *t* tests: activation or suppression to saline-bitter (green squares), to the neutral stimulus (blue triangles), both (red diamonds), or neither (black circles). The diagonal line indicates identity. Pearson's correlation $r = 0.63$; $P < 10^{-8}$. Of these 72 neurons, 8, 2, and 62 were from the ventral tegmental area, retrorubral field, and substantia nigra, respectively; 35 were from the dorsal tier, and 37 were from the ventral tier.

explicitly or implicitly, that neurons represent "total value" along a single dimension.

Prior studies supported the proposition that dopamine neurons are activated or suppressed by anything that is better or worse than expected, respectively (*2*, *8*). They have been proposed to signal a "reward prediction error" that drives reinforcement learning, teaching dopamine-recipient neurons both what is good and what is bad (*2*, *9*). One would expect that if dopamine represents both reward and aversiveness on a single dimension of total value, so too may dopamine-recipient neurons throughout much of the brain. However, it has not been shown that either dopamine or any other reward-sensitive neuron is also sensitive to aversiveness, as required by the "single-dimension" hypothesis. The alternative "two dimensions" hypothesis is that such neurons are sensitive only to reward, and that other neurons should be sensitive to only aversiveness.

Testing these alternatives is more challenging than it may initially appear. First, neuronal responses are not necessarily related to motivational value. Short latency activation (<100 ms) of dopamine neurons by aversive air puff is related to its high sensory intensity, not its aversiveness (*16*, *17*). This sensory-related activation is to be expected of any neuron that represents value in a general manner (*16*), and it appears to have been misattributed to aversiveness in at least one study (*6*), as shown previously (*17*). Second, to characterize any single neuron both appetitive and aversive stimuli must be presented in temporal proximity to one another. This creates challenges because if a stimulus is overly aversive, it will interfere with performance of an appetitive task. The aversive stimulus must therefore be mild (such as an air puff to the face), and a low cost-avoidance response (such as eye blink) does not insure a net aversive value (as in the case of blinking in response to a cool breeze on a hot day). It is questionable whether the stimuli tested in some previous studies did in fact have net aversive value. Third, we need to estimate the subjective value of aversive stimuli (aversiveness) on a common scale with subjective reward value and to then compare neuronal responses to stimuli of approximately equal but opposite values. If aversiveness is too low it may be ineffective in modulating neurons, especially if it is overshadowed in the context of a reward stimulus with much greater absolute value [as expected given principles of predictive (optimal) coding exemplified by dopamine neurons (*18*)]. Studies that have examined responses to both appetitive and aversive stimuli in the same neurons have generally not addressed these issues and are thus inconclusive with respect to the present hypotheses (*4*, *6*, *11*–*15*, *19*–*21*). None of the past studies discussed the possibility that reward and aversiveness could be two discrete dimensions to be represented by discrete neurons.

Data are from electrophysiological single-unit recordings of 195 dopamine neurons in two rhesus macaques (*22*, *23*). Previous analyses of this same data set characterized the multiphasic temporal dynamics of neuronal responses, as well as their dependence on anatomical location within the ventral midbrain, among other issues (*16*, *17*, *24*). A critical and distinguishing feature of these experiments was the use of a choice task to quantify how much juice reward a monkey would sacrifice in order to avoid an aversive stimulus (air puff to the nose or oral delivery of saline or bitter solution). The subjective value of each stimulus was repeatedly measured and adjusted in intensity until it was eventually fixed to have an aversiveness comparable with a typical drop of juice (130 µl), with average values of –70 to –110 µl for each stimulus (except –200 µl in the case of concentrated bitter solution) (*16*). The aversiveness of the air puff was at least an order of magnitude greater than that necessary to elicit conditioned eye blink, and it is thus likely to have been much greater than that used in previous studies (*16*). Neurons were not recorded during the choice task, but in simple Pavlovian tasks that used identical aversive stimuli (fig. S1). Eye position was measured, and gaze toward or away from Pavlovian conditioned stimuli demonstrated that monkeys had learned to expect the appetitive or aversive outcomes, respectively (fig. S2).

In accord with the single-dimension hypothesis, it is well known that aversive stimuli suppress the firing of dopamine neurons. However, that hypothesis also proposes that aversive or neutral stimuli that are not as bad as ("better than") expected should cause activation. Given a simple and well-established experimental design, we can be very precise about the amplitude of the activation. When a Pavlovian conditioned stimulus (CS) (or instrumental action) predicts subsequent reward or no reward with equal probability, reward delivery causes strong activation, and its omission causes suppression of firing rate, as shown here (Fig. 1A) and elsewhere (*6*, *18*, *22*). In fact, the amplitude of this activation was previously found not to depend on the value of the reward, at least over a range of 50 to 500 µl of juice (this may appear strange, but it is evidence of optimally efficient coding) (*18*). All of the aversive stimuli studied here had absolute values greater than 50 µl. Therefore, the single-dimension hypothesis makes the strong prediction that the omission of any of the aversive stimuli in this task will cause virtually the same activation as the delivery of juice reward shown in Fig. 1A.

