PERSONALITY FACTOR CORRELATES OF GROWTH HORMONE AND HYPOTHERMIC RESPONSE TO BUSPIRONE CHALLENGE IN SUICIDAL SOLDIERS

Col MSVK RAJU*, Lt Col MK GARG⁺,
Mrs B RAJGURU[#], Ms K SRIVASTAVA**

ABSTRACT

The biological underpinnings of suicidal behaviour and possible rational pharmacotherapy of persons exhibiting such behaviour is the focus of this study. The study was conducted on 25 male Armed Forces personnel who attempted suicide and 25 matched healthy controls. Hypothermic and Growth Hormone response to Buspirone challenge was measured serially. 11 cases of attempted suicide had subsensitive postsynaptic 5 HT-1A receptors as indicated by blunted Growth Hormone response, while in other suicidal soldiers hypothermic response was markedly blunted indicating subsensitive presynaptic 5HT-1A receptors in the latter. Personality factor assessment carried out by 16 personality factor test, indicated overt extraversion marks for subsensitive postsynaptic 5 HT-1A receptors, while overt introversion marks for subsensitive presynaptic 5 HT-1A receptors, in suicidal soldiers. In the light of the above, therapeutic options of Serotonin reuptake inhibition, agonist load at presynaptic 5 HT-1A and reciprocal stimulation of postsynaptic 5 HT-1A receptors for prevention of future attempts and completed suicides is discussed.

MJAFI 2002; 58 : 114-119

KEY WORDS : Attempted suicide; Buspirone; Personality factors; Serotonin receptors; Soldiers.

Introduction

Suicidal behaviour appears rather atavistic in the human context, as it runs counter to the fundamental drive to survive. From the perspective of a suicidologist, the milieu of Armed Forces exemplifies a paradoxical situation as the means (lethal weapons) to complete suicide are accessible at the same time opportunities to survive after an attempt are high due to the proximity of medical help and peer support. Goel [1] made the first attempt to study attempted suicides in the Armed Forces of India. Recently Valdiya et al [2] in an observational study design analysed the socio-demographic and clinical data of 149 suicidal soldiers.

Except for the epidemiological catchment area study in USA, no national level data on attempted suicides are available. In India, suicide rate was estimated to be 9.9 per 100,000. As the attempted suicides are estimated to be 10-20 times of the suicides [3], 1 to 2 million people may be attempting suicides in India every year. In the Army, suicide rate was reported to be 5 per 1 lakh [4]. By conventional estimate about 600-1200 service personnel would be attempting suicide and 10% of these would ultimately die by their own hand. Therefore interventions to reduce the progression of attempted suicides to completed suicides

as well as to prevent future attempts assume significance.

Suicide behaviour including suicide prevention is a recent entrant in the area of biological research. Development of techniques to uncover valid correlations between central nervous system and psychopathology may lead to the identification of a marker with clinically useful predictive value.

Ever since Asberg [5] reported reduced concentration of 5 Hydroxy Indole Acetic Acid (5 HIAA) in the CSF of attempted suicides brain serotonergic system has become the focus of researchers' attention. After initial efforts at direct measurement of serotonin and its metabolite 5 HIAA, serotonin receptors have become the object of study of late. Pre and postsynaptic Serotonin (5HT) receptor alterations have been observed in the prefrontal cortex of people who commit suicide by autoradiographic and ligand binding techniques. Reduced serotonergic function in the ventral prefrontal cortex is considered as a critical element that imparts vulnerability to suicidal behaviour. Serotonin synthesizing neurons innervating the forebrain are primarily located in the dorsal and median raphe nuclei of the brainstem [6]. Central 5 HT dysregulation seems to correlate not only temporally with suicidal attempts but with lifetime history of suicidal be-

* Senior Advisor (Psychiatry), Base Hospital, Delhi Cantt 110 010. ⁺Classified Specialist (Medicine and Endocrinology), Command Hospital (Central Command), Lucknow 226 002. [#]Senior Scientific Officer (Clinical Psychologist), Command Hospital, (Southern Command), Pune - 411 040. ^{**}Scientist 'D', Department of Psychiatry, Armed Forces Medical College, Pune - 411 040.

behaviour as well [7]. Currently, only pharmacochallenge offers a means to assess physiological function in vivo of targeted neuroendocrine pathways. 5 HT system appears to be the only system involved in anterior pituitary activation. The administration of m-chlorophenylpiperazine (m-CPP), a non-selective post synaptic agonist leads to reliable increase in Prolactin (PRL), ACTH and Cortisol concentrations. Studies aimed at examining m-CPP induced hormonal responses in suicide attempters yielded negative findings [7]. The importance of 5 HT-1A receptor needs to be appreciated against this background.