However, no activation was observed (Fig. 1, B to D). Of 72 neurons tested with saline or bitter,

only one was significantly activated by the neutral outcome, whereas 40 and 49% (29 and 35 neurons) were significantly suppressed by the neutral and aversive outcomes, respectively, and 32% (23 neurons) were suppressed by both (Fig. 1D) ($P < 0.05$, unpaired t tests). Even among 12 neurons tested with a high concentration of bitter having an aversiveness of −0.2 ml of juice (a greater absolute value than that of the juice in Fig. 2A and in most primate studies), six were significantly suppressed by omission of bitter, and none were activated. Similarly, not one of 35 neurons was significantly activated by omission of air, whereas 11 were significantly suppressed. The lack of activation to a neutral outcome was not due to a lack of sensory stimulation because omission of the aversive stimulus was signaled by the onset of a distinct sound (72 dB, similar intensity to the sound caused by the opening of valves that deliver juice, saline, and bitter solutions).

The single-dimension hypothesis implies that dopamine neurons should signal prediction errors for aversiveness in the same manner that they do for appetitiveness. However, whereas reward stimuli only caused substantial activation when they are unpredicted (Fig. 2A), prediction had at most a marginal effect on suppression by aversive stimuli (Fig. 2, B to D). Across the population of neurons, there was no significant difference between responses to predicted versus unpredicted air or saline-bitter ($P > 0.5$ for each stimulus in each monkey; paired t tests across 30 to 47 neurons in each of the four groups). Among 67 neurons, 11 had significantly higher firing rates (less suppression) to predicted versus unpredicted saline or bitter, and eight had the opposite relationship (Fig. 2D). Similarly, 15 and 7 of 77 neurons had higher firing rates for predicted and unpredicted air, respectively.

These data clearly contradict the single-dimension hypothesis but can be explained if reward and aversiveness are represented as two dimensions. It is proposed that dopamine neurons add together evidence for (excitation) and against ("opponent" inhibition) reward (*16*) but are not directly influenced by aversiveness. In this view, aversive and neutral stimuli suppress firing because they provide evidence against reward. Stimuli explicitly conditioned to predict absence of reward have been shown to suppress activation of dopamine neurons (*25*). The aversive and neutral stimuli studied here became familiar through conditioning, and they predicted an absence of reward within a general context that was associated with reward (indeed, there is a chance of reward in any context).

As a final test, aversive stimuli were delivered together with juice. The single-dimension hypothesis states that the only important factor is net value, the sum of reward and aversive values. The two-dimensions hypothesis predicts that a purely aversive stimulus will affect dopamine neurons only if it alters the value of a reward stimulus. Because concentrated saline and bitter solutions were delivered into the mouth together with juice, they would be expected to strongly devalue it. In contrast, simultaneous delivery of air to the nose would be expected to have little interaction with juice and thus should be less effective in devaluing it.