5 HT-1A receptors are found in both presynaptic and postsynaptic locations. Stimulation of the presynaptic receptor by agonists like Buspirone, Ispipirone, Gepirone or Flesinoxan results in hypothermic response [8], while postsynaptic stimulation with the same agonists result in increase in ACTH, PRL, Cortisol and Growth Hormone (GH) concentrations [9].

So far, only two neuroendocrine challenge studies attempted to correlate suicidal behaviour with indices of 5HT-1A receptor function. Moeller et al [10] reported no co-variance between Buspirone induced PRL responses and history of suicide attempt in depressed male patients. Since Buspirone has some D2 antagonist action PRL response is not free from controversy. Pitchot et al [11] using Flesinoxan in evaluating depressed patients with and without suicide attempts demonstrated a blunting of both Cortisol and hypothermic responses in suicide attempters. No differences for PRL, ACTH or GH were discerned. However, no investigator appeared to have attempted to study GH response to agonist challenge in attempted suicides per se and correlate the same to personality variables. The co-variance of depressive illness with suicidality has been a confounding factor in the neuroendocrinology of suicide research [10,11]. Since neuro-endocrine response might offer a rationale for secondary prevention of suicides and since personality variables associated with such reponsivity might serve to identify sub or hypersensitive 5 HT-1A receptors, this study is attempted to ascertain GH and hypothermic response to Buspirone challenge and to further ascertain any personality variables that may be associated with the level of functioning of the pre and post synaptic 5 HT-1A receptors.

Material and Methods

25 male Armed Forces personnel who were admitted to a large, referral hospital after attempting suicide, formed the sample. 25 healthy male soldiers constituted the control. Persons with significant medical conditions and weight loss were excluded from the study. Informed consent was obtained from all cases. Clinical psychiatric assessment was carried out in all cases.

1. Neuro-endocrine testing

After a light meal the previous night neuro-endocrine testing was carried out in the morning at rest in supine position 7 a.m., onwards. Two blood samples at 30 minute intervals were collected by means of an indwelling IV cannula to estimate baseline GH levels. 30mg of Buspirone was administered to each person orally after collecting baseline blood samples. Six venous blood samples were collected thereafter at 30 minute intervals. Plasma GH levels were measured by a double Antibody Human GH Radioimmunoassay kit (Diagnostic Products Corporation - Los Angeles, USA).

GH estimations were carried out in batches as per procedure described in the manual of DPC. A single well I 125 Gamma counter (Electronic Corporation of India, Hyderabad) was utilised for the purpose. Oral temperature was measured at 30 minute intervals keeping the thermometer in situ for 10 minutes each time.

2. Personality assessment

(a) Rorschach test [12]. It is a projective personality test consisting of 10 standard chromatic and achromatic inkblots. It is based on the psychodynamic principle of unconscious perception. Scoring was done as per guidelines of Klopfer and Kelly [13].

(b) Beck Depression Inventory [14]. The scale focuses on the cognitive symptoms of Depression. Subjects are asked to rate 21 items from 0 to 3 according to how they feel at the present time. The result can be scored into 4 grades i.e., minimal 0-9, mild 10-16, moderate 17-29, severe 30 and above.

(c) 16 Personality Factor Test [15]. It is a multidimensional set of sixteen questionnaire scales arranged in omnibus form. The raw scores that are obtained after administering the test are converted into "Sten" scores in respect of each of the 16 primary factors and 4 secondary factors. Population mean is fixed at a Sten score of 5.5.

3. Measurement and Statistical Analysis

Baseline temperature in Fahrenheit was taken as zero irrespective of the actual temperature recorded. The difference in temperature at each 30 minute interval from baseline was recorded. Means of each 30 minute recording in respect of sample and control were compared using Student's 't' test. Difference between highest baseline and peak GH response is taken as Delta Response. A Delta response of 0.5 ng/ml and below is considered as blunting. Area under the curve (AUC) was also determined for GH response. AUC was correlated with Beck Depression Inventory (BDI) scores. Delta GH response was also correlated to temperature response.

Personality variables in respect of blunted (BAS) and non blunted (NBAS) GH responders were compared for significance of difference. Personality variables in respect of all attempted suicides were also compared with control.

Results

In the Rorschach test significantly more detail (D), color (Sum C), movement (M), responses in comparison to controls are seen. The F+% in both controls and attempted suicides (AAS) is high but comparatively the F+% in AAS is low (Table 1). It is also seen that M:Sum C in respect of BAS was 2.84:1, while it was 0.81 in NBAS group. Apperceptive type is 'W' in AAS. 9 out of 25 AAS had mild symptomatic depression. Clinical evaluation however excluded Depressive Disorder in all the 9 cases. Though the difference at categorical level is significant, comparison of depression scores of the AAS and control showed no statistically significant depression (Table-2). Hypothermic responses to Buspirone in

TABLE 1

Rorschach test results in attempted suicide patients (n-25) and controls (-25)

	W%	D%	Dd + S%	F + %	VIII + IX + X	Sum C	M	FK + FC/F
AAS	55.24	32.92*	10.16	53.48**	31.7	1.3*	2.04*	4.89*
CON	39.24	24.44	6.43	61.08	31.3	0.56	0.96	1.04
		t 1.77		t 2.56		t 2.75		t 1.96
		*p < 0.05		**p < 0.02		*p < 0.05		*p < 0.05

AAS - All attempted suicides; CON - Controls.

TABLE 2

Beck depression inventory (BDI) scores

	Depression	No depression	Mean depression score	SD
AAS	9*	16	10.45	7.36
CON	1	24	6.77	4.68
	* χ^2 4.37		t 1.08	
	p < 0.05		p > 0.05	

AAS - All attempted suicides; CON - Controls

TABLE 3

Hypothermic response to buspirone challenge

	A +30 min	B +60 min	C +90 min	D +120 min	E +150 min	F +180 min
AAS	-0.80 (2.10)	-1.32 (2.5)	-1.2 (2.5)	-1.24* (2.83)	-1.56 (3.01)	-0.64** (3.36)
CON	-1.68 (2.37)	-1.68 (2.75)	-1.92 (2.45)	-2.72 (2.76)	-2.84 (2.85)	-3.08 (2.78)
				t 1.87		t 2.69
				*p < 0.05		**p < 0.001

AAS - All attempted suicides; CON - Controls

AAS are subdued throughout. The difference is found to be statistically significant at 2 and 3 hours post challenge (Table-3). 11 out of the 25 attempted suicides had shown blunted growth hormone response to Buspirone challenge. The difference in the mean Delta GH response between AAS and controls is also found to be highly significant statistically (Table-4). Blunting of hypothermic response to Buspirone challenge was more marked in those who had shown no blunting in GH response (Table-5). Though not reflected in table form, for the sake of brevity, no significant correlation was found between BDI scores and the AUC of GH responses ($r+0.26p=>0.05$). Out of the total 10 who had mild depression, only one had shown blunted GH response (α 20.67 $p>0.05$). In the 16 personality factor test (16 PF) significant differences were noted between AAS and controls in factors B, C, E, F, I, M, Q2 and Q3 first order factors. AAS group scores lie on the lower side in respect of B, C, F, q2 and q3 while the scores are on the higher side in respect of E, I and M factors. Attempted suicide with blunted GH response (BAS) had significantly high scores on E, H, and I factors, while they scored low on factor Q2. Those who had not shown blunted GH response (NBAS) have scored low on E, F and H factors (Table-7a and 7b)

Discussion

The fact that attempted and completed suicides represent a very serious public health problem in our

TABLE 4

Growth hormone response to buspirone challenge

	Blunting	No blunting	Mean	SD
AAS	11**	14	3.78**	5.74
CON	1	24	8.162	5.09
		χ^2 = 8.2		t 2.86
		**p < 0.01		**p < 0.001