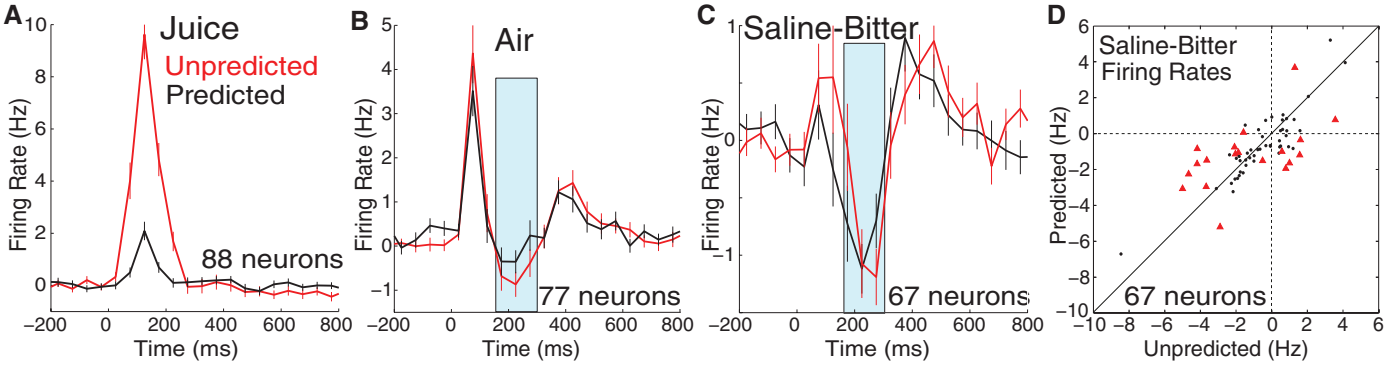

Fig. 2. Suppression by aversive stimuli is insensitive to prediction. Predicted stimuli occurred 1.0 s after a CS, whereas "unpredicted" stimuli were delivered once every 2 to 16 s with no CS (fig. S1B). There are differences in scales of y axes across (A) to (D). (**A**) Unpredicted (red) but not predicted (black) juice reward caused strong activation. (**B**) Prediction only marginally diminished the sensory-related activation, and subsequent suppression, to air. (**C**) Prediction of saline or bitter had little or no effect on suppression. (**D**) Firing rate [150 to 300 ms; shaded region in (C)] of each neuron to predicted and unpredicted saline or bitter (with baseline rates subtracted). The diagonal indicates identity. Red triangles indicate a significant difference between responses to predicted and unpredicted saline-bitter.

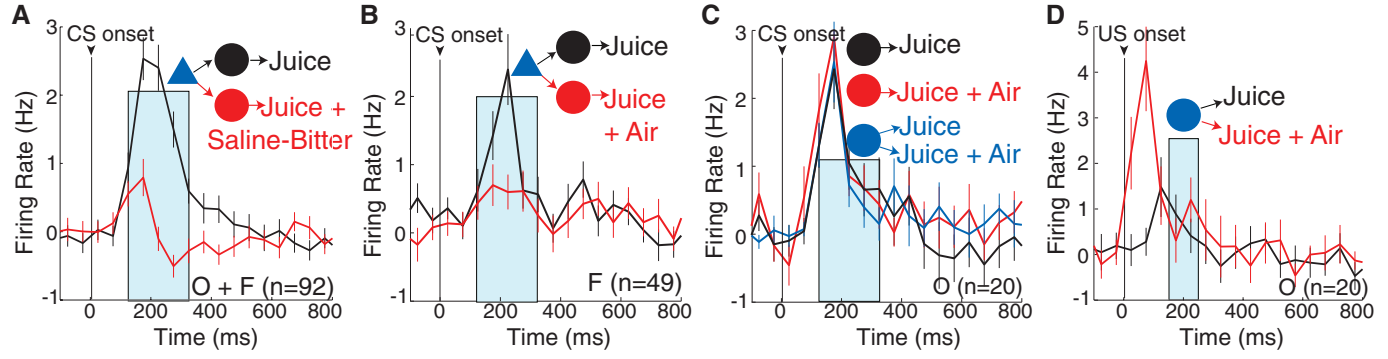

Fig. 3. In the context of juice, dopamine neurons are highly sensitive to saline and bitter, but not air. One CS predicted juice alone (180 μl), and another predicted simultaneous delivery of juice plus an aversive stimulus (insets and fig. S1, C and D). (**A**) Prediction of saline (or bitter) suppressed activation to CS onset in 92 neurons from monkeys O and F. (**B**) Prediction of air caused only a modest suppression of activation to CS onset in monkey F. (**C**) Prediction of air in monkey O had no effect. Unlike (A) and (B), no cue predicted CS onset. (**D**) After the "blue" CS in (C), firing rates did not discriminate delivery of air plus juice from juice alone during the period of 150 to 250 ms after unconditioned stimulus (US) onset, in which reward value is best discriminated. The short latency activation to air (40 to 100 ms) is due to its high sensory intensity and was more prominent in monkey O than in monkey F (*16*).

Monkeys learned that one CS predicted only juice, whereas another predicted juice plus a simultaneous aversive stimulus (fig. S1C). Consistent with both hypotheses, the CS predicting juice alone caused a much stronger activation than the CS predicting juice plus saline or bitter (Fig. 3A). However, in contrast to the single-dimension hypothesis, prediction of air caused only a small suppression of the CS response in monkey F (Fig. 3B) and no suppression in monkey O (Fig. 3C). Across all 49 cells in monkey F in which experiments were performed both with air (Fig. 3B) and saline (Fig. 3A), the effect of saline (in suppressing firing rates) was significantly greater than that of air ($P = 0.02$, paired t test). When air was delivered together with juice but with a probability of 0.5 (following a CS), its aversiveness had no effect on firing rate (Fig. 3D). Analogous experiments in which a loud (90 dB) but neutral sound replaced air yielded similar results, with the sound being ineffectual (fig. S3).

The insensitivity of dopamine neurons to aversiveness suggests that other neurons should represent aversiveness. Reward and aversiveness could be represented independently by discrete sets of neurons because they are experienced by the brain as statistically independent of one another, displaying neither strong positive nor negative correlations. They would not be represented as opposites along a single dimension because in general, they are not anticorrelated with one another. This is essentially the same explanation that has been given for receptive field formation in sensory systems, in which distinct neurons learn to recognize statistically independent features as discrete "objects" (*26*, *27*).

Past and present results do support the existence of opponent representations for reward (*3*, *13*, *16*, *28*), and the same is likely to be the case for aversiveness. Thus, one can infer from the present results that there are four types of value representations, which could be denoted as reward-ON (R_{ON}), reward-OFF (R_{OFF}), aversive-ON (A_{ON}), and aversive-OFF (A_{OFF}). The "ON" neurons would be activated by evidence for reward, or for aversiveness, and the "OFF" neurons by evidence against reward, or against aversiveness. These four putative types of neurons would mediate the four types of reinforcement distinguished at the behavioral level. Skinner denoted these, esoterically, as positive reinforcement (R_{ON}), positive punishment (A_{ON}), negative reinforcement (A_{OFF}), and negative punishment (R_{OFF}) (*1*). Because dopamine represents R_{ON}, it is natural to ask whether the other three major modulatory neurotransmitters might represent the other three value signals. Although some recordings have been made from neurons containing norepinephrine, serotonin, and acetylcholine, it remains uncertain how they represent value, in part because of the challenges described above in characterizing neuronal responses to both reward and aversiveness. Regardless of the other classic neuromodulators, the present results suggest the existence of at least three other modulatory signals to represent the other three aspects of value and to "teach" value throughout large parts of the brain in a manner analogous to that proposed for dopamine (*2*, *7*, *9*).

References and Notes

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23. Of 195 dopamine neurons, 134 were from monkey O, and 61 were from monkey F. It was estimated that 81, 13, and 6% were in substantia nigra, ventral tegmental area, and retrorubral field, respectively, with 45% of all neurons being in the "ventral tier" (ventral substantia nigra compacta and reticulata) and the other 55% being in the "dorsal tier" (*17*).
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Acknowledgments: I thank W. T. Newsome for advice and helpful discussions, J. R. Brown for excellent technical assistance, and W. A. Phillips, J. R. Wickens, and M. R. Song for constructive comments on the manuscript. Research was supported by grants from the Basic Science Research Program (2012R1A1A2006996) and World Class University (WCU) program (R32-2008-000-10218-0) of the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology, and a grant to W. T. Newsome from the Howard Hughes Medical Institute.

Supplementary Materials

www.sciencemag.org/cgi/content/full/341/6145/546/DC1
Materials and Methods
Figs. S1 to S3
Reference (*29*)

3 April 2013; accepted 4 June 2013
10.1126/science.1238699

Functional Lysine Modification by an Intrinsically Reactive Primary Glycolytic Metabolite

Raymond E. Moellering and Benjamin F. Cravatt

The posttranslational modification of proteins and their regulation by metabolites represent conserved mechanisms in biology. At the confluence of these two processes, we report that the primary glycolytic intermediate 1,3-bisphosphoglycerate (1,3-BPG) reacts with select lysine residues in proteins to form 3-phosphoglyceryl-lysine (pgK). This reaction, which does not require enzyme catalysis, but rather exploits the electrophilicity of 1,3-BPG, was found by proteomic profiling to be enriched on diverse classes of proteins and prominently in or around the active sites of glycolytic enzymes. pgK modifications inhibit glycolytic enzymes and, in cells exposed to high glucose, accumulate on these enzymes to create a potential feedback mechanism that contributes to the buildup and redirection of glycolytic intermediates to alternate biosynthetic pathways.

Regulation of protein structure and function by reversible small-molecule binding (*1*, *2*) and covalent posttranslational modification (PTM) (*3*) are core tenets in biochemistry. Many intermediates in primary metabolic pathways reversibly bind to proteins as a form of feedback or feedforward regulation (*2*). Covalent PTMs are, however, typically introduced onto proteins by enzyme-catalyzed processes, but can also result from enzyme-independent interactions between reactive metabolites and nucleophilic residues in proteins (*4*–*7*). The scope and broad functional significance of nonenzymatic modifications of proteins, however, remain poorly understood. In this context, we wondered whether intrinsically reactive intermediates in primary