AAS - All attempted suicides; CON - Controls

TABLE 5

Hypothermic response in blunted (BAS) and non blunted (NBAS) growth hormone responders

	A +30 min	B +60 min	C +90 min	D +120 min	D +150 min	E +180 min
BAS	-0.75	-1.42	-1.0	-1.0	-2.08	-1.92
NBAS	-0.46	-0.92*	-0.69	-0.92	-0.85*	0.23
				t 2.42		t 2.44
				*p < 0.05		*p < 0.05

country, is not fully appreciated. Fortunately, in the Armed Forces there is a refreshing trend of concern for deaths that come too soon by design.

It is by now clear that suicidality runs in families [16]. Atleast two factors are proposed as underlying the heritability - a common genetic factor predisposing for mental illness and an equally important independent risk factor for suicide [17]. Suicidal ideas are very common in non-clinical population. It is those who are predisposed to suicide, translate ideas into action [3,17]. While the biological predisposition may be reduced 5 HT turnover, the psychological factors were found to be impulsivity and aggression. These psychological factors were noted to be associated with reduced PRL response to neuro-endocrine challenge with serotonergic agents like fenfluramine and m-chlorophenylpiperazine [18]. This PRL response is mediated through 5 HT-1A receptors. The investigators believe that the present study linking neuro-endocrine challenge responses to personality variables is the first of its kind in our country.

The best instrument for evaluating unconscious material and ego functioning is Rorschach test [19]. The overall Rorschach trend of AAS shows an exaggera-

TABLE 6

16 PF first order factor scores of all attempted suicides (AAS) compared to controls (CON) and attempted suicides with blunted GH responses (BAS) compared to those showing no blunting (NBAS)

	A	B	C	E	F	G	H	I
AAS	5.04 (2.16)	4.92* (2.8)	4.69* (1.93)	5.32* (1.31)	4.68* (1.93)	5.96 (1.24)	5.8 (2.14)	6.32 (1.89)
CON	6.28 (1.21)	6.52 (2.16)	6.2 (1.84)	4.44 (2.27)	5.64 (1.11)	6.0 (1.53)	5.92 (1.58)	5.32 (1.21)
BAS	5.74 (2.38)	4.25 (3.1)	5.17 (1.07)	5.67** (1.97)	5.5** (1.93)	5.67 (1.5)	6.91* (1.78)	7.0** (1.90)
NBAS	5.54 (2.02)	5.54 (2.4)	4.15 (2.15)	3.54 (1.85)	3.92 (1.66)	6.23 (0.93)	4.85 (1.99)	5.09 (1.70)
	NS	NS	NS	*t 1.69 p < 0.05	*t 2.18 p < 0.05	NS	*t 2.71 p < 0.02	*t 2.27 p < 0.05
				**t 2.8 p < 0.02	**t 2.26 p < 0.05			**t 1.18 p < 0.05

TABLE 7

16 PF first order factor scores of all attempted suicides (AAS) compared to controls (CON) and attempted suicides with blunted GH response (BAS) compared to those showing no blunting (NBAS)

	L	M	N	O	q1	q2	q3	q4
AAS	5.92 (1.98)	6.12* (1.88)	4.72 (2.2)	6.4 (2.66)	5.16 (1.7)	4.68* (2.48)	6.36* (2.9)	4.83 (2.05)
CON	5.64 (1.82)	4.88 (2.31)	5.4 (1.38)	5.28 (3.46)	5.12 (1.83)	6.0 (1.68)	7.008 (2.93)	4.56 (2.42)
BAS	6.41 (1.45)	5.67 (1.3)	3.58* (1.5)	5.75 (2.67)	5.33 (1.38)	3.5** (2.07)	6.83 (2.91)	4.58 (1.78)
NBAS	5.46 (2.3)	6.54 (2.6)	5.77 (2.88)	7.0 (2.61)	5.0 (2.0)	5.76 (2.38)	5.92 (2.93)	5.07 (2.33)
	NS	*t 2.10 p < 0.05	*t 2.80 p < 0.05	NS	NS	*t 2.24 p < 0.05 **t 2.54 p < 0.05	*t 2.06 p < 0.05	NS

tion of normal (control) trend of introversion (M:Sum C=1.57:1) and impaired common sense (more 'W' responses). A significant need for affection (high FK+FC/F ratio) in AAS is a notable difference as well as the tendency for high aspiration not complemented by adequate ability (W=>2M). Suiciders are known to be introversive and expect too much of themselves. Mild symptomatic depression, actually bordering on minimal, was noted in 36% of the present sample. This figure is comparable to that of other workers [20]. Apparently the low level of depression (mean BDI score 10.45) averaged out in the group as there was no significant difference between the means and controls. There was no correlation between depression and GH response. The blunted hypothermic response to Buspirone shown by AAS indicates subsensitive presynaptic 5 HT-IA receptors. Pitchot et al [21] reported similar findings. However, all of their cases had depression. 5 HT-IA autoreceptor subsensitivity should lead to increased 5 HT synthesis and turnover

[21], which runs counter to the commonly accepted view of reduced turnover in suicides unless one assumes sequestration of 5 HT in the synapse due to impaired functioning of the serotonin transporter. Significantly, Asberg [5] had reported reduced 5 HIAA in only 29% of his cases. 44% of the present sample had subsensitive postsynaptic 5 HT-IA receptor as indicated by blunted GH response to Buspirone challenge. Postsynaptic 5HT-IA receptors were found to be functioning normally by Pitchot et al [11]. The down regulation of postsynaptic 5 HT-IA could be compensatory to increased 5HT firing in DRN brought about by subsensitive presynaptic 5 HT-IA. But presynaptic down regulation is more marked in those who have not shown blunting of GH response (NBAS). This raises the possibility that 5 HT-IA receptor subtype changes are independent of each other. At this point it appears that attempted suicides are biologically heterogeneous. As per the Rorschach protocol [13] the BAS group are inherently introversive (M:Sum C=2.84:1) while the

NBAS group are extravertive (M:SumC=0.81) which once again highlights the inherent heterogeneity of attempted suicides. It is here that their performance on 16 PF, which indicates more consciously perceived attitudes, become more interesting. The NBAS group scored significantly low in the E, F and H factors which makes them introspective, shy, timid, and restrained. This is quite in contrast to their Rorschach profile. Further, the BAS group scored high in E and H factors which makes them aggressive, assertive, venturesome and socially bold [14]. This is also quite in contrast to their Rorschach performance. Hence, it appears that the outward behaviour of NBAS and BAS groups is in contrast to their inherent predisposition.

From the foregoing, the parsimonious inference that overt extroverts among the attempted suicides have subsensitive postsynaptic 5 HT-1A receptors and those who are overt introverts, as inferred from 16 PF test, have subsensitive presynaptic 5 HT 1A receptors, can be drawn.

Pharmacotherapy effects on the threshold for suicidal acts per se have not invited independent attention of researchers from the secondary prevention point of view [17]. Receptors are dynamic structures whose density and sensitivity undergo adaptive changes in response to the alteration in agonist supply [21]. An adequate supply of agonist to overt introverts might stabilize their presynaptic 5 HT-1A receptors. Lopez et al [22] have reported increased 5 HT mRNA after chronic administration of Buspirone. Buspirone is a commonly used anxiolytic with a good safety profile. Exhibiting therapeutic doses of Buspirone on maintenance paradigm might be an useful strategy to stabilize serotonin imbalance in overtly introverted attempted suicides.

Increasing agonist load by administering serotonin specific reuptake inhibitors (SSRIs) might not be beneficial to overtly extroverted attempted suicides, as it may further reduce the sensitivity of postsynaptic 5 HT-1A as a compensatory phenomenon. In fact, that is what might be happening in the BAS. It is known that post synaptic 5 HT-2 receptors have opposing action on 5 HT-1A [21]. Administering specific 5 HT-2 antagonists like Ritanserin and Ketanserin might merit consideration. However, these drugs are not commercially available yet. The serotonin dopamine group of drugs Clozapine, Risperidone and Olanzapine also have significant effects at 5 HT-2 receptors. These drugs are quite safe and are widely used. As Clozapine use requires stringent monitoring, Risperidone and Olanzapine appear ideal in this respect. Hence, exhibiting these drugs to extroverted attempted suicides

might reduce subsequent suicide attempts as well as completed suicides. As predisposition to suicide attempts is independent of psychiatric disorders, it is logical that specific anti suicidal pharmacotherapy should be instituted in conjunction with specific pharmacotherapy of any coexisting psychiatric disorder.

As attempted suicides appear to be behaving in a way against their natural disposition and aspire beyond their capabilities, establishing a positive therapeutic alliance and counselling for setting realistic goals and develop more mature skills in communication of their needs might bring much benefit. With such efforts along with the suggested antisuicidal pharmacotherapy, the 'Disease of Suicide' can probably be more effectively controlled.

References

1. Goel DS. Attempted suicide in the Armed Forces. A study of psychosocial and preventive aspects in an active command. *Indian Journal of Psychiatry* 1975;17:163-73.
2. Valdiya PS, Sharma CS, Rajguru B. Study of suicide attempts (deliberate self harm) in army personnel. An Armed Forces Research Committee Project No. 2054/95.
3. Unni Sadanandan KE. Human self destructive behaviour. In : Vyas JN, Ahuja N, editors. *Text book of Postgraduate Psychiatry*, 2nded, New Delhi : Jaypee Brothers, 1999;525-56.
4. Annual Health Report of the Army. Dte Gen Medical Services (Army), 1995.
5. Asperg M, Traskman L, Thoren P. 5 HIAA in the cerebrospinal fluid : A biochemical suicide predictor. *Arch Gen Psychiatry* 1976;33:1193-7.
6. Arango V, Underwood MD, Mann JJ. Biological alteration in the brain stem of suicides. *Psych Clin North Am* 1997;20:582-93.
7. Weiss D, Coccaro EF. Neuroendocrine challenge studies of suicidal behaviour. *Psych Clin North Am* 1997;20:563-79.
8. Anderson IM, Cowen PJ, Greham Smith DG. Effect of Gepirone on neuroendocrine function and temperature in humans. *Psychopharmacol* 1990;100:498-503.
9. Cowen PJ, Grahame Smith DG. Neuroendocrine effects of Azapirones. *J Clin Psychopharmacol* 1990;10:215-55.
10. Moeller FG, Steinberg JL, Ulton M. A preliminary study with Buspirone in major depression. *Neuropsychopharmacology* 1994;10:75-81.
11. Pitchot W, Ansseau M, Moreno G. The flesinoxan 5 HT-1A receptor challenge in major depression. *Pharmacopsychiatry* (German), 1995;28(S), 91-5.
12. Rorschach H. *Psychodiagnostics*. Berne:Hans Huber 1969;1-42.
13. Klopffer B, Kelly DM. *The Rorschach technique*. New York : World Book Company, 1946;60-182.
14. Beck AT, Wessler R, Redmor C. *Beck Depression Inventory*. New York : The Psychological Corporation, 1993;1-4.
15. Cattell RB, Eber HW, Tatsoukd MM. *Handbook for the 16 PF questionnaire*. Illinois : Institute of personality and ability testing, 1970;1-7.

16. Moscicki EK. Identification of suicide risk factors using epidemiological studies. *Psych Clin North Am* 1997;20:499-517.
17. Malone KM. Pharmacotherapy of affectively ill suicidal patient. *Psych Clin North Am* 1997;20:499-517.
18. Roy A, Rylander G, Sarchiapone M. Genetic studies of suicidal behaviour. *Psych Clin North Am* 1997;20:595-611.
19. Eyman JT, Eyman SK. Psychological testing for potentially suicidal individuals. In: Bonger B, editor. *Suicide. Guidelines for assessment and management*. 1st ed. Oxford : Oxford university press, 1992;127-43.
20. Roy A. Suicide. In: Kaplan II, Sadock BJ, editors. *Comprehensive Text Book of Psychiatry*, Vol 2, 5th edn. Baltimore : William & Wilkins, 1989;1414-27.
21. Ashton H. *Brain function and psychotropic drugs*. Oxford : Oxford University Press, 1992;43-5.
22. Lopez JF, Chalmers DT, Watson SJ. Modulation of serotonin 1A receptor gene expression by antidepressants. *Biological Psychiatry*. 1995;37:599-600